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REVIEW

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Cardiotoxicity of small-molecule kinase inhibitors in cancer therapy

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Abstract

Cancer is one of the leading causes of death worldwide. Recent advances in precision oncology have enabled many specific cancer patient populations to respond well and achieve longer survival with small-molecule kinase inhibitors, which have become a new therapeutic strategy for tumors. Since 2001, the Food and Drug Administration has approved 108 and 63 new anticancer drugs for treating solid tumors and hematological malignancies, respectively, 89 of which belong to the large group of small-molecule kinase inhibitors (SMKIs). Compared to conventional chemotherapeutic agents such as cyclophosphamide, doxorubicin, and 5-FU, SMKIs offer better efficacy with fewer toxic side effects. Nevertheless, with the development of more novel SMKIs and their wider clinical application to a larger population of cancer patients, variable degrees of cardiotoxic adverse events have emerged for some SMKIs during cancer therapy. This review comprehensively summarizes the most updated progress in the cardiotoxicity of SMKIs in cancer therapy and discusses the new findings and mechanisms, which will provide emerging strategies for the prevention of cardiotoxicity caused by small molecule targeted drugs and the design of the next generation of low cardiotoxicity targeted drugs.

Keywords Cancer, Small-molecule kinase inhibitors, Cardiotoxicity

Introduction

Based on GLOBOCAN 2020 data, approximately 4.82 million and 2.37 million new cancer cases, and 3.21 million and 0.64 million cancer deaths were reported in China and the United States of America in 2022, respectively [1–3]. Traditional treatment strategies, including surgery, radiotherapy, chemotherapy, and immunotherapy, are still the mainstay of cancer therapy. However, tumor recurrence, drug resistance, distant metastasis, radiation resistance, and treatment-related serious adverse events are the main causes of failure of conventional cancer therapies. With the advances in medical science research in recent years, molecular targeted therapy and cancer immunotherapy have shown unprecedented success in the treatment of various cancer types [4]. Following the Food and Drug Administration (FDA) approval of the first-in-class tyrosine kinase inhibitor (TKI) imatinib for the treatment of chronic myeloid leukemia in 2001, there has been a growing interest in the development of targeted drugs for cancer treatment [5]. Chemotherapy agents, such as cyclophosphamide, doxorubicin, and 5-FU, primarily target various stages of tumor cell proliferation, effectively inhibiting or

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eradicating malignant cells. Unlike conventional chemotherapy, targeted drugs are capable of specifically recognizing tumor cells and effectively impeding cancer growth and proliferation. Cancer treatment with targeted drugs is more precise, and there is a lower chance of developing toxic side effects [6]. Consistently, the number and proportion of targeted drugs approved by the FDA have increased significantly (Fig. 1).

Targeted therapeutics are broadly divided into small molecules and large molecules. Small molecular drugs are chemicals with low molecular weight, which are primarily kinase inhibitors (receptor TKIs and non-receptor TKIs). On the other hand, large molecular drugs are usually made of proteins that are manufactured or extracted from living organisms. They encompass monoclonal antibodies and antibody-drug conjugates [7, 8]. Since 2001, the FDA has approved 108 new anticancer agents for solid tumors and 63 for hematologic malignancies. Among these newly approved anticancer drugs, 89 are small molecular drugs [9]. Small-molecule kinase inhibitors (SMKIs) are usually smaller than 500 Da in molecular weight, thus allowing their efficient penetration across cell membranes. Moreover, they are usually administered orally to facilitate better patient compliance, and they are also substantially less expensive than the large molecular biologic drugs [10].

Cardiovascular toxicity, such as heart failure (HF), arrhythmias, and coronary artery disease, represent notable adverse effects of cancer therapy [11]. (Fig. 2) They are becoming more prominent with the longer duration of cancer treatment, which seriously affects the therapeutic effect and prognosis of cancer patients [12]. For example, TKIs and angiogenesis inhibitors are known to cause cardiotoxicity in cancer patients [13]. It has been estimated that approximately 62.92% of SMKIs may potentially mediate adverse cardiac events. Substantial research has been conducted to understand the etiology of cancer treatment-related cardiotoxic events. However, the specific mechanism(s) inducing cardiotoxicity by targeted anticancer drugs remain to be further explored.

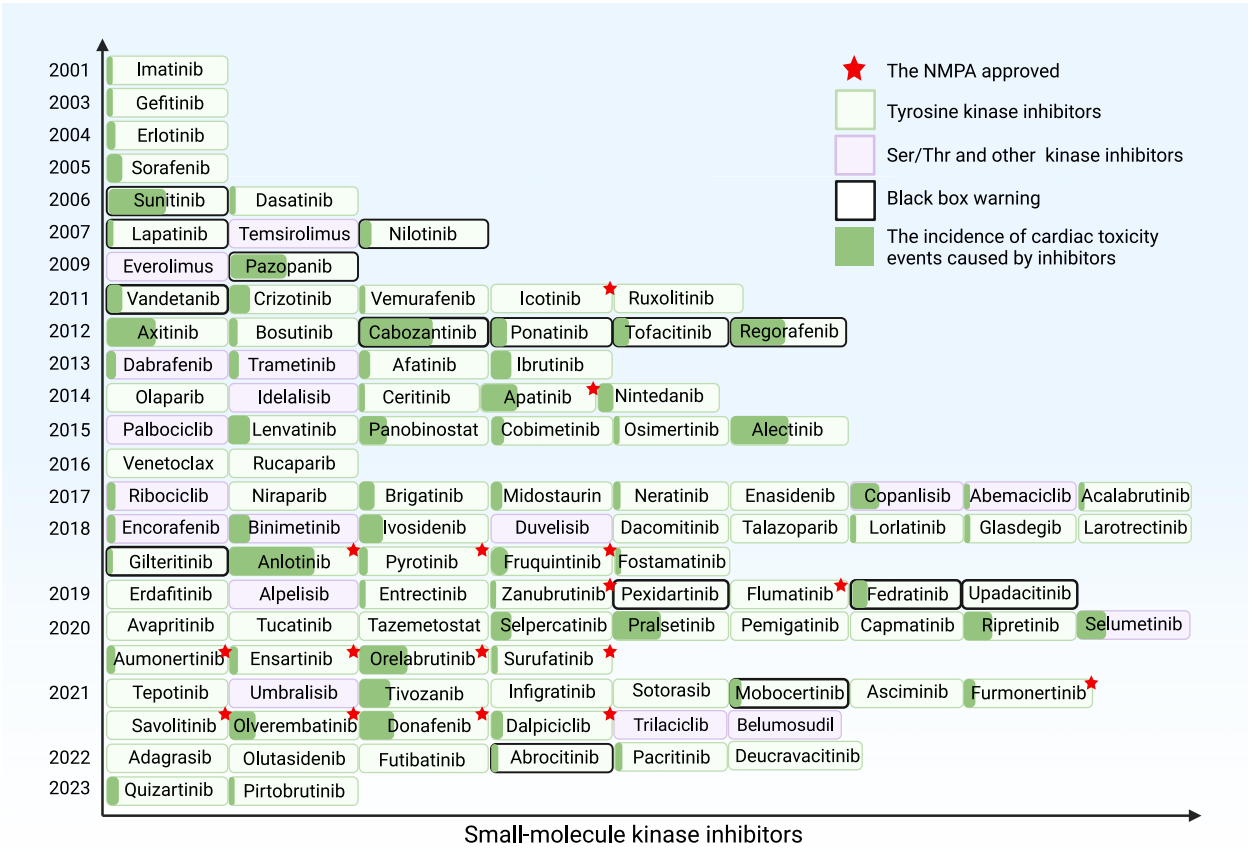


Fig. 1 Timeline for the FDA and NMPA approval of small-molecule kinase inhibitors. The figure shows the small-molecule kinase inhibitors approved by the FDA and NMPA from 2001 to 2023. Except for the red star representing small-molecule inhibitors approved by NMPA, all others are FDA-approved. The green box shows tyrosine kinase inhibitors, while the pink box shows ser/thr kinase inhibitors, and the black box shows drugs with black box warnings. Green represents the incidence of cardiotoxicity events induced by small molecule inhibitors

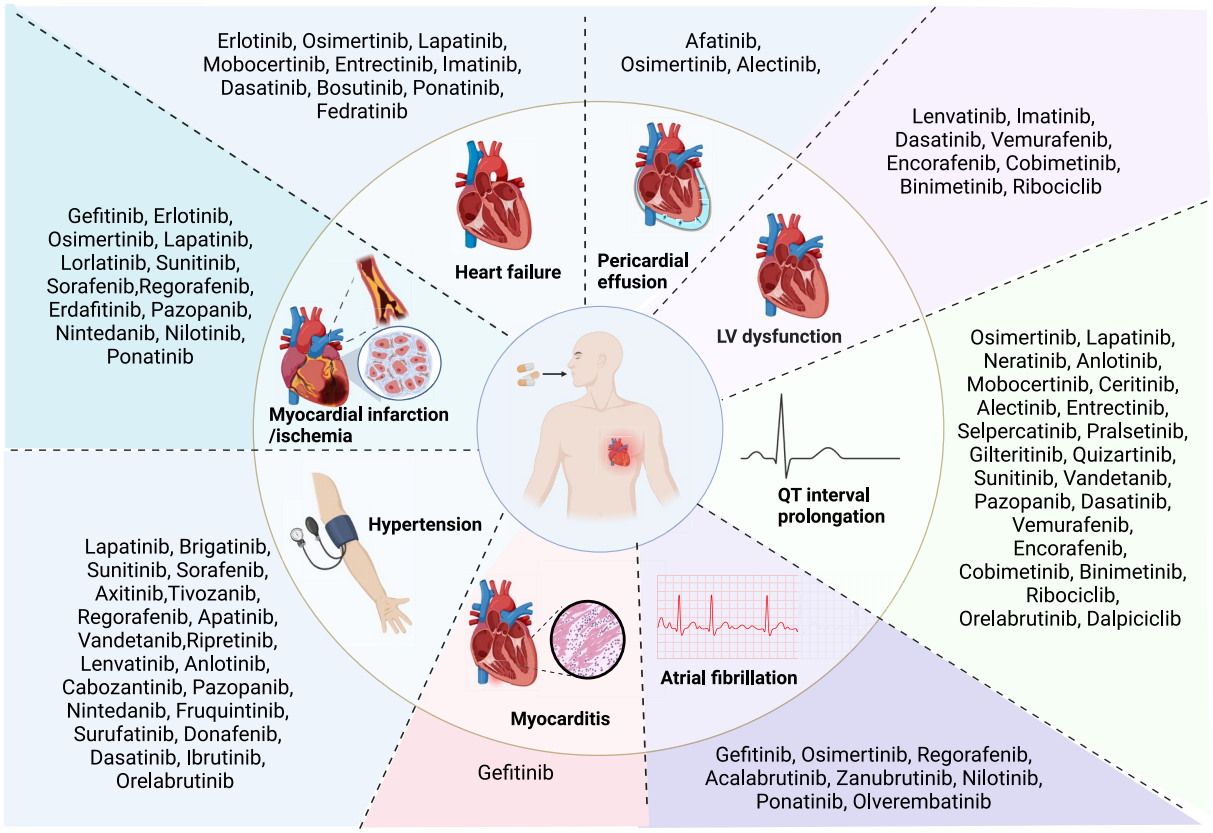


Fig. 2 Cardiovascular toxicities of small-molecule kinase inhibitors. The figure shows the cardiotoxicity events induced by small molecule inhibitors, including myocarditis, atrial fibrillation, hypertension, QT interval prolongation, LV dysfunction, pericardial effusion, heart failure, and myocardial infarction or ischemia. We have identified small molecule inhibitors that induce corresponding cardiotoxicity

This review will provide an updated summary of the cardiotoxicity caused by the clinically approved SMKIs. We will discuss the latest research on the mechanisms responsible for cardiotoxic effects in cancer patients and highlight novel strategies for their management.

