Cardiotoxicity associated with targeted cancer therapies (Review)

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Received July 28, 2015; Accepted January 25, 2016

DOI: 10.3892/mco.2016.800

Abstract. Compared with traditional chemotherapy, targeted cancer therapy is a novel strategy in which key molecules in signaling pathways involved in carcinogenesis and tumor spread are inhibited. Targeted cancer therapy has fewer adverse effects on normal cells and is considered to be the future of chemotherapy. However, targeted cancer therapy-induced cardiovascular toxicities are occasionally critical issues in patients who receive novel anticancer agents, such as trastuzumab, bevacizumab, sunitinib and imatinib. The aim of this review was to discuss these most commonly used drugs and associated incidence of cardiotoxicities, including left ventricular dysfunction, heart failure, hypertension and thromboembolic events, as well as summarize their respective molecular mechanisms of cardiovascular adverse effects.

Contents

1. Introduction

It has been nearly a century since the first drug treatment of cancer. Since then, chemotherapy has become a powerful tool for controlling malignancy, with significant benefits in terms of survival (1). Chemotherapy is also one of the most commonly used cancer therapeutics in modern medicine, along with radiation therapy and surgery (1). Traditional chemotherapy agents, such as alkylating agents and antimetabolites, eliminate rapidly dividing cells, including not only tumor cells, but also normal tissue cells, such as those in digestive endothelia, hair follicles and bone marrow. This non-specific targeting treatment is associated with a broad range of side effects, including gastrointestinal (GI) symptoms, alopecia and even lethal adverse effects, such as bone marrow suppression. These negative effects significantly limit the applications of traditional agents and unnecessarily compromise the quality of life of cancer patients. In targeted cancer therapy, drugs interfere with key signaling molecules and inhibit tumorigenesis and metastasis, with fewer associated adverse effects (2).

In the human kinome, 90 of the 518 kinases are tyrosine kinases (TKs) (3) which play a central role in maintaining homeostasis, such as cell growth, differentiation, migration and apoptosis (4,5). Mutations of TKs transduce aberrant signaling into cells and result in tumor growth and/or metastasis. Novel cancer strategies target key TKs and have been proven to be a remarkable achievement in cancer management. The two main categories of agents used in targeted cancer therapy are TK antibodies and TK inhibitors (TKIs).

Cardiotoxicity, a commonly encountered adverse effect, may be associated with traditional as well as novel targeted chemotherapeutic agents, and is grouped into two categories, namely type I (traditional) and type II (targeted), based on distinct pathological changes and clinical characteristics. Anthracyclines are the prototype of type I agents. Anthracycline-based chemotherapy is associated with a significant risk of left ventricular dysfunction (LVD) or congestive heart failure (CHF), compared with non-anthracycline regimens [odds ratio (OR)=5.43; 95% confidence interval (CI): 2.34-12.62, P<0.0001] (6). The incidence of subclinical LVD may be as high as 36% in patients with a history of prior anthracycline therapy (7). Type I agents cause irreversible ultrastructural damage to cardiomyocytes, such as vacuole formation, contractile element disarray, or even necrosis (8). Trastuzumab is the representative agent in the type II category, resulting in cardiac dysfunction with an incidence reportedly ranging from 3 to 64% in single-agent or combination regimens (Table I). Type II agents result in benign ultrastructural changes in cardiomyocytes, with reversible cardiac function changes (8-10). In addition to cardiac dysfunction, targeted cancer therapy-induced cardiotoxicities may manifest as elevated blood pressure, thromboembolism,

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Key words: tyrosine kinase inhibitor, trastuzumab, bevacizumab, imatinib, sunitinib

pericardial thickening and arrhythmia. The aim of this review was to discuss the representative drugs in targeted cancer therapy, the monoclonal antibodies to TKs (trastuzumab and bevacizumab) and small-molecule TKIs (sunitinib and imatinib).

2. Monoclonal antibodies to TKs

Trastuzumab

Background. Human epidermal growth factor receptor 2 (HER2) is a 185-kd transmembrane glycoprotein receptor, encoded by the ErbB2 proto-oncogene. Overexpression of HER2 promotes tumorigenesis in a variety of cancers, such as breast and colon cancer (11-13). Being a humanized monoclonal antibody against human HER2 with reduced immunogenicity, trastuzumab is highly effective in treating primary as well as metastatic breast cancer, thereby improving survival. Trastuzumab was the first Food and Drug Administration (FDA)-approved therapeutic antibody targeting molecular markers in cancer; it may be used as first-line therapy in combination with paclitaxel chemotherapy, and also as a single agent for patients who have priorly received chemotherapeutic regimens (14).

Cardiotoxