Supplement submission

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Pathophysiology of cardiotoxicity from target therapy and angiogenesis inhibitors

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The progress in cancer therapy and the increase in number of long-term survivors reveal the issue of cardiovascular side-effects of anticancer drugs. Cardiotoxicity has become a significant problem, and the risks of adverse cardiac events induced by systemic drugs need to be seriously considered. Potential cardiovascular toxicities linked to anticancer agents include arrhythmias, myocardial ischemia and infarction, hypertension, thromboembolism, left ventricular dysfunction, and heart failure. It has been shown that several anticancer drugs seriously affect the cardiovascular system, such as ErbB2 inhibitors, vascular endothelial growth factor (VEGF) inhibitors, multitargeted kinase inhibitors, Abelson murine leukemia viral oncogene homolog inhibitors, and others. Each of these agents has a different mechanism through which it affects the cardiovascular system. ErbB2 inhibitors block the ErbB4/ErbB2 heterodimerization pathway triggered by Neuregulin-1, which is essential for cardiomyocyte survival. VEGF signaling is crucial for vascular growth, but it also has a major impact on myocardial function, and the VEGF pathway is also essential for maintenance of cardiovascular homeostasis. Drugs that inhibit the VEGF signaling pathway lead to a net reduction in capillary density and loss of contractile function. Here, we review the mechanisms and pathophysiology of the most significant cardiotoxic effects of ErbB2 inhibitors and antiangiogenic drugs. Moreover, we highlight the role of cardioncology in recognizing these toxicities, developing strategies to prevent or minimize cardiovascular toxicity, and reducing long-term cardiotoxic effects.

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Introduction

Worldwide, more effective treatment options have increased the number of long-term cancer survivors. However, some of these antineoplastic drugs have been implicated in adverse cardiovascular outcomes in the long term. In the past, cardiovascular side-effects were less relevant because of the poorer prognosis of malignant neoplasms. However, because cancer patients now have improved prospects and longer life expectancy, the risks of adverse cardiac events induced by systemic drugs need to be evaluated. The biological drugs 'targeted' to inhibit specific growth signaling pathways do not exclusively affect cancer cells, but instead can contribute to cardiomyocytes injury.[1] Potential cardiovascular toxicities linked to anticancer agents (Table 1) include arrhythmias, myocardial ischemia and infarction, hypertension (HTN), thromboembolism, left ventricular (LV) dysfunction, and heart failure. Here, we discuss the two broad molecularly targeted anticancer drug families: epidermal growth factor receptor 2 (ErbB2/HER2) and angiogenic inhibitors. In addition to these, we will try to explain the cardiotoxicity (CTX) of direct Abelson murine leukemia viral oncogene homolog (ABL) and proteasome inhibitors.

ErbB2 inhibitors

ErbB2 is a member of the HER/ErbB transmembrane receptor tyrosine kinase family, it is associated with a poor prognosis in breast cancer,[2] and it is a validated target of therapeutic intervention. ErbB2 participates in an important pathway for growth, repair, and survival of adult cardiomyocytes.[3–5]

Four HER2-targeted therapies have been approved for HER2-positive breast cancer: two antibodies (trastuzumab and pertuzumab), an antibody–drug conjugate (adotrastuzumab emtansine), and a small-molecule kinase inhibitor (lapatinib). A schematic representation of the mechanisms of action of ErbB2 inhibitors is reported in Fig. 1.

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Table 1 Summary of ErbB2 inhibitors and angiogenic inhibitors and relevant cardiotoxicities

Drug	Indications	Arrhythmia	LV dysfunction/CHF	HTN	Myocardial ischemia	Thromboembolism
ErbB2 inhibitors						
Trastuzumab	Breast, gastric	++	+++	++	–	+
Trastuzumab-DM1	Breast	–	++	–	–	–
Pertuzumab	Breast	–	++	–	–	–
Lapatinib	Breast	NE	++	–	–	–
Angiogenic inhibitors						
Bevacizumab	RCC, NSCLC	++	++	+++	++	++
Sunitinib	GIST, RCC	+	+++	+++	++	++
Sorafenib	RCC, HCC	+	++	+++	++	++
Ponatinib	GIST, RCC, HCC	++	–	–	–	+++
Axitinib	RCC	–	+	+++	–	++
Regorafenib	GIST	–	–	+++	+	–
Vandetanib	MTC	++	–	+++	–	–
Direct ABL inhibitors						
Imatinib	CML	–	++	–	+++	+
Dasatinib	Leukemia	++	++	++	++	+/++
Nilotinib	CML	++	++	++	NE	+