Receptor tyrosine kinase inhibitors

Epidermal growth factor receptor (EGFR) inhibitors

Non-small cell lung cancer (NSCLC) is a histological subtype of lung cancer constituting more than 85% of all cases. Numerous EGFR mutations (e.g., exon 19 deletion or L858R mutation) are constitutively active and they drive "addictive" oncogenic signaling in cancer cells. EGFR TKIs are developed to target this "addictive" signaling and disrupt the downstream pathways to selectively kill cancer cells [14]. While EGFR TKIs are generally well tolerated, cardiotoxicities (including QT interval prolongation, left ventricular ejection fraction (LVEF) reduction, myocardial infarction (MI), atrial fibrillation (AF), and heart failure (HF)) have been reported for some TKIs [15] (Table 1).

The first-generation EGFR-TKIs

EGFR-TKIs are widely used to treat NSCLC patients. Erlotinib, gefitinib, and icotinib are the first-generation EGFR-TKIs that bind reversibly to EGFR and compete with ATP for binding to the TK domain.

Gefitinib According to the analysis results of the FDA Adverse Event Reporting System (AERS) database, the incidence of cardiotoxicity induced by gefitinib is approximately 1.6% [16]. A series of case reports found that gefitinib could induce cardiotoxicity such as MI, left bundle branch block, AF, myocarditis, and venous thromboembolism [17–20].

Gefitinib was found to enhance the expression of phosphatase and tensin homolog (PTEN) in cardiomyocytes, while also increasing the expression of FoxO3a through the inhibition of the PI3K/AKT signaling pathway, ultimately leading to cardiotoxicity [21]. In a rat cardiotoxicity model, gefitinib induced cardiac hypertrophy by elevating the expression of a hypertrophic gene marker (BNP) and suppressing an anti-hypertrophic gene

Table 1 The cardiotoxicity of EGFR-TKIs

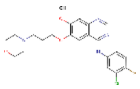
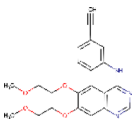
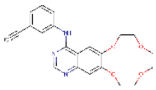
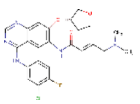
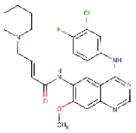
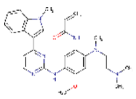
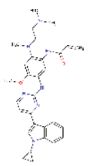
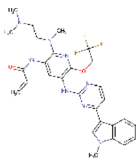
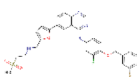
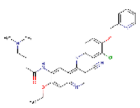
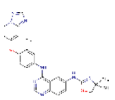
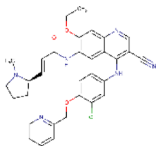
Generation	Name	Chemical structure	Targets	Approved for indications on	Cardiotoxicity	Corporation
EGFR						
First-	Gefitinib (Iressa)		EGFR	NSCLC 05/05/2003	MI, myocarditis, cardiac hypertrophy, AF, left bundle branch block	AstraZeneca
	Erlotinib (Tarceva)		EGFR	NSCLC (2004) Pancreatic cancer (2005)	Myocardial ischemic, MI, HF, venous thromboembolism	Roche/Astellas
	Icotinib (Conmana)		EGFR	NSCLC 06/07/2011	ND	BettaPharma
Second-	Afatinib (Gilotrif)		EGFR	NSCLC 07/2013	diastolic dysfunction, left ventricle enlargement, pericardial effusion	Boehringer Ingelheim
	Dacomitinib (Vizimpro)		EGFR	NSCLC 10/2018	ND	Pfizer
Third-	Osimertinib (Tagrisso)		EGFR	NSCLC 11/2015	Acute coronary syndrome, QT interval prolongation, MI, HF, mitral or tricuspid valve regurgitation, AF, pericardial effusion, decreased LVEF, supraventricular tachycardia	AstraZeneca
	Aumonertinib (Ameile)		EGFR	NSCLC 2020	QT interval prolongation	Hansoh
	Furmonertinib (Alflutinib)		EGFR	NSCLC 03/2021	QT interval prolongation, AF	Allist Pharmaceuticals
HER						
HER2	Lapatinib (Tykerb)		EGFR/HER2	Breast cancer 03/2007	Cardiomyopathy, hypotension, arrhythmia, ischemic heart disease, QT prolongation, decreased LVEF, HF	Novartis
	Neratinib (Nerlynx)		EGFR/HER2/HER4	Breast cancer 07/2017	Arrhythmia, ischemic heart disease, QT interval prolongation, decreased LVEF, HF	Puma Biotech
	Tucatinib (Tukysa)		HER2	HER2-positive breast cancer 04/2020	ND	Seagen

Table 1 (continued)

Generation	Name	Chemical structure	Targets	Approved for indications on	Cardiotoxicity	Corporation
	Mobocertinib (Exkivity)		EGFR/HER2	NSCLC 09/2021	QT interval prolongation, HF	Takeda Pharmaceutical Company
	Pyrotinib		pan-HER	HER2-positive breast cancer 08/2018	QT interval prolongation	Hengrui Medicine

All data statistics from the FDA (https://www.accessdata.fda.gov)

EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; MI: myocardial infarction; AF: arial fibrillation; HF: heart failure; HER2: human epidermal growth factor receptor 2; LVEF: left ventricular ejection fraction; ND: No data

(α-MHC) in a concentration-dependent manner. Furthermore, gefitinib has been reported to induce apoptosis in cardiomyocytes via upregulating caspase 3 and P53 [22].

Currently, studies have indicated that liraglutide, a receptor agonist of glucagon-like peptide-1, possesses the ability to mitigate gefitinib-induced cardiac injury by upregulating the ERK/AKT pathway while downregulating the JNK/P38 pathway [23]. The expression of angiotensin II (AngII) and its receptors was upregulated in myocardial tissue induced by gefitinib. Valsartan inhibits the AngII type 1 receptor (AT1R), which leads to the downregulation of the JNK/P38 MAPK pathway and ultimately alleviates gefitinib-induced myocardial hypertrophy [24]. Focusing on the development of drugs that down-regulate the JNK/P38 pathway may be a promising strategy for reducing the cardiotoxicity induced by gefitinib.

Erlotinib Additionally, myocardial ischemia (3.1%) and venous thromboembolism (3.9%) have also been reported among cancer patients receiving erlotinib [25, 26].

The second-generation EGFR-TKIs

Afatinib Afatinib is a second-generation irreversible EGFR-TKI primarily targeting EGFR and human epidermal growth factor receptor 2 (HER2), which may contribute to its mechanism for inducing cardiotoxicity in NSCLC patients [27, 28].

There is a case report indicating that symptoms of heart failure (HF) induced by afatinib returned to normal following replacement therapy with gefitinib [29]. However, this finding contradicts previous observations regarding the induced cardiotoxicity of gefitinib, and therefore further investigation into the underlying causes is warranted.

The third-generation EGFR-TKIs

Osimertinib Osimertinib was approved for the treatment of patients with EGFR T790M-positive NSCLC. Compared to the first- and second-generation EGFR-TKIs, osimertinib is associated with a significantly higher incidence of HF, AF, and QT interval prolongation following treatment [30, 31].

Previous studies have indicated that up to 4.9% of patients receiving osimertinib experienced grade 3 or higher cardiotoxicity, such as MI, HF, and severe mitral or tricuspid valve regurgitation [32]. Although QT interval prolongation and ventricular arrhythmias induced by osimertinib are uncommon, they can easily develop into severe arrhythmias and can be life-threatening once they occur. Currently, temporary pacemaker implantation and excessive pacing have been proposed as potential treatments for torsade de pointes induced by osimertinib [33]. In addition, AF and pericardial effusion may occur in 4% and 8.2% of patients after osimertinib treatment, and can also lead to QT interval prolongation and cardiomyopathy [34].

Clinicians are therefore advised to be able to identify tip-torsional ventricular tachycardia, to routinely monitor electrocardiograms and echocardiograms, and to avoid the use of drugs that prolong the QT interval when used in combination with other medications when treating patients with osimertinib. To more accurately identify osimertinib-induced cardiotoxicity, Li et al. employed whole-cell patch clamp technology to illustrate that osimertinib concurrently inhibited hERG (human ether-a-go-go-related gene) potassium channels, Nav1.5 sodium channels, and L-type Ca^{2+} channels involved in

cardiomyocyte conduction, resulting in an elongation of the PR interval and QT interval [35]. This discovery establishes a foundation for future research.

Aumonertinib and furmonertinib Aumonertinib (almonertinib), a novel and irreversible third-generation EGFR-TKI, was employed as a second-line treatment of NSCLC patients with the T790M mutation following the progression to EGFR-sensitive mutation therapy [36, 37]. Clinical statistics indicated that 6.1% of NSCLC patients experience QT interval prolongation after receiving aumonertinib treatment [37]. It is noteworthy that an elderly patient experienced severe HF after receiving treatment with osimertinib. However, after switching to aumonertinib, the patient's HF symptoms gradually recovered [38].

Furmonertinib is an irreversible, third-generation EGFR-TKI for the treatment of advanced or metastatic NSCLC patients with EGFR T790M mutations [39]. Treatment with furmonertinib has been associated with prolonged QT interval (9%) and AF (1%) [40].

Other EGFR-TKIs

Lapatinib Lapatinib is a dual TKI that exerts its anticancer activity primarily through the inhibition of both the EGFR and the HER2 [41]. It has been estimated that lapatinib may cause a reversible reduction of LVEF in approximately 2.7% of cases [42].

Currently, anthracyclines are known to induce cardiotoxicity, and Hsu et al. have proposed that lapatinib could reverse this phenomenon by inhibiting inducible nitric oxide synthase (iNOS) [43]. However, the combination of lapatinib and doxorubicin may result in more pronounced cardiotoxicity, primarily due to lapatinib's capacity to induce oxidative stress in cardiomyocytes through the inhibition of the PI3K/AKT signaling pathway, thereby exacerbating the cardiotoxicity induced by doxorubicin [44].

Neratinib Neratinib is another HER2 inhibitor that has been indicated for the treatment of advanced HER2-positive breast cancer (BC) [45]. According to the result of the phase III clinical trial, the incidence of arrhythmia, ischemic heart disease, QT interval prolongation, and LVEF reduction in patients treated with neratinib was 3.3%, 0.7%, 2.3%, and 4.3%, respectively [46].

In conclusion, lapatinib has a relatively weak cardiotoxicity profile in comparison to other EGFR TKIs. Concerning the reduction in LVEF associated with EGFR-TKIs, clinical guidelines recommend that in cases where LVEF is greater than 50%, clinical physicians should monitor patients' echocardiograms or follow-up with them during treatment. In the event of an asymptomatic decline in LVEF during the follow-up period, the echocardiogram evaluation should be conducted within one month. If the LVEF is less than 40%, the clinician is recommended to suspend the medication and seek counseling or referral to a cardiologist for further treatment. Furthermore, the guidelines advise the monitoring of biomarkers such as CK-MB, TnT, and BNP throughout treatment, as these are more indicative of the likelihood of cardiotoxicity [47, 48].

Anaplastic lymphoma kinase (ALK) inhibitors

Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase that belongs to the insulin receptor superfamily. Following the binding of a ligand to its extracellular domain, ALK undergoes dimerization and subsequent autophosphorylation of its intracellular kinase domain, thereby activating the downstream oncogenic pathways, including the mitogen-activated protein kinase (MAPK) signaling cascades, which promote cancer growth and transformation [49]. Mutations in the ALK gene have been identified in a range of tumors, including NSCLC, anaplastic large cell lymphoma (ALCL), and diffuse large cell lymphoma [50–52]. The most commonly reported adverse cardiac events associated with ALK inhibitors are prolonged QT interval and bradycardia (Table 2).

The first-generation ALK inhibitors

Crizotinib Several ALK-TKIs have been granted clinical approval for the treatment of NSCLC in patients with ALK rearrangement. Crizotinib, a first-generation ALK inhibitor, is indicated for treating patients with ALK/ROS1-positive NSCLC as well as ALK-positive ALCL [53, 54].

During the treatment with crizotinib, a decrease in heart rate (below 45 bpm) may occur in most patients, leading to bradycardia [55, 56]. Conversely, a minor subset of patients experienced myocardial infarction, elevated creatinine levels, and potential sepsis [57]. The decreased heart rate may be attributed to the hyperpolarization of cardiomyocytes resulting from the inhibition of hyperpolarization-activated cyclic nucleotide-gated channel 4 by crizotinib [58]. Doherty and colleagues have reported that crizotinib suppressed hERG channels and caused cardiotoxicity by increasing ROS production, cholesterol accumulation, and activating the apoptotic cascade in cardiomyocytes in vitro [59]. Furthermore, Xu et al. have confirmed that the primary mechanism underlying the cardiotoxicity induced by crizotinib is the reduction of autophagy activity within myocardial cells. The administration of metformin has been shown to facilitate the restoration of autophagy in myocardial cells by reactivating the phosphorylation of PRKAA/AMPK (protein kinase, AMP-activated, α catalytic subunit),

Table 2 The cardiotoxicity of ALK/ROS1/c-Met/RET/FLT3 inhibitors

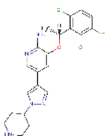
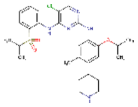
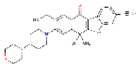
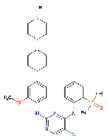
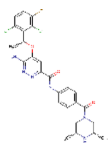
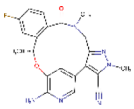
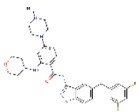
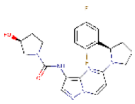
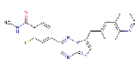
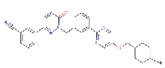
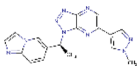
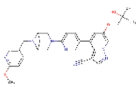
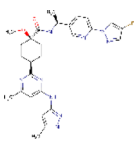
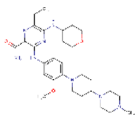
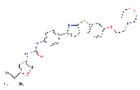
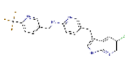
Generation	Name	Chemical structure	Targets	Approved for indications on	Cardiotoxicity	Corporation
ALK						
First-	Crizotinib (Xalkori)		ALK/ROS1/c-Met	NSCLC 08/2011	Bradycardia, pericarditis	Pfizer
Second-	Ceritinib (Zykadia)		ALK/ROS1	NSCLC 04/2014	QT interval prolongation	Novartis
	Alectinib (Alecensa)		ALK	NSCLC 12/2015	QT interval prolongation, bradycardia, pleural and pericardial effusions	Roche/Chugai
	Brigatinib (Alunbrig)		ALK/ROS1/ IGF-1R/ FLT-3/EGFR	NSCLC 04/2017	Bradycardia and hypertension	Ariad
	Ensartinib		ALK	NSCLC 11/2020	Arrhythmia	BettaPharma
Third-	Lorlatinib (Lorbrena)		ALK	NSCLC 11/2018	MI	Pfizer
ROS1						
	Entrectinib (Rozlytrek)		ALK/ROS1/TRKA/B/C	Solid tumors with NTRK Fusion 08/2019	CHF, QT interval prolongation	Roche
	Larotrectinib (Vitrakvi)		TRKA/B/C	Solid tumors with NTRK Fusion 11/2018	ND	Bayer
c-MET						
	Capmatinib (Tabrecta)		c-Met	NSCLC 05/2020	ND	Novartis
	Tepotinib (Tepmetko)		c-Met	NSCLC 02/2021	ND	Novartis
	Savolitinib (Volitinib)		c-Met	NSCLC 06/2021	ND	Hutch-medicine
RET						
	Selpercatinib (Retevmo)		RET	NSCLC, MTC, Thyroid cancer 05/08/2020	Hypertension, QT interval prolongation	Loxo

Table 2 (continued)

Generation	Name	Chemical structure	Targets	Approved for indications on	Cardiotoxicity	Corporation
	Pralsetinib (Gavreto)		RET	NSCLC, MTC, Thyroid cancer 09/04/2020	Hypertension, QT interval prolongation	Blueprint Medicines
FLT3						
First-	Midostaurin (Rydapt)		FLT3	AML 04/28/2017	Hypertension	Novartis
Second-	Gilteritinib (Xospata)		FLT3	AML 11/28/2018	QT interval prolongation	Kotobuki/Astellas
	Quizartinib (Vanflyta)		FLT3	AML 7/20/2023	QT interval prolongation	Daiichi Sankyo
Other	Pexidartinib (Turalio)		CSF1R/Kit/FLT3	Tenosynovial giant cell tumor 08/02/2019	ND	Daiichi Sankyo Inc

All data statistics from the FDA (https://www.accessdata.fda.gov)

ALK: anaplastic lymphoma kinase; IGF-1R: insulin-like growth factor-1 receptor; FLT-3: FMS-like tyrosine-3; NSCLC: non-small cell lung cancer; MI: myocardial infarction; CHF: congestive heart failure; CRC: colorectal cancer; MTC: medullary thyroid carcinoma; AML: acute myeloid leukemia; ND: No data

thereby representing a potential therapeutic strategy for alleviating crizotinib-induced cardiotoxicity. This study corroborates the assertion that metformin exerts a further novel effect [60].

Pericarditis is a frequently observed primary side effect in cancer patients undergoing treated with ALK inhibitors. The precise mechanism underlying the development of pericarditis remains unclear. The drug may exert an unidentified effect on the target, which may contribute to the onset of this adverse event [61].

The second-generation ALK inhibitors

Second-generation ALK inhibitors, including ceritinib, alectinib, and brigatinib, have been developed to treat cancer patients who have experienced crizotinib resistance [62–64].

Ceritinib and ensartinib The prolongation of the QT interval has been reported in cancer patients treated with ceritinib [65]. In a case report, the patient received pacemaker treatment due to severe bradycardia induced by alectinib [66]. Furthermore, alectinib-induced pleural and pericardial effusions have been documented in an individual case of NSCLC patient, with resolution of effusion upon switching from alectinib to brigatinib [67]. In the ALTA trial, NSCLC patients experienced bradycardia and hypertension following brigatinib treatment [68].

Ensartinib is also a second-generation ALK inhibitor [69]. Arrhythmia has been observed in 5.9% of patients treated with ensartinib, with spontaneous resolution upon discontinuation of the medication [70].

The third-generation ALK inhibitors

Lorlatinib Lorlatinib is a third-generation ALK inhibitor that has been demonstrated to be effective against all ALK mutations (excluding L1198F). It was approved as a first-line treatment option for advanced ALK-positive NSCLC [71, 72]. The occurrence of MI in patients with ALK-positive NSCLC who received lorlatinib was reported to be 0.7%, resulting in permanent discontinuation of the drug [73].

In conclusion, the most frequently observed adverse cardiac effects associated with ALK inhibitors are arrhythmia and pericarditis. Electrocardiograms and echocardiograms are recommended for monitoring in patients undergoing clinical application of ALK inhibitors.

VEGFR/FGFR/PDGFR inhibitor

Tumor angiogenesis plays a pivotal role in supporting tumor cell proliferation, invasion, and metastasis [74].

Currently, the prevailing strategy for anti-angiogenic treatment is to inhibit the function of their receptors, including vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR). The most commonly used drugs in this class, such as sunitinib and sorafenib are both multi-kinase inhibitors [75]. The primary cardiotoxicity associated with this agent is hypertension, with other cardiotoxicity including decreased LVEF, congestive heart failure (CHF), and MI (Table 3).

Sunitinib

Sunitinib is a multi-kinase inhibitor that targets VEGFR-1/2/3, PDGFRα/β, c-Kit, colony-stimulating factor 1 receptor (CSF1R), RET, and FLT3, it has been approved for treating renal cell carcinoma and imatinib-resistant gastrointestinal mesenchymal tumor (GIST) [76].

The findings from a subsequent Phase III clinical trial demonstrated that treatment with sunitinib was associated with grade 3 hypertension in 8% of patients and significant reduction in LVEF in 2% of patients. Both of these adverse cardiotoxic effects were resolved after discontinuation of sunitinib [77]. Furthermore, sunitinib has been reported to induce cardiotoxicity in patients with imatinib-resistant GIST, including hypertension (47%), CHF (8%), MI (2%), and decreased LVEF (20%) [78]. Notably, the incidence of sunitinib-induced cardiotoxic events in this study was substantially higher than in previous studies, potentially due to the inclusion of a population with a high prevalence of cardiovascular diseases or a history of cardiotoxic medications, such as imatinib. The incidence of symptomatic HF was observed in 2.7% of patients after 22 days of sunitinib therapy, this was not reversible after the drug was discontinued [79, 80]. One patient experienced a severe transient ischemic attack during treatment with sunitinib [81]. Furthermore, sunitinib is also associated with a risk of ventricular arrhythmias, and it affects the QT interval in a dose-dependent manner [82].