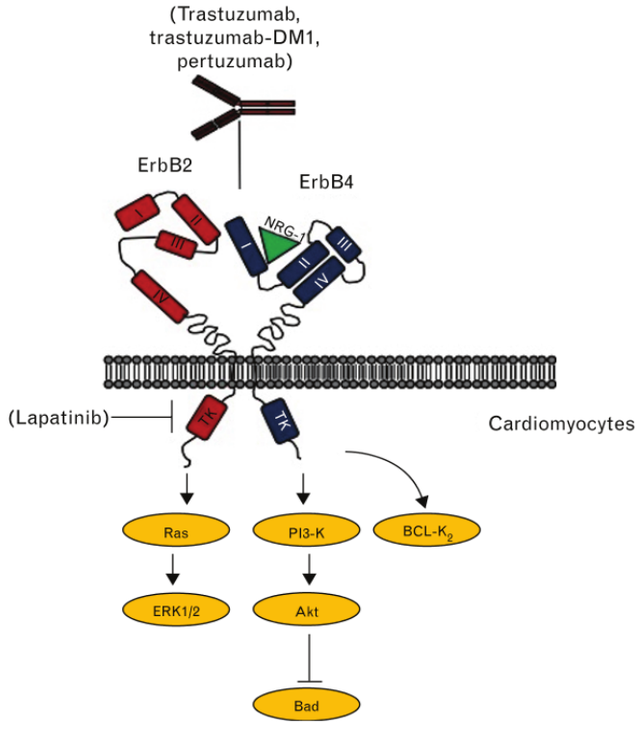
+++ represents >10%; ++ represents 1–10%; + represents <1%; NE represents precise incidence not well established; – represents not well recognized. ABL, Abelson murine leukemia viral oncogene homolog; CHF, congestive heart failure; CML, chronic myeloid leukemia; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; LV, left ventricular; MTC, metastatic thyroid cancer; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma.[67]

Trastuzumab

Trastuzumab, the first antibody approved for the treatment of a solid tumor, has proven to be effective in the immunotherapy of breast carcinoma.[6]

Several adjuvant studies demonstrated that trastuzumab, either following or in combination with chemotherapy, reduced the risk of relapse by ~50% and the risk of death by 33% in patients. Unfortunately, CTX was recognized as an important side-effect. Moreover, clinical trials of trastuzumab have reported heart failure in 1.7–4.1% of study participants and reduced left ventricular ejection fraction (LVEF) in 7.1–18.6% of study participants treated with adjuvant chemotherapy.[7] Trastuzumab CTX has been related to the inhibition of the Neuregulin-1-activated pathway, which promotes cardiomyocyte survival via ErbB2/ErbB4 heterodimerization.[8,9] This pathway is essential in the survival of adult cardiomyocytes as described above.

Fig. 1



Schematic representation of the mechanisms of action of ErbB2 inhibitors. Trastuzumab and Pertuzumab block ErbB2/ErbB4 heterodimerization in cardiac cell.[9] Lapatinib inhibits tyrosine Kinase (TK) activity of ErbB2 receptor.[36]

Trastuzumab-related CTX is often manifested as an asymptomatic decrease in LVEF and less often by clinical heart failure.[10–12] In contrast to CTX from anthracyclines, trastuzumab-related CTX does not appear to be related to cumulative dose. It is often reversible with treatment discontinuation, and rechallenge is often tolerated after recovery. In addition, cardiac biopsy specimens after trastuzumab exposure do not show the significant myocyte destruction that is typical of anthracycline-induced dysfunction.

For these reasons, two categories of cardiotoxic side-effects of antineoplastic drugs have been proposed by Ewer[13] as follows: Type I and Type II CTX. Type I, related to the anthracyclines, results in myocyte destruction and clinical heart failure. Type II, related to target therapy, is associated with a loss of contractility (presumably a form of stunning or hibernation) that less often causes clinical heart failure and is often reversible. In the last few years, several doubts have emerged about reversibility of trastuzumab-related CTX; in fact recent studies suggest that cardiotoxic side-effects of trastuzumab should be carefully reconsidered, as they can persist many years after the conclusion of the therapy.[14]

Different mechanisms are proposed for trastuzumab CTX. For HER2 function, receptor dimerization is

required. Trastuzumab binds to domain IV of the HER2 extracellular domain and prevents its hetero and homodimerization. Heterodimers are stimulators of downstream pathways such as Phosphoinositide 3-kinase/Protein kinase B and mitogen-activated protein kinases. A particularly important mechanism of trastuzumab-mediated CTX is via specific signaling pathways, including Notch and nuclear factor-κB. Notch signaling regulates cardiovascular development and homeostasis and plays a role in regulating cardiac hypertrophy, cardiomyopathy, and heart failure.[15,16] Trastuzumab activity is also associated with the inhibition of these pathways, leading to an increase in cell cycle arrest, and suppression of cell proliferation and cell survival. In addition, impaired intracellular antioxidant/oxidant balance contributes to trastuzumab-mediated cell death.[17] In the Calu-3 cell line trastuzumab treatment was associated with an increase in cellular reactive oxygen species (ROS) production, glutathione depletion, and a decrease in the activities of superoxide dismutases and catalase enzymes. Recent results show that, in mice, trastuzumab treatment induces major effects on the expression of myocardial genes that are involved in myocardial functions, adaptation to stress, and DNA repair. These alterations are associated with increased myocardial oxidative and nitrosative stress, and they activate apoptotic pathways.[18]

Trastuzumab binds to HER2 with high affinity, thereby eliminating its ability to dimerize with other HER receptors. By blocking HER2 signaling, cardiomyocytes are unable to activate the cell survival pathways associated with excess ROS. Therefore, blockade of HER2 allows the accumulation of ROS within cardiomyocytes, which leads to the development of cardiac dysfunction associated with cellular apoptosis. Moreover, trastuzumab is able to attract immune cells to tumor sites that overexpress HER2 with antibody-dependent cellular cytotoxicity.

Considering the above regarding cardiotoxic mechanisms of trastuzumab-related CTX, in our laboratory of experimental cardioncology, we are testing the ability of ranolazine to prevent trastuzumab-related cardiotoxic effects. Ranolazine has been shown[19] to prevent the oxidative damage induced by doxorubicin treatment. Late sodium current (I_{Na}) hyperactivation, induced by Ca^{2+} overload, can initiate a vicious cycle leading to sustained oxidative and energetic stress with serious ATP depletion similar to that occurring after the exposure of hearts or isolated cardiomyocytes to anthracyclines. This progression of events can be interrupted by blocking the I_{Na} with ranolazine.[20,21]

The inhibition of ErbB2 signaling by trastuzumab in patients receiving doxorubicin may interfere with the protective effects of Neuregulin on the anthracycline-damaged myocardium.

The oxidative damage induced by anthracyclines is free to progress when ErbB2 function is blocked.[22] This may explain the increased clinical CTX observed with concurrent and sequential administration of anthracycline and trastuzumab.[23] It also appears that the angiotensin II type 1-mediated signaling pathway plays an important role in doxorubicin-induced cardiac failure.[24] More recently, an indirect relationship has been considered between the renin–angiotensin system and trastuzumab-induced cardiac dysfunction. The increased stress on the heart leads to the upregulation of circulating angiotensin II, which, in turn, contributes to detrimental effects on the heart.[25]

The incidence of cardiac toxicity in this setting has been reported to be approximately 28%, although it has been shown to be less in a large chart review by Russell *et al.*[4,26,27] One approach that seems promising is separating anthracycline dosing and the initiation of trastuzumab by at least 90 days, which may help to alleviate some of these safety concerns.[28,29] This theory is supported by a lower incidence of cardiac toxicity (4.3%) in the HERceptin Adjuvant trial cohort, which has led to the recommendation that anthracyclines and trastuzumab not be used concomitantly in clinical practice to minimize their synergistic cardiac toxicity.[28–30]

Ado trastuzumab emtansine

Ado trastuzumab emtansine is an antibody–drug conjugate consisting of trastuzumab covalently linked to the highly potent microtubule inhibitory agent DM1 (a cytotoxic derivative of maytansine) via a stable thioether linker.[31]