The mechanisms contributing to sunitinib-induced cardiotoxicity include the inhibition of VEGFR, PDGFR, and AMPK expression, hypoxic stress, the activation of endothelin-1, and ferroptosis (Fig. 3). And the downregulation of VEGFR or PDGFR expressions may potentially result in a reduction in the density of coronary capillaries, thereby limiting the contraction or expansion of the left ventricle [83]. Cardiomyocytes have been demonstrated to express PDGFRs, and elevated levels of PDGF have been associated with cardiomyocyte viability. Nevertheless, the inhibition of PDGFRs has the potential to induce apoptosis and cause cardiotoxicity [84].

It has been established that the AMPK signaling pathway promotes the survival of cardiomyocytes. It can be inferred that sunitinib may exert its cardiotoxic effect by inhibiting AMPK activity. This is corroborated by the observation that transfection with an adenoviral vector expressing AMPK is capable of significantly alleviating sunitinib-induced cardiomyocyte death. Additionally, trimetazidine is an antianginal drug that has been demonstrated to mitigate cardiotoxicity by activating the AMPK/mTOR/autophagy signaling pathway [85].

Hypertension represents a significant risk factor for the development of left ventricular dysfunction and HF in patients receiving sunitinib. It has been confirmed that sunitinib-induced hypertension is primarily associated with the activation of endothelin-1 and the inhibition of the renin-angiotensin system [86, 87].

Furthermore, sunitinib activates the hypoxia-responsive gene HIF-1α, which can result in cardiomyocyte damage and a range of cardiomyopathies such as CHF [88]. The results of various animal studies indicate that thalidomide, FGF2 mRNA, endothelin receptor antagonist macitentan, sacubitril/valsartan, and AMPK activator may be employed as therapeutic methods for heart protection [83, 89–91].

Moreover, sunitinib induces cardiomyocyte apoptosis and cardiotoxicity through autophagic degradation of CCN2 (cellular communication network factor 2), and HMGB1 (high mobility group box 1) serves as an important regulatory factor for cardiotoxicity. Consequently, the inhibition of HMGB1 can alleviate the cardiotoxicity of sunitinib [92].

Recent studies have shown that sunitinib induces cardiotoxicity by promoting oxidative stress and Nrf2-dependent ferroptosis [93].

Therefore, it is imperative that clinicians meticulously monitor the patients' blood pressure and LVEF throughout treatment, particularly in individuals with a history of hypertension or coronary artery disease.

Sorafenib

Sorafenib is the first clinically approved multikinase inhibitor for anti-angiogenesis therapy, exhibiting potent inhibitory effects on VEGFR-1/2/3, c-Kit, FLT3, RET, PDGFRβ, and RAF [94]. It has been approved for treating unresectable hepatocellular carcinoma, advanced renal cell carcinoma, and differentiated thyroid carcinoma [95].

However, it is important to note that VEGFR inhibitors have the potential to induce hypertension and thromboembolic events. It has been reported that sorafenib causes acute coronary syndrome (including MI) in patients [96]. Furthermore, in a phase III clinical trial involving renal cancer patients, sorafenib was shown to

Table 3 The cardiotoxicity of VEGFR/FGFR/PDGFR inhibitors

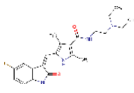
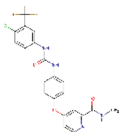
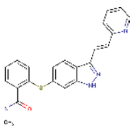
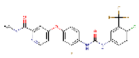
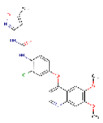
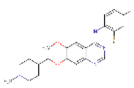
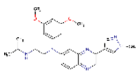
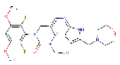
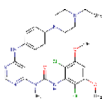
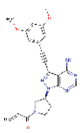
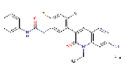
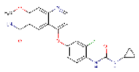
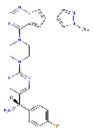
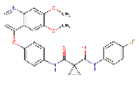
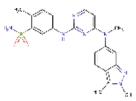
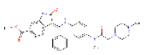
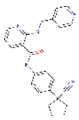
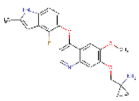
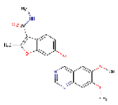
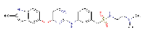
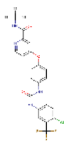
Generation	Name	Chemical structure	Targets	Approved for indications on	Cardiotoxicity	Corporation
VEGFR						
First-	Sunitinib (Sutent)		VEGFRs/ PDGFRα/β/ c-Kit/CSF1R/RET/ FLT3	RCC, imatinib-resistant GIST 01/2006	hypertension, CHF, MI, decreased LVEF, QT interval prolongation, ventricular arrhythmias, transient ischemic attack	Pfizer
	Sorafenib (Nexavar)		VEGFRs/c-Kit/FLT3/ RET/PDGFRβ/RAF	RCC (2005) HCC (2007) DTC (2013) Thyroid cancer (2014)	Acute coronary syndrome, hypertension, cardiac ischemia, MI, thromboembolism	Bayer
Second-	Axitinib (Inlyta)		VEGFRs	RCC after failure of sunitinib therapy 01/2012	Hypertension, HF	Pfizer
	Regorafenib (Stivarga)		VEGFRs/TIE2/FGFR1/ PDGFRβ/c-KIT/RET	CRC (2012) GIST (2013) HCC (2017)	Hypertension, AF, MI, cardiac arrest	Bayer
	Tivozanib (Fotivda)		VEGFRs	RCC 02/2021	Hypertension, HF, cardiac ischemia, arterial/venous thromboembolism, bleeding	Aveo Pharms
Third-	Vandetanib (Caprelsa)		EGFR/VEGFR/RET	MTC 04/2011	QT interval prolongation, hypertension	Genzyme
FGFR						
	Erdafitinib (Balversa)		FGFRs	Urothelial carcinoma 04/2019	ND	Janssen
	Pemigatinib (Pemazyre)		FGFRs	Cholangiocarcinoma 04/2020	ND	Incyte
	InStrratinib (Truseltiq)		FGFRs	Cholangiocarcinoma 05/2021	ND	Helsinn Hlthcare
	Futibatinib (Lytgobi)		FGFRs	Intrahepatic cholangiocarcinoma 9/2022	ND	Taiho Pharmaceutical Co., Ltd
PDGFR						
	Ripretinib (Qinlock)		PDGFRα, PDGFRα mutants/Kit	GIST 05/2020	Hypertension, LV dysfunction	Deciphera
	Lenvatinib (Lenvima)		PDGFR-α/VEGFRs/ FGFRs/c-Kit/ RET	DTC (2015) Thyroid cancer (2015) RCC (2016) HCC (2018) Endometrial carcinoma (2019)	LV dysfunction, HF, hypertension	Eisai

Table 3 (continued)

Generation	Name	Chemical structure	Targets	Approved for indications on	Cardiotoxicity	Corporation
	Avapritinib (Ayvakit)		PDGFRα, PDGFRα mutants/Kit	GIST 01/2020	ND	Blueprint Medicines
	Cabozantinib (Cabometyx, Cometriq)		BRAF/MET/VEGFRs/ AXL/RET/ROS1/c-KIT/TRK/ FLT-3	MTC (2013) RCC (2016) HCC (2019)	Hypertension, bleeding*	Exelixis
	Pazopanib (Votrient)		PDGFR-β/VEGFRs/ FGFR-1/3/c-Kit/c-GSK	RCC (2009) STS (2012)	QT interval prolongation, HF, arrhythmia, ischemia, MI, hypertension	Novartis
	Nintedanib (Ofev)		VEGFR-1/2/3/PDGFR-α/β/ MDR1/BCRP/ FGFR-1/3	NSCLC 2015	Hypertension	Boehringer Ingelheim
	Apatinib (Aitan)		VEGFR-2/Src/c-Kit	GC 11/2014	Hypertension	Hengrui Medicine
	Anlotinib (Focus V)		VEGFR-2/3/PDGFR-β/ FGFRs	NSCLC (2018) STS (2019) SCLC (2020)	Hypertension, sinus tachycardia, and QT interval prolongation	Chia Tai Tianqing
	Fruquintinib (Elunate)		VEGFR-1/2/3	CRC 2018	Hypertension	Chi-Med/Lilly
	Surufatinib		VEGFR1/2/3, FGFR1, and CSF-1R	Neuroendocrine tumor 12/2020	Hypertension	Hutch-medicine
	Donafenib		VEGFR and PDGFR	HCC 09/2021	Hypertension	Zelgen

All data statistics from the FDA (https://www.accessdata.fda.gov)

VEGFR: vascular endothelial growth factor receptor; PDGFR: platelet-derived growth factor receptor; GSF1R: colony stimulating factor 1 receptor; RCC: renal cell carcinoma; GIST: gastrointestinal mesenchymal tumors; FLT-3: FMS-like tyrosine-3; CHF: congestive heart failure; MI: myocardial infarction; LVEF: left ventricular ejection fraction; LV: left ventricular; AF: arial fibrillation; HCC: hepatocellular carcinoma; DTC: differentiated thyroid carcinoma; CRC: colorectal cancer; MTC: medullary thyroid carcinoma; FGFR: fibroblast growth factor receptor; STS: soft tissue sarcomas; NSCLC: non-small cell lung cancer; ND: No data

induce a significantly higher incidence of grade 3 or 4 hypertension in 16.8% of patients and cardiac ischemia or MI in 2.6% of patients [97, 98]. Overall, the incidence of sorafenib-induced hypertension during sorafenib treatment did not exceed 20% of patients. Moreover, a meta-analysis of clinical trials revealed that 1.7% and 1.3% of patients experienced thromboembolic events following treatment with sorafenib and sunitinib, respectively [99].

The potential cardiotoxic mechanism of sorafenib has been the subject of investigation. The cardiotoxicity induced by sorafenib mainly involves the loss of rapidly accelerated fibrosarcoma 1 (RAF1), promotion of myocardial cell ferroptosis, and inhibition of endothelial nitric oxide synthase (NOS) and nitric oxide (NO) in endothelial cells.