Given the favorable safety profile in advanced diseases, the use of T-DM1 is also of interest in early stage diseases, in which T-DM1 could potentially replace the use of trastuzumab plus a taxane. The tolerability of 1 year of T-DM1 following anthracycline-based chemotherapy was suggested in the following trial: 153 patients with HER2-positive early breast cancer and a prechemotherapy LVEF at least 55% received neoadjuvant doxorubicin plus cyclophosphamide or epirubicin plus fluorouracil and cyclophosphamide, followed by T-DM1 for four cycles; patients could then receive three or four cycles of optional docetaxel with or without trastuzumab. T-DM1 was then resumed with optional radiotherapy for a total of 1 year of HER2-directed therapy. At a median follow-up of 25 months, four patients had asymptomatic LVEF declines ($\geq$10% points from baseline to <50%), which led to discontinuation of T-DM1 in only one. There were no other prespecified cardiac events or episodes of symptomatic heart failure. This study was performed as a pilot to precede testing of T-DM1 in a more formal future adjuvant trial. T-DM1 should not be used in the adjuvant setting until large randomized trials are completed.[32]

Pertuzumab

Pertuzumab is a humanized monoclonal antibody for the treatment of HER2-positive breast cancer, in

combination with trastuzumab and docetaxel. It inhibits the HER heterodimer that binds to the HER2 dimerization domain, thereby preventing the interaction of HER2 with other HER family members. Although trastuzumab was used as monotherapy for the treatment of HER2-positive breast cancer, recent studies suggest that dual antibody therapy may provide a more comprehensive HER pathway blockade in patients with locally recurrent or metastatic HER2-positive adenocarcinoma. The promising results obtained by dual antibody therapy in phase II studies of patients with HER2-positive breast cancer confirm this.[33]

In the study by Baselga *et al.*, patients with HER2-positive metastatic breast cancer were randomized to receive either antibody therapy with pertuzumab plus trastuzumab plus docetaxel (pertuzumab group), or placebo plus trastuzumab plus docetaxel (control group). The addition of pertuzumab did not affect the cardiac toxicity of the backbone regimen of trastuzumab plus docetaxel. LV systolic dysfunction was actually higher in the control group than in the pertuzumab group (8.3 vs 4.4%), as was the rate of grade 3 or higher LV systolic dysfunction (2.8% in the control group vs 1.2% in the pertuzumab group). Furthermore, of the patients who had baseline assessment of LVEF, only 3.8% of those who received pertuzumab experienced a decline of more than 10% from baseline that resulted in an LVEF of less than 50%, compared with 6.6% in the control group.[34] Phase III studies that are now underway will yield further information regarding the cardiac safety of dual antibody therapy.

Lapatinib

Lapatinib is a dual tyrosine kinase inhibitor (TKI) that targets both ErbB1 and ErbB2 and is used in the treatment of HER2-positive metastatic breast carcinoma.[35]

Early clinical studies suggest usefulness of lapatinib in women with advanced breast cancer. The development of brain metastases in patients with advanced breast cancer is a relatively common event; as many as one-half of women with HER2 positive metastatic disease will be found to have developed brain metastases during the course of their illness. Several studies indicate that combination therapy of lapatinib and capecitabine may be an effective treatment option for brain metastasis of HER2-positive breast cancer.

The cardiotoxic side-effects of lapatinib were studied in a large retrospective chart review of 3689 patients by Perez *et al.* in 2008; an incidence of 1.6% for adverse cardiac events after treatment was found. In this study, cardiotoxic side-effects included symptomatic congestive heart failure (CHF) or an asymptomatic decrease in LVEF of more than 20% relative to the patient's baseline or to below the institution's lower limit of normal.[36] Only 0.2% of the patients who experienced a cardiac event developed symptomatic CHF. Adverse cardiac events were mostly reversible, and patients demonstrated partial or full recovery of cardiac function within 7 weeks.[36] The reversible nature of lapatinib-induced CTX suggests a cellular mechanism of dysfunction. As with trastuzumab, that is to say it is a Type II CTX. The reduced incidence of cardiac events associated with lapatinib compared with trastuzumab may be because of lapatinib-induced AMP-activated protein kinase activity, which increases ATP production, thus protecting cardiomyocytes against apoptosis induced by TNFα and other cytokines that can induce cardiomyopathy.[37]

Angiogenic inhibitors

Angiogenesis inhibitors are widely used in cancer therapy. Following advances in knowledge of the role of angiogenesis in promoting tumor growth,[38] multiple trials have shown that angiogenesis inhibitors yield incremental improvements in outcomes for a variety of advanced solid tumors.