It's established that sorafenib exerts a potent inhibitory effect on the activity of the RAF kinase family, which is a member of the mitogen-activated protein kinase (MAPK) kinases [100]. The key member of this family, RAF1, is a proto-oncogene product and a Ser/Thr kinase that may play an important role in normal cell growth and oncogenic transformation. In the context of oxidative stress-induced injury, RAF1 has been observed to inhibit the pro-apoptotic kinases ASK1 (apoptosis signal-regulating

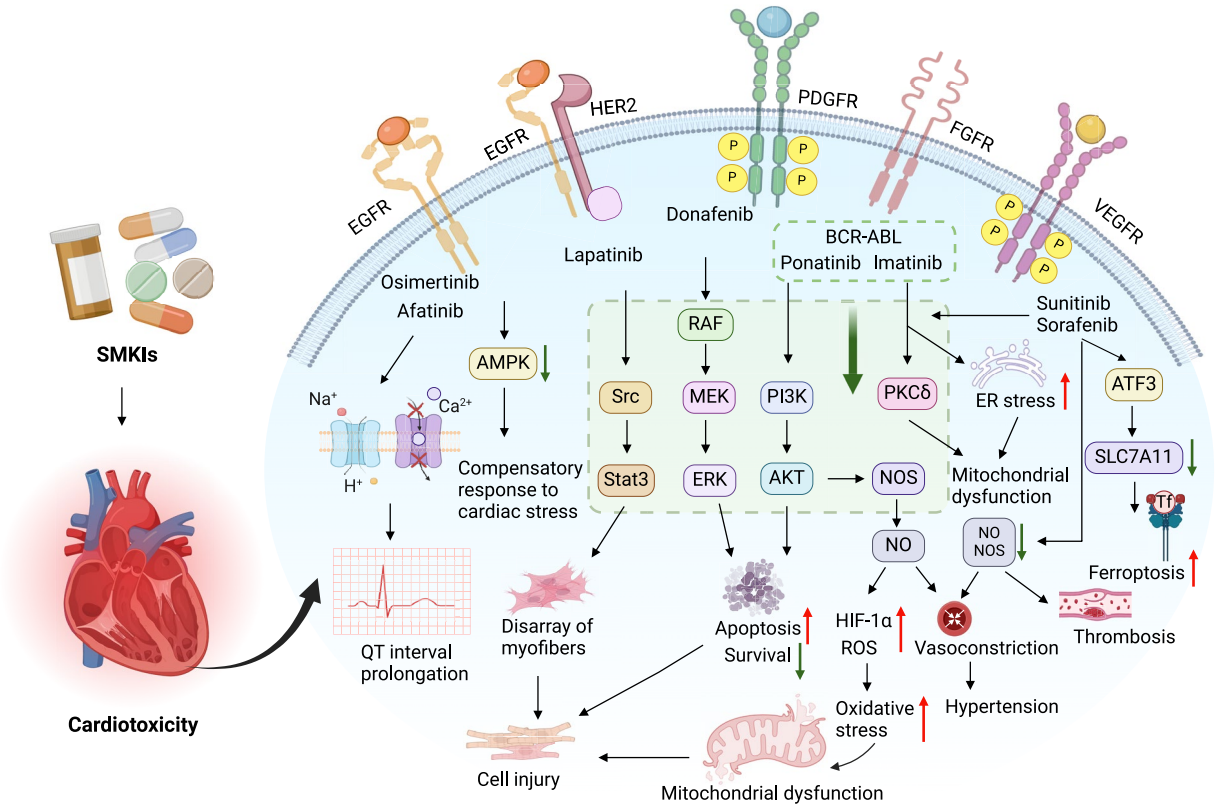


Fig. 3 Mechanisms of SMKIs-induced cardiotoxicity. Osimertinib exhibits simultaneous inhibition of the hERG potassium channel, Nav1.5 sodium channel, and L-type Ca^{2+} channel, all of which are involved in myocardial cell conduction. This inhibition leads to the prolongation of both the PR interval and QT interval. Afatinib specifically targets the EGFR and HER2 receptors, resulting in the blockade of the PI3K/AKT pathway. This blockade subsequently leads to the accumulation of ROS and the initiation of cell apoptosis, resulting in mitochondrial damage, ultimately inducing heart failure. Moreover, lapatinib also induces oxidative stress in myocardial cells through the PI3K/AKT pathway, further contributing to cardiotoxicity. Lastly, TKIs such as sorafenib or sunitinib selectively target the VEGFR and PDGFR receptors. Hypertension is a prevalent cardiotoxicity associated with VEGFR inhibitors, primarily attributed to the inhibition of downstream signaling pathways, such as ERK/AKT, after VEGF inhibition. This inhibition results in a reduction in the production of NOS and NO by endothelial cells, leading to vasoconstriction and the eventual development of hypertension. Furthermore, elevated blood pressure imposes an increased afterload on the heart, exacerbating cardiotoxicity. Additionally, following sorafenib treatment, there is an observed elevation in ATF3 expression within myocardial cells, which inhibits the expression of SLC7A11 and promotes ferroptosis of myocardial cells, resulting in cardiotoxicity. Imatinib induces cardiotoxicity by promoting endoplasmic reticulum (ER) stress and mitochondrial dysfunction, and ponatinib induces cardiomyocyte apoptosis by inhibiting the AKT/ERK signaling pathway, leading to cardiotoxicity. EGFR: epidermal growth factor receptor; HER2: human epidermal growth factor receptor 2; ROS: reactive oxygen species; TKIs: tyrosine kinase inhibitors; PDGFR: platelet-derived growth factor receptor; NOS: nitric oxide synthase; NO: nitric oxide; ER: endoplasmic reticulum

kinase 1) and MST2 (mammalian Ste20-like kinase 2), thereby preventing excessive tissue damage. The knockdown of the RAF1 gene has been demonstrated to result in an increase in cardiomyocyte apoptosis, a decline in myocardial contractility, and ultimately cardiac dilation [101, 102].

A series of recent studies have demonstrated that sorafenib additionally induces cardiotoxicity by triggering ferroptosis in myocardial cells. The expression of ATF3 in myocardial cells in patients treated with sorafenib was found to be significantly up-regulated. The results of both in vivo and in vitro experiments corroborate the hypothesis that ATF3 inhibits the expression of SLC7A11 and promotes ferroptosis in myocardial cells, ultimately inducing cardiotoxicity [103]. Jiang et al. have confirmed that ATF4 can reverse sorafenib-induced cardiotoxicity by upregulating SLC7A11 expression and inhibiting ferroptosis [104]. Moreover, ferrostatin-1, a ferroptosis inhibitor, attenuated sorafenib-induced cardiac fibrosis by reducing KLF11-mediated ferroptosis [105].

In conclusion, targeted ferroptosis may be a promising treatment option for preventing sorafenib-induced cardiotoxicity.

The induction of hypertension by sunitinib and sorafenib may be attributed to their inhibitory effect on NOS (nitric oxide synthase) and NO production by endothelial cells, leading to vasoconstriction and ultimately elevated blood pressure [106]. Additionally, the reduction of NO contributes to thrombosis. Similarly, sunitinib and sorafenib may lead to thrombosis by disrupting endothelial cell integrity and exposing prethrombotic phospholipids [107]. VEGFR inhibitors promote platelet aggregation leading to thrombosis by activating the platelet FcδRIIa immunoglobulin G receptors through binding to VEGF [108].

Axitinib

Axitinib, a second-generation VEGFR inhibitor with higher selectivity than sorafenib, was approved for treating advanced renal cell carcinoma following the failure of sunitinib therapy [109]. In a phase III trial of axitinib in 359 patients with advanced renal cell carcinoma, 42% of patients experienced all-grade hypertension, with 17% of these patients presenting with grade 3 or above hypertension [110]. When hypertension is poorly controlled, it can lead to serious cardiovascular events. It is therefore incumbent upon clinicians to monitor the blood pressure of patients on axitinib closely and adjust the drug dose accordingly.

Regorafenib

Regorafenib, a multi-targeted kinase inhibitor, is indicated for patients treated for CRC, GIST, and hepatocellular carcinoma (HCC) [111, 112]. As is the case with other multikinase inhibitors, regorafenib may cause cardiac adverse events. In a phase 3 trial of GIST patients treated with regorafenib, the incidence of all grade, grade 3, and grade 4 hypertension was 48.5%, 22.7%, and 0.8%, respectively, with one patient experiencing cardiac arrest [113]. In another CONCUR trial, AF and MI were reported in two CRC patients treated with regorafenib [114].

Vandetanib

Vandetanib is an EGFR, VEGFR, and RET inhibitor, which has been approved for treating medullary thyroid cancer [115]. Among the most frequent adverse events associated with vandetanib were hypertension and extended QT interval. Zang et al. reported that 12% and 18% of patients encountered all-grade and high-grade QT interval prolongation in thyroid cancer patients [116]. In a meta-analysis of 3154 patients, it was found that 24.2% of patients experienced all-grade hypertension, and 6.4% experienced high-grade hypertension during vandetanib treatment [117].

Nintedanib and others

Nintedanib was initially approved for the treatment of idiopathic pulmonary fibrosis, however, recent evidence has demonstrated its efficacy in the treatment of metastatic esophageal and gastric cancer. The primary targets of nintedanib are the VEGFR-1/2/3, FGFR1/2, and PDGFR α/β. A clinical trial reported that 15% of 32 patients with metastatic esophageal gastric cancer developed grade 3 hypertension after receiving treatment with nintedanib [118]. Other multikinase inhibitors, including ripretinib, cabozantinib, and pazopanib, have also demonstrated cardiotoxicities, such as QT interval prolongation, hypertension, and MI [119–122].

Similar to other VEGFR inhibitors, apatinib has been found to induce hypertension. In a phase III clinical trial, it was observed that 35.23% of patients developed hypertension (below grade 4) after two weeks of apatinib administration [123]. Research has shown that apatinib induces hypertension by activating the RhoA/ROCK (rho-associated coiled-coil-containing kinase) pathway, which can be reversed by the ROCK inhibitor Y-27632 [124]. The principal cardiotoxicities associated with anlotinib encompass hypertension (67.35%), sinus tachycardia (35.71%), and QT interval prolongation (26.19%) [125].

Hypertension has similarly been identified as significant cardiotoxicity in multi-kinase inhibitors, including fruquintinib, surufatinib, and donafenib [126–128]. Consequently, it is advised that patients' blood pressure be monitored regularly to prevent hypertensive crises.

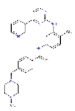
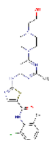
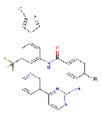
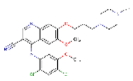
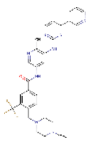
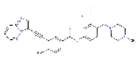
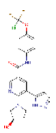
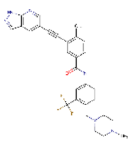
It is noteworthy that the risk of cardiotoxic events triggered by multi-kinase inhibitors is typically associated with the pre-existing cardiovascular disease of the patients. It is hypothesized that TKI-induced hypertension may exacerbate cardiac stress. It is therefore important to obtain a patient's cardiovascular history before treatment and to monitor blood pressure during treatment. It has been proposed that pharmacological intervention with appropriate antihypertensive agents, such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), may be beneficial for cancer patients experiencing hypertension [129].

Non-receptor tyrosine kinase inhibitors

BCR-ABL inhibitors

BCR-ABL is a fusion gene generated primarily by the Philadelphia (Ph) chromosome translocation. It encodes the oncoprotein p210 Bcr-Abl1, which has aberrant

Table 4 The cardiotoxicity of BCR-ABL inhibitors

Generation	Name	Chemical structure	Targets	Approved for indications on	Cardiotoxicity	Corporation
First-	Imatinib (Glivec)		BCR-ABL/PDGFR/c-Kit	2001 (CML) 2003 (GIST) 2006 (ALL)	LV dysfunction, CHF	Novartis
Second-	Dasatinib (Sprycel)		BCR-ABL/PDGFR/c-Kit	Ph^+ ALL, CML, and as a therapeutic strategy after imatinib resistance 06/2006	QT interval prolonged, CHF, LV dysfunction, hypertension	Bristol-Myers Squibb
	Nilotinib (Tasigna)		BCR-ABL/PDGFR/c-Kit/CSF-1R	Ph^+ CML patients who are resistant to imatinib 10/2007	Atherosclerosis, AMI, atrial flutter and fibrillation	Novartis
	Bosutinib (Bosulif)		BCR-ABL/PDGFR/c-Kit/CSF-1R	Ph^+ CML patients who are resistant to imatinib 09/2012	HF	Pfizer
	Flumatinib		BCR-ABL	CML 11/2019	ND	Hansoh Pharma
Third-	Ponatinib (Iclusig)		BCR-ABL/PDGFR-α/VEGFR-2/FGFR-1/Src/FLT3/c-Kit	imatinib-resistant patients 12/2012	Arrhythmia, hypertension, angina, MI, atherosclerosis, atrial fibrillation and atrial flutter, venous/arterial thrombosis*, CHF*	Incyte/Takeda
	Asciminib (Scemblix)		BCR-ABL	Ph^+ CML patients with concomitant T315I mutation 10/2021	Induced weaker cardiotoxicity	Novartis
	Olverembatinib		BCR-ABL	Ph^+ CML, ALL 11/2021	Hypertension, pericardial effusion, outdoor systolic phase, AF, and supraventricular extraventricular contractions	Ascentage Pharma

All data statistics from the FDA (https://www.accessdata.fda.gov)

PDGFR: platelet-derived growth factors receptor; CML: chronic myeloid leukemia; GIST: gastrointestinal stromal tumor; ALL: acute lymphoblastic leukemia; LV: left ventricular; CHF: congestive heart failure; CSF-1R: colony-stimulating factor 1 receptor; AMI: acute myocardial infarction; VEGFR-2: vascular endothelial growth factor receptor 2; FGFR-1: fibroblast growth factor receptor-1; FLT3: fms-like tyrosine kinase 3

tyrosine kinase activity and drives the proliferation of leukemia cells [130]. Imatinib, dasatinib, and nilotinib are the major clinically approved BCR-ABL inhibitors for treating chronic myeloid leukemia (CML). Inhibition of the BCR-ABL tyrosine kinase can prolong patient survival but is often associated with cardiac toxic events (Table 4).

Imatinib

Imatinib is the first-generation BCR-ABL inhibitor and also the first small-molecule TKI developed for targeted cancer therapy [131]. It was approved for treating CML in 2001. It has been reported that imatinib therapy is inevitably associated with cardiac adverse events [132].

The initial finding of imatinib-induced CHF was considered a rare adverse event, with an incidence of only 0.7% [133, 134]. Using human and rat

cardiomyocyte models, Kerkela et al. found that imatinib activated endoplasmic reticulum stress, which triggered reduced mitochondrial function and cell death [135]. Imatinib was demonstrated to elevate protein kinase Cδ (PKCδ) expression and induce apoptosis in cardiomyocytes [136].

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a diagnostic test for contractile dysfunction in left ventricular cardiomyocytes. The plasma level of brain natriuretic peptide was found to be markedly elevated in two patients with GIST who had developed HF following treatment with imatinib. In light of these findings, Park et al. proposed the use of BNP as a diagnostic or predictive marker for imatinib-induced HF [137].

Furthermore, studies in mouse models have demonstrated that the mitochondrial damage and myocardial cell death induced by imatinib are age-dependent [138]. Consequently, it's recommended that the heart function of elderly patients should be monitored more closely during imatinib treatment.

A variety of research strategies have been developed to reduce the cardiotoxicity associated with imatinib therapy. Marslin et al. developed a stable poly(lactide-co-glycolide) nanoparticle formulation of imatinib to reduce its cardiotoxicity through the sustained release of the drug [139]. As the cardiotoxic effect of imatinib was derived from the inhibition of the c-Abl kinase, imatinib has been structurally modified to reduce its Bcr-Abl inhibition while increasing the inhibitory effect on c-Kit and an additional target JNK [140]. The modified compounds were found to maintain c-Kit inhibition and exhibit a potent anticancer effect in a mouse GIST model with a marked reduction in cardiotoxicity [140]. It may therefore be postulated that JNK activation by oxidative stress is related to imatinib-induced cardiotoxicity, and that inhibition of the JNK signaling pathway can reduce mitochondrial dysfunction and cell apoptosis [141].

In conclusion, the clinical applications of imatinib in cancer treatment should be approached with caution. The current guideline recommends that patients with risk factors for coronary artery disease or HF should have their left ventricular function assessed before initiation of imatinib therapy [142].

Dasatinib

Second-generation BCR-ABL inhibitors, such as dasatinib, nilotinib, and bosutinib, have been developed due to the inevitable emergence of drug resistance [143].

Dasatinib is a multikinase inhibitor that targets c-KIT, PDGFR-α/β, and BCR-ABL. It is indicated for treating adult and pediatric Ph^+ ALL (acute lymphoblastic leukemia) and CML and it is also commonly considered a therapeutic strategy following imatinib resistance [144].

However, dasatinib is known to induce more severe cardiotoxicity than imatinib. CHF with prolonged QT interval and pulmonary hypertension was reported in 2.2% of patients after dasatinib treatment [145]. As dasatinib-induced pulmonary hypertension may be due to hypoxia-induced attenuation of the vasoconstrictor response, it could be resolved after dasatinib discontinuation [146].

Ponatinib

Ponatinib, the third-generation BCR-ABL inhibitor, is particularly effective against the BCR-ABL T315I mutation, which confers resistance to imatinib [147].

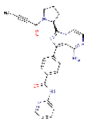
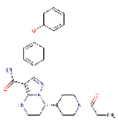
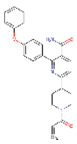
However, ponatinib induces the most severe cardiotoxicity of all BCR-ABL inhibitors. According to a study evaluating CML patients diagnosed from 2002 to 2017, cardiotoxic events occurred in approximately 1 in 5 patients, including angina in 15.6% of patients, atherosclerosis in 13.7% of patients, and AF or atrial flutter in 8.7% of patients, which are potentially life-threatening adverse effects [145]. In addition, ponatinib-induced cardiotoxicity events also include hypertension (13.3%), pericardial effusion (8.5%), outer systolic phase (4.2%), and supraventricular extraventricular contractions (3%) [148].

Recently, ponatinib was shown to induce excessive inflammatory responses in cardiomyocytes by activating the S100A8/A9-NLRP3-IL-1β signaling pathway, which could be counteracted by dexamethasone [149]. Singh et al. proposed that ponatinib induced apoptosis in cardiomyocytes by inhibiting the AKT/ERK signaling pathway [150]. Hnatiuk et al. developed novel ponatinib analogs that retain antitumor activity against CML but with significantly reduced cardiotoxicity [151, 152]. Research suggests that aspirin may be effective in the reduction of adverse events such as ponatinib-induced thrombosis [153].

ROCK inhibition has been shown to reverse endothelial dysfunction induced by dasatinib and ponatinib, thereby alleviating cardiotoxicity. Thus, ROCK has been suggested to have great potential as a molecular target to address BCR-ABL inhibitor-associated cardiotoxicity [154].

Based on the above research findings, the risk–benefit ratio of ponatinib should be carefully assessed before selecting it for CML patients. Once ponatinib is initiated, it is important to closely monitor the patient's cardiopulmonary function.

Table 5 The cardiotoxicity of BTK inhibitors

Generation	Name	Chemical structure	Targets	Approved for indications on	Cardiotoxicity	Corporation
First-	Ibrutinib (Imbruvica)		BTK	MCL (2013) CLL (2014) WM (2015) SLL (2016) MZL (2017)	Ventricular arrhythmias, hypertension	AbbVie/Johnson & Johnson
Second-	Acalabrutinib (Calquence)		BTK	MCL 10/2017	AF, hypertension	AstraZeneca
	Zanubrutinib (Brukinsa)		BTK	MCL 11/2019	AF, hypertension	BeiGene
	Pirtobrutinib (Jaypirca)		BTK	MCL 01/2023	AF	Eli Lilly
	Orelabrutinib		BTK	MCL, CLL, SLL 12/2020	Hypertension, QT interval prolongation	Innocarepharma

All data statistics from the FDA (https://www.accessdata.fda.gov)

BTK: Bruton's tyrosine kinase; MCL: mantle cell lymphoma; CLL: chronic lymphocytic leukemia; WM: Waldenstrom's macroglobulinemia; SLL: small lymphocytic lymphoma; MZL: marginal zone lymphoma; AF: atrial fibrillation; HF: heart failure; ND: No data

Bruton's tyrosine kinase (BTK) inhibitors

Bruton's tyrosine kinase (BTK), a member of the TEC family of non-receptor protein tyrosine kinases, plays a critical role in driving oncogenic signaling to support leukemic cell proliferation and survival in many B-cell malignancies [155]. In recent years, the FDA has approved several BTK inhibitors, including ibrutinib, acalabrutinib, and zanubrutinib, for treating patients with CLL (chronic lymphocytic leukemia) and lymphoma [156, 157]. Although BTK inhibitors have revolutionized the treatment strategy for B-cell malignancies, induction of AF, hypertension, and ventricular arrhythmias has been demonstrated by BTK inhibitors in clinical use [158, 159] (Table 5).

Ibrutinib

Ibrutinib, the first irreversible BTK inhibitor, binds to the Cys-481 residue in the ATP binding site of BTK and prevents autophosphorylation. Ibrutinib has received FDA approval for the treatment of newly diagnosed CLL, although the manufacturer has voluntarily withdrawn its indication for use in adult patients with mantle cell lymphoma [156, 160].

A comprehensive analysis of the current data suggests that the prevalence of ibrutinib-induced AF is in the range of 5–20%, and is predominantly observed in patients aged 65 years or older and in those with an underlying cardiovascular disease [161]. In addition, ibrutinib-induced AF occurred over approximately 3–5 months, but the symptoms of AF were resolved in most patients within approximately one week of discontinuing the drug [162].