The increasing use of agents that target vascular endothelial growth factor (VEGF) and its signaling pathway in cancer therapy has unearthed the relevant issue of a wide spectrum of side-effects and toxicities, which, in a small number of cases, may be fatal.[39,40] These agents principally target the tumor vasculature rather than the tumor cells, resulting in atypical toxicities not usually observed with conventional cytotoxic agents.

In this review we discuss the cardiovascular adverse effects of the anti-VEGF agents (HTN, thromboembolic disease, LV dysfunction, myocardial ischemia, and thrombotic microangiopathy).

Several classes of molecularly targeted antiangiogenic agents are available for cancer therapy, including the VEGF ligand inhibiting agents (e.g. bevacizumab) and TKIs that target angiogenesis by blocking VEGF signaling (e.g. sunitinib, sorafenib, ponatinib, axitinib, regorafenib, and vandetanib), as reported in Fig. 2.

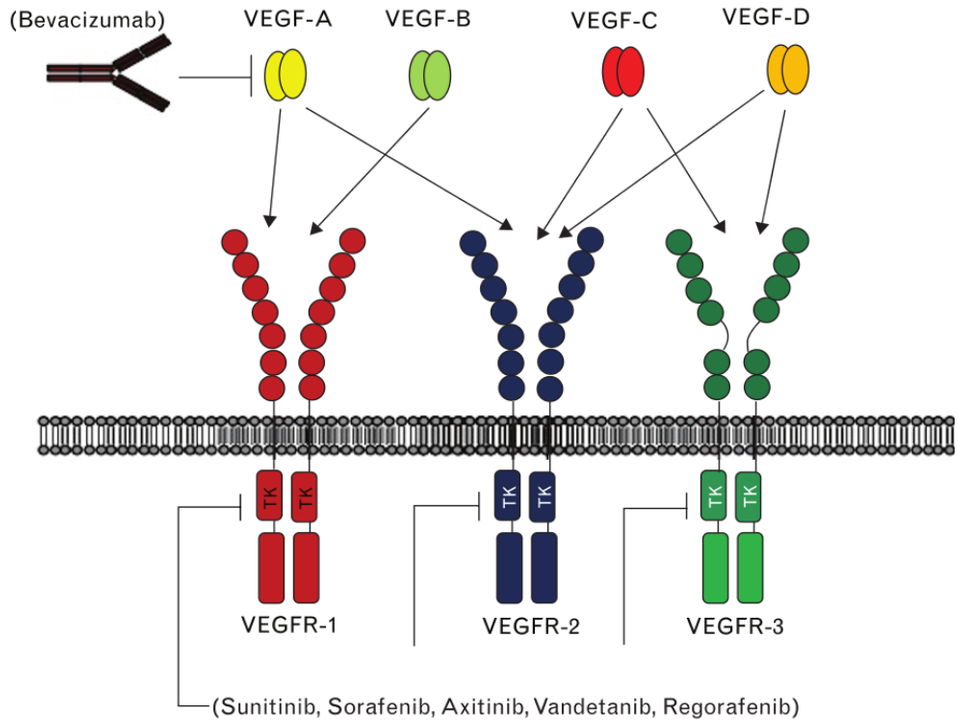
Monoclonal antibodies

Bevacizumab

Bevacizumab is a recombinant humanized monoclonal antibody against VEGF that blocks angiogenesis by inhibiting the bond of the normal VEGF ligand to its receptor. In the United States, the approval of bevacizumab for metastatic colorectal cancer (mCRC) by the US Food and Drug Administration (FDA) introduced us to the modern era of antiangiogenic therapy. The European Medicines Agency granted approval for bevacizumab in mCRC in January 2006. Subsequently, bevacizumab has been approved for treatment of metastatic nonsquamous, non-small cell lung cancer, renal cell carcinoma, glioblastoma multiforme, and ovarian cancer.[41]

Bevacizumab is associated with a small increase in the risk of LV dysfunction.[42,43] This cardiac toxicity may be

Fig. 2



Schematic representation of the mechanisms of action of angiogenic inhibitors. Bevacizumab blocks angiogenic pathway-binding VEGF ligand.[42] tyrosine kinase inhibitors inhibit TK activity of VEGF receptor.[58] VEGF, vascular endothelial growth factor.

related to disruption of VEGF-mediated angiogenesis and endothelial maintenance thought to be important in protecting cardiac myocytes from oxidative stress.[44] Alternatively the toxicity could be connected to its propensity for inducing HTN as precipitation of underlying cardiac dysfunction.[44]

Multitargeted kinase inhibitors

Sunitinib and sorafenib

Sunitinib and sorafenib are TKIs of VEGF. They have been associated with several side-effects, including HTN, intracranial hemorrhage, and CHF. In patients treated with sunitinib, the incidence of HTN has been estimated at 15–47%, and in patients treated with sorafenib, at 17–42%.[45–47] Patients may develop CHF after treatment with sunitinib or sorafenib; sunitinib causes a high risk of CHF (8.0–12.5%), with a decrease in LVEF of 1.5–2.0% after each treatment.[46–48] Risk factors associated with LV dysfunction include prior cardiac disease and preexisting HTN.[45] In addition, sunitinib and sorafenib have direct effects on vasculature; they result in HTN caused by endothelial dysfunction, dysfunction in nitric oxide metabolism, and vascular rarefaction.[49] Sunitinib also destroys pericytes, which wrap around blood vessels and are essential for blood vessel formation and maintenance. Destruction of these pericytes leads to blood vessel hyperdilation and hemorrhage.

Sunitinib was developed to inhibit angiogenesis by targeting the tyrosine kinase domain of vascular endothelial growth factor receptor (VEGFR). By silencing the VEGF–VEGFR signaling pathway, sunitinib reduces capillary density and mitigates formation and vasodilating effects of nitric oxide, thereby causing HTN that stresses the heart. The VEGF signaling pathway is not the only mechanism triggering sunitinib-related cardiotoxic side-effects; sunitinib also inhibits the kinase domain of platelet-derived growth factor receptor (PDGFR) and prevents cardiomyocytes from responding to stress by secreting proangiogenic factors.[50] Nevertheless, VEGFR and PDGFR are only two limited examples of the very many potential targets of sunitinib.

CHF may occur as a result of direct cardiomyocyte mitochondrial damage and cytochrome C-induced apoptosis.[45] Sunitinib therapy also compromises myocyte energy homeostasis and inhibits the compensatory upregulation of AMP-activated protein kinase, which is important in maintaining the favorable myocardial energetics that reduce cell death.[51,52]

In addition to its inhibition of VEGFR1–3, FMS-like tyrosine kinase-3, tyrosine-protein kinase Kit (KIT), and PDGFR signaling, which is thought to lead to loss of vascular integrity, sorafenib also affects the downstream pathway of rapidly accelerated fibrosarcoma kinase or its homolog B, increasing oxidant-stress-induced injury as well as causing apoptosis.[5]

Ponatinib

Ponatinib is a multitarget TKI that blocks angiogenesis by inhibiting the actions of VEGF and other growth factors (e.g. platelet-derived growth factor). This drug received approval for treatment of a variety of tumors, including renal cell carcinoma, hepatocellular cancer, gastrointestinal stromal tumors, thyroid cancer, pancreatic neuroendocrine tumors, soft tissue sarcomas, refractory chronic myelogenous leukemia (CML), and refractory mCRC. Higher rates of arterial thromboembolic events are reported with ponatinib. Among patients receiving ponatinib therapy for refractory CML, 11% developed arterial thrombosis of any grade; 8% had serious arterial thrombosis.[53] Thirty of the 34 patients who developed arterial thrombosis had one or more cardiac risk factors (coronary artery disease, stroke, transient ischemic attack, HTN, obesity, diabetes, hyperlipidemia, history of smoking). However, the risk of serious thromboembolic events may be higher. In October 2013, the FDA issued a drug safety communication regarding reports of serious and life-threatening blood clots and severe narrowing of blood vessels (both arteries and veins) in at least 20% of patients taking ponatinib for CML. Given the high rate of thromboembolic events in patients treated with ponatinib, clinicians should carefully consider whether the benefits of treatment are likely to exceed the risks, particularly for patients with one or more cardiac risk factors. Approximately 1% of patients treated with ponatinib developed symptomatic bradyarrhythmias and 5% developed supraventricular tachyarrhythmias (predominantly atrial fibrillation).[53] QTc prolongation is not reported.