Ibrutinib-induced AF was mediated by an off-target effect of the drug on the C-terminal SRC kinase (CSK) [163]. Administration of ibrutinib in a BTK kinase-deficient mouse model was found to induce AF, left atrial enlargement, and myocardial fibrosis, which surprisingly was not found in the treatment with the acalabrutinib mouse model. Furthermore, the knockdown of CSK also induced the development of AF, implying that inhibition of CSK expression may contribute to the induction of AF by ibrutinib [163].

On the other hand, ibrutinib not only upregulates the expression of calmodulin kinase 2 (CaMKII) but also increases the phosphorylation of ryanodine receptor 2 (RyR2) within the endoplasmic reticulum of cardiomyocytes, which ultimately leads to ectopic

electrical activity of intracellular calcium ions [164]. BTK has also been reported to activate its downstream PI3K, which is a key molecule associated with cardiac rhythm. And after PI3K is inhibited, AF is more likely to occur [165, 166].

A series of studies have documented that patients undergoing treatment with ibrutinib have experienced ventricular arrhythmias (VA) and sudden cardiac death, despite the majority of these individuals lacking a prior history of cardiovascular conditions [167–169]. Although VA is relatively rare in the context of ibrutinib-induced cardiotoxicity, it warrants significant attention from clinicians due to its status as one of the most severe arrhythmias associated with ibrutinib use [170, 171]. The mechanism of VA induced by ibrutinib mainly involves calcium imbalance, electrophysiological instability, and inhibition of the activity of AMPK and PI3K/AKT signaling pathways.

Ibrutinib has been reported to induce VA through dysregulation of calcium release and repolarization in cardiomyocytes [172]. Research has shown that ibrutinib inhibited the activation of the AMPK pathway, which further suppressed sarcoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a) levels, leading to calcium handling abnormalities and ultimately to uneven repolarization of cardiomyocytes, resulting in VA. The AMPK agonist 5-aminoimidazole-4-carboxamide-1-β-ribofuranoside prophylaxis could potentially attenuate ibrutinib-induced VA [173, 174]. Recent studies have demonstrated that metformin mitigates ibrutinib-induced VA, primarily by enhancing the activity of the AMPK and PI3K/AKT signaling pathways [175]. And, there was a significant increase in the risk of VA during follow-up in patients treated with ibrutinib. Consequently, it is imperative to closely monitor patient changes, and discontinue the drug if necessary [167]. In addition, Du et al. reported that ibrutinib induced ventricular fibrillation by reducing the amplitude of calcium peaks in an elderly rat model of spontaneous hypertension, but this phenomenon was not observed in a young rat model [176].

It is common for patients treated with ibrutinib to discontinue treatment because the drug has been significantly associated with an increased incidence of AF, thromboembolism, or stroke, as well as an increased risk of bleeding due to administration of anticoagulants for AF management. Therefore, acalabrutinib, a newer generation BTK inhibitor has been developed as a replacement for ibrutinib [177, 178].

Acalabrutinib

Acalabrutinib, the second-generation BTK inhibitor with greater selectivity, has been approved by the FDA for use in previously treated mantle cell lymphoma and newly diagnosed CLL [179, 180]. Similar to the earlier generation BTK inhibitors, acalabrutinib has also been reported to cause AF, hypertension, and VA.

A recent follow-up study of patients with B-cell malignancies (n = 1063) receiving acalabrutinib showed that 8 of these patients experienced VA. This was the first report of a VA event associated with the clinical use of acalabrutinib [181]. The most common cardiotoxic event induced by acalabrutinib was AF, with an incidence of 3–4% [182–184]. In the ELEVATE-RR trial, AF occurred in 9% and 16% of the 533 CLL patients who received acalabrutinib and ibrutinib, respectively. Moreover, ibrutinib-induced AF led to treatment discontinuation in approximately 3.4% of patients, whereas no patients in the acalabrutinib group discontinued treatment due to AF [185, 186]. These results suggested that acalabrutinib had a lower propensity to induce cardiotoxicity than ibrutinib. Therefore, acalabrutinib could be considered to treat CLL patients who have discontinued ibrutinib due to its toxicity [187].

The mechanism underlying the induction of AF by acalabrutinib is not clear. Unlike ibrutinib, ascalabrutinib did not inhibit CSK in mouse models and the pathophysiology leading to ascalabrutinib-induced AF remains to be elucidated [163].

Zanubrutinib

Zanubrutinib, another novel irreversible BTK inhibitor, is also approved for treating mantle cell lymphoma and demonstrates more potent anticancer activity compared to ibrutinib [188]. AF was observed in 2.5% of CLL patients receiving zanubrutinib in the phase III ALPINE trial [189].

Hypertension is a recognized adverse effect associated with both ibrutinib and zanubrutinib, suggesting that hypertension may be a class effect of BTK inhibitors. Specifically, hypertension is a documented side effect of ibrutinib treatment [190, 191]. Long-term analyses indicate that 28% of patients treated with ibrutinib developed hypertension of grade 3 or higher [192]. Furthermore, data suggest that 78.3% of patients experienced new or worsening hypertension during ibrutinib treatment, a rate significantly higher than that predicted by the Framingham Heart Study [193]. These findings collectively imply that ibrutinib may contribute to the increase in blood pressure. Subsequent studies revealed that 48.9% of patients developed hypertension following treatment with acalabrutinib [194]. Results from a phase III clinical trial demonstrated that the incidence of hypertension induced by zanbrutinib was lower than that induced by ibrutinib,

with 5% of patients experiencing ≥ grade 3 hypertension [195, 196].

The precise mechanism by which BTK inhibitors induce hypertension remains unclear. Should patients develop hypertension during treatment with BTK inhibitors, clinicians are advised to intervene promptly in accordance with established guidelines for antihypertensive medications, such as ACEIs and ARBs. It is uncommon for patients to discontinue treatment due to hypertension-related side effects, except in instances of grade 3 or higher hypertension. However, the dosage of BTK inhibitors may be adjusted once blood pressure is stabilized [194].

BTK inhibitors remain a mainstay of treatment for B-cell lymphomas. There is an unmet medical need to develop novel BTK inhibitors with minimal off-target effects. When choosing a drug selection, clinicians must reduce the potential risk of cardiotoxicity and closely monitor the cardiac adverse events to ensure patients receive the greatest therapeutic benefit [197].

Animal model of SMKIs-induced cardiotoxicity

Currently, several animal models are used to observe or study the mechanism of SMKI-induced cardiotoxicity. We have summarized some common in vivo animal models in Table 6.

Current therapeutic strategies

Treatment strategies for SMKIs-induced cardiotoxicity currently emphasize dose reduction or discontinuation of the offending agent, switching to alternative medications, and symptomatic management.

Patients diagnosed with cancer should be comprehensively assessed before treatment with SMKIs, with particular attention to cardiovascular risk factors such as hyperlipidemia and previous history of cardiovascular disease. In high-risk patients, pre-treatment ECG, echocardiography, and blood pressure monitoring are essential to effectively manage potential adverse events. Consultation with cardiac oncologists may also be warranted to develop safer and more detailed treatment strategies. Continuous monitoring during treatment is essential for the early detection of cardiotoxicity, and targeted interventions, such as electrocardiography, echocardiography, and markers of myocardial injury can serve as effective monitoring. Cardiac oncology guidelines provide tailored monitoring recommendations based on individual patient risk factors [198].

Preventing the occurrence of cardiotoxicity is a primary goal, as it can significantly reduce the risk of adverse effects in patients. The American Heart Association and the American Association of Cardiovascular and Pulmonary Rehabilitation have identified exercise, dietary modification, weight management, and psychological counseling, among other interventions, as fundamental components of a cardiac rehabilitation program [199–201]. Additionally, pharmacological preventive strategies may include the administration of ACE inhibitors (ACEIs), angiotensin II receptor blockers, β-blockers, or statins in high-risk hypertensive patients before starting treatment [202]. β-blockers such as nebivolol are considered the preferred agents for the treatment of left ventricular dysfunction associated with SMKIs. Furthermore, metoprolol or diltiazem may be employed to reduce QT interval prolongation associated with pazopanib therapy. Follow-up during the later stages of treatment is also critical to understanding delayed cardiotoxicity and providing effective solutions for patients.

In specific cases, it's important to analyze each situation individually. For example, in patients with multiple cardiovascular risk factors, clinicians should choose drugs with less cardiotoxicity. In patients with T315I mutations, ponatinib should be discontinued in favor of ascimitinib to reduce unnecessary toxic side effects. Additionally, BTK inhibitors are not recommended in individuals with ventricular arrhythmia, uncontrolled hypertension, or crisis. The individual circumstances of each patient must be assessed along with their clinical status to formulate an appropriate treatment plan through multidisciplinary consultation [203].

In conclusion, clinicians should proactively address SMKI-induced cardiotoxicity by implementing strategies such as preventive measures, pre-treatment assessments, monitoring throughout therapy, and timely interventions aimed at minimizing the risk of cardiotoxicity. Multidisciplinary consultation can further enhance the development of optimized therapeutic strategies, thus individualized approaches are critical in reducing patients' exposure to cardiotoxicity. This strategy can effectively minimize the risk without compromising overall therapeutic outcomes and ultimately benefit the patient's prognosis.

Conclusion

Although small molecule kinase inhibitors (SMKIs) are central to cancer therapy, the incidence of cardiotoxicity events cannot be overlooked. These include QT interval prolongation, hypertension, arrhythmias, HF, myocardial ischemia, or infarction.

The mechanism of SMKIs-induced cardiotoxicity involves several key aspects, such as signaling pathway inhibition, cardiac ion channel disturbances, reactive oxygen species (ROS) accumulation, and vascular

Table 6 The available models to investigate drug cardiotoxicity from SMKIs in vivo

Target	Drug	Dose	Time	Animals	indications	Mechanism	Treatment	Refs.
EGFR	Gefitinib	30 mg/kg/day	2W	Adult male Sprague–Dawley rats	Cardiac hypertrophy	Increasing PTEN and FoxO3a gene expression	CYP1A1 inhibitor (α-naphthoflavone)	[21]
	Gefitinib	30 mg/kg/day	3W	Wistar albino rats	Cardiac hypertrophy	Upregulating caspase 3 and P53	ND	[22]
	Gefitinib	30 mg/kg/day, oral gavage	3W	Male Wistar albino rats	Cardiac hypertrophy	Downregulating ERK/AKT, upregulating JNK/P38	Liraglutide	[23]
	Gefitinib	30 mg/kg/day	4W	Male Wistar albino rats	Cardiac hypertrophy	Increasing the level of AngII and its receptors	AT1R blocking valsartan	[24]
	Lapatinib	10 mg/kg/day, *i.p.*		Male, C57BL/6 mice, – 8w Human pluripotent stem cell-derived cardiomyocytes (HpsC-CMs)		Increasing iNOS expression and pronouncing production of NO	iNOS inhibition	[43]
ALK	Crizotinib	100 mg/kg/day, intragastric administration	6W	C57BL/6J mice 7–9w	Left ventricular dysfunction, myocardial injury cardiomyocyte apoptosis and mitochondrial injury	Inhibition of PRKAA/AMPK phosphorylation	Metformin	[60]
VEGFR	Sunitinib	26.7 mg/kg	8 days	Male Wistar-Kyoto rats	Blood pressure (hypertension)	Activation of the endothelin-1 system, suppression of the renin-angiotensin system	Sunitinib withdrawal	[86]
	Sunitinib	50 mg/kg/day, intragastric administration	6W	C57BL/6 mice, 6W	Hypertension, increase in ejection fraction and cardiac fibrosis	Increasing in cardiac uptake of [18F] fluorodeoxyglucose	Co-administration of macitentan	[89]
	Sunitinib	40 mg/kg/day, intragastric administration	32 days	C57BL/6 mice or athymic nude mice BALB/c-nude, 5–6W	Cardiomyocyte death and cardiotoxicity	The autophagic degradation of CCN2	HMGB1-specific inhibitor glycyrrhizic acid	[92]
	Sunitinib	10 mg/kg/day, intragastric administration	2W	C57BL/6J male mice, 8–10W	Tachycardia	Reduced the expression of Nrf2, HO-1, NQO1, GPX4 and FTH1, enhanced the TfR expression (Nrf2-dependent ferroptosis)	ND	[93]
	Sunitinib	20 mg/kg/day, intragastric administration	2W	C57BL/6J male mice, 8-10W	Bradycardia			
	Sunitinib	25 mg/kg, three times a week, intragastric administration	4W	Male Wistar albino rats, 8W	Cardiac fibrosis	Upregulation of NF-KB/Wnt/β-catenin/SOX9 pathway	Sacubitril/valsartan	[90]
	Sunitinib	40 mg/kg/day, intragastric administration	4W	Male 129S1/SvImJ mice	Hypertension, left ventricular dysfunction	inhibition of AMPK/mTOR/autophagy pathway	Trimetazidine	[85]
	Sunitinib	50 mg/kg/day, intragastric administration	5 days	Female C57BL/6, 15 weeks	Myocardial fibrosis	Upregulates glycolysis and downregulates oxidative metabolism in cardiac mitochondria	Macitentan	[91]

Table 6 (continued)

Target	Drug	Dose	Time	Animals	indications	Mechanism	Treatment	Refs.
	Sorafenib	30 mg/kg/day, *i.p.*	2W	Male C57BL/6 mice, 6W	loss in cardiac contractile function	Upregulated ferroptosis-related protein expression: PTGS2, Slc7a11 and GPX4 were decreased	Ferrostatin-1	[103]
	Sorafenib	50 mg/kg twice daily, intragastric administration	3W	8-week-old male C57BL/6 mice	cardiomyocytes hypertrophy	SOR evoked ferroptosis of cardiomyocytes, and the cytosolic lipid ROS accumulation in ferroptosis cardiomyocytes triggered ER stress and UPR	ATF4 overexpression	[104]
	Sorafenib	30 mg/kg/day, *i.p.*	2W	C57BL/6 mice	Heart injury	KLF11 promoted ferroptosis by suppressing transcription of FSP1	Targeting ferroptosis	[105]
	Apatinib	50 mg/kg/day, intragastric administration	4W	Female BALB/C nude mice (4–6 weeks old, 20 ± 5 g)	Hypertension	Mediating the significant upregulation of RhoA, ROCK1 and ROCK2 expression	ROCK1 inhibitor Y27632	[124]
BCR-ABL	Ponatinib	APOE−/− TACE, 15 mg/kg/day, intragastric administration	6W	8-week-old male and female C57Bl/6J mice	Cardiac inflammation	Activating the S100A8/A9-TLR4-NLRP3-IL-1β signaling pathway	glucocorticoid dexamethasone or NLRP3 inhibitor (CY-09) or S100A9 inhibitor (paquinimod)	[149]
	Ponatinib	10 μM		Zebrafish	Cardiomyocytes death	Inhibiting cardiac prosurvival signaling pathways AKT and ERK, induces cardiomyocyte apoptosis	Neuregulin-1β	[150]
	Ponatinib	10 μM		Tg (cmlc2: GFP) transgenic zebrafish	Cardiac edema, abnormal heart structure, low heart rate, cardiac cell death, and thrombosis	AKT, MAPK, MAP3K and TEK were downregulated, COX-1 was up-regulated	COX-1 inhibitor aspirin	[153]
	Ibrutinib	25 mg/kg/day, *i.p.*	4W	C57BL/6J mice, 3- to 4-month-old	Atrial fibrillation	Inhibition of C-Terminal Src Kinas	ND	[163]
	Ibrutinib	25 mg/kg/day, orally	4W	C57BL/6J mice	Atrial fibrillation	Inducing structural remodeling and calcium dysregulation in the atrium	ND	[164]
	Ibrutinib	10 mg/kg/day, orally	4W	Male Sprague–Dawley rats, age range: 10–14 months	Ventricular arrhythmias	Impairment of myocardial AMPK activity	AMPK activator 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside	[174]
	Ibrutinib	30 mg/kg/day, orally	4W	Male C57BL/6J mice aged 3 months	Ventricular arrhythmias	Decreasing AMPK and PI3K-AKT pathway activity	Metformin	[175]

I.p.: intraperitoneal injection; AT1R: AngII type 1 receptor; InoS: Inducible nitric oxide synthase; CCN2: Cellular communication network factor 2; HMGB1: High mobility group box 1; FSP1: Ferroptosis suppressor protein 1; TLR4: Toll-like receptor 4; NLRP3: NLR family pyrin domain-containing 3; COX-1: Cyclooxygenase-1

endothelial dysfunction. SMKIs targeting kinases (e.g., EGFR, HER2, c-Kit, and PDGFR), such as gefitinib, ibrutinib, and sorafenib, may interfere with the signaling pathways required for cardiomyocyte survival (e.g., PI3K/Akt, ERK), leading to apoptosis or necrosis of cardiomyocytes. Another example is imatinib, which affects myocardial repair mechanisms by inhibiting c-Kit and PDGFR. Furthermore, cardiac ion channel disturbances, including hERG potassium channel blockade and calcium homeostasis imbalance, have been identified as mechanisms by which SMKIs induce cardiotoxicity. For instance, the inhibition of hERG channels caused by osimertinib and sunitinib has been observed to prolong myocardial repolarization, resulting in QT interval prolongation and the subsequent development of ventricular tachycardia. Moreover, ibrutinib has been shown to interfere with sarcoplasmic reticulum calcium-regulated proteins (e.g., SERCA2a), leading to calcium overloading or release abnormalities, which, in turn, can induce arrhythmias or contractile dysfunction. SMKIs-induced cardiotoxicity is also associated with reactive oxygen species (ROS) accumulation. For instance, crizotinib induced the production of ROS, which have been demonstrated to inflict damage to myocardial cell membranes, proteins, and DNA, thereby triggering oxidative damage. Inhibition of fatty acid/glucose metabolism in cardiomyocytes can also induce cardiotoxicity, and drugs targeting the AMPK pathway, such as crizotinib, sunitinib, and ibrutinib, may interfere with myocardial energy substrate utilization, leading to metabolic remodeling. Finally, vascular endothelial dysfunction can lead to vascular and microcirculatory disorders, such as sunitinib inhibition of the VEGF pathway leading to apoptosis of endothelial cells, reducing NO production, and triggering myocardial ischemia or hypertension.

Several cardiotoxicity events may be life-threatening to the patient, clinicians are therefore challenged with the dual task of minimizing cardiotoxicity without compromising cancer treatment. A comprehensive understanding of SMKIs-induced cardiotoxicity is essential for clinicians to improve patient outcomes and quality of life. Clinicians can intervene to prevent life-threatening cardiotoxicity from SMKIs. Interventions consist primarily of early monitoring, targeted interventions, and individualized medications. For example, certain SMKIs have a high susceptibility to cardiotoxicity, necessitating a comprehensive cardiac assessment before administration. In susceptible populations, such as patients with heart failure, clinicians regularly monitor cardiac-related tests, including electrocardiogram (QT interval), echocardiogram (LVEF), and biomarkers (troponin, BNP). The vast majority of patients have been shown to recover from SMKI-induced cardiotoxicity after discontinuation of the drug or treatment. In addition to the aforementioned measures, the use of targeted drugs such as dexrazoxane, which acts as a ROS scavenger, and β-blockers, which act as antiarrhythmics, has been shown to mitigate drug-induced cardiotoxicity. Finally, the use of individualized medications by clinicians can help avoid cardiotoxic events that may be caused by drug combinations.

This review summarizes only the cardiotoxicity of SMKIs that has been reported to date. As more SMKIs are developed for the treatment of tumors, more cardiotoxic adverse effects will be reported. For the SMKIs newly approved in recent years, more extensive clinical trials recruiting larger cohorts of subjects will be needed to reveal the extent of their cardiotoxicity. Although we have summarized the mechanistic work investigating the cardiotoxicity induced by some SMKIs, the detailed mechanisms leading to some cardiotoxic adverse events have not been fully elucidated and remain to be explored.

Abbreviations

ACE	Angiotensin-converting enzyme
AF	Atrial fibrillation
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALL	Acute lymphocytic lymphoma
AML	Acute myeloid leukemia
ARB	Angiotensin II receptor blocker
BC	Breast cancer
BNP	Brain natriuretic peptide
BTK	Bruton's tyrosine kinase
CaMKII	Calmodulin kinase 2
CHF	Congestive heart failure
CLL	Chronic lymphocytic leukemia
c-Met	Cellular-mesenchymal-epithelial transition factor
CML	Chronic myeloid leukemia
CNS	Central nervous system
CRC	Colorectal cancer
CSF1R	Colony-stimulating factor 1 receptor
CSK	C-terminal SRC kinase
ECG	Electrocardiogram
EF	Ejection fraction
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
FLT3	FMS-like tyrosine kinase 3
GIST	Gastrointestinal mesenchymal tumors
HCC	Hepatocellular carcinoma
HER2	Human epidermal growth factor receptor 2
HF	Heart failure
HGF	Hepatocyte growth factor
iNOS	Inducible nitric oxide synthase
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
NO	Nitric oxide
NOS	Nitric oxide synthase
NSCLC	Non-small cell lung cancer
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PDGFR	Platelet-derived growth factor receptor
PKCδ	Protein kinase Cδ
PTC	Papillary thyroid carcinoma
SERCA2a	Sarcoplasmic reticulum Ca^{2+}-ATPase 2a

SLL	Small lymphocytic lymphoma
SMKIs	Small-molecule kinase inhibitors
TKI	Tyrosine kinase inhibitor
TME	Tumor microenvironment
VEGFR	Vascular endothelial growth factor receptor

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