Axitinib

Axitinib is suggested for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy. It may induce the following cardiotoxic side-effects: HTN (40%; grades 3/4: 16%), venous thrombotic events (grades 3/4: 3%), arterial thrombotic events (2%; grade 3/4: 1%), deep vein thrombosis (1%), transient ischemic attack (1%), and heart failure less than 1%.[41]

Regorafenib

Regorafenib is a TKI targeting multiple cancer-associated kinases, including angiogenic (VEGFR1–3, endothelium-specific receptor tyrosine kinase – TIE2-), stromal (PDGFR-β, fibroblast growth factor receptor – FGFR) and oncogenic receptor tyrosine kinases (KIT, REarranged during Transfection – RET and Rapidly Accelerated Fibrosarcoma).[54,55] Regorafenib has been associated with HTN and an increased incidence of myocardial ischemia and infarction.[56,57]

Vandetanib

Vandetanib is an oral, once-daily kinase inhibitor of tumor angiogenesis and tumor cell proliferation. Vandetanib was approved by the FDA to treat nonresettable locally advanced or metastatic medullary thyroid cancer in adult patients. Vandetanib is an ATP mimetic small molecule that inhibits VEGFR2 and epidermal growth factor receptors.[58,59] Vandetanib has been associated with arrhythmia and HTN.[57,60]

Directed Abelson murine leukemia viral oncogene homolog inhibitors

Imatinib

Imatinib is a competitive TKI of the breakpoint cluster region-ABL enzyme that is used in the treatment of multiple forms of cancer, but most notably for Philadelphia-positive (Ph+) CML. Treatment with imatinib may cause CHF in approximately 2.0% of patients.[61] The physiologic mechanism of the drug's CTX is similar to that of sunitinib; it involves mitochondrial damage and cell death.[52]

Dasatinib and nilotinib

Dasatinib and nilotinib are two second-generation multitargeted TKIs that are used for the treatment of Ph+ CML; dasatinib targets KIT, PDGFR, and the nonreceptor tyrosine kinase sarcoma (SRC) family of kinases, and nilotinib targets KIT and PDGFR. Both target breakpoint cluster region-ABL.

Dasatinib has also been associated with chest pain, pericardial effusion, ventricular dysfunction, heart failure, and pulmonary arterial HTN (http://www.sprycel.com/).

Proteasome inhibitors

Bortezomib and carfilzomib are proteasome inhibitors that are used for the treatment of multiple myeloma.

In clinical trials with carfilzomib, a second-generation proteasome inhibitor, approximately 7% of patients show new onset or worsening of preexisting heart failure with decreased LV function or myocardial ischemia, and deaths because of cardiac arrest have occurred within 1 day of drug administration.[62] In addition, pulmonary arterial HTN has been reported in 2% of patients treated with carfilzomib. CTX might be an effect of the whole class of proteasome inhibitors, as heart failure events (acute pulmonary edema, cardiac failure, and cardiogenic shock) have also been described in patients treated with bortezomib, a first-generation proteasome inhibitor.[63] Abnormalities appear to be largely reversible with prompt cessation of therapy and initiation of traditional heart failure treatment.[64]

Conclusion

Cardiovascular safety has been one of the most challenging aspects in drug development. It is now clearly demonstrated that treatment with several chemotherapeutic agents is associated with an increased risk of myocardial disease. The uncertainty of the reversibility and long-term safety of anticancer agents has

complicated decision-making consequences with regard to treatment regimens.[65]

Even targeted therapies that were once considered less toxic have now been shown to affect the cardiovascular system in ways that require further investigation.

The emerging field of cardioncology recognizes these toxicities, develops strategies to prevent or minimize cardiovascular toxicity, and works to prevent long-term cardiotoxic effects. Understanding the mechanisms by which these therapies affect the heart is critical for improving drug design and finding alternative therapies.[66] These aspects are needed to protect patients predisposed to cardiovascular disease.

A multidisciplinary team that includes both oncologists and cardiologists has formed to further investigate these toxicities and to develop methods to reduce risk factors, as well as prevent, detect, and treat potential CTX. Early detection requires awareness of chemotherapy-related cardiac dysfunction, as well as appropriate prevention, cardiac evaluation, and follow-up. Many of the patients who develop adverse cardiovascular events have preexisting cardiac risk factors or known cardiovascular disease for which they should receive appropriate treatment.

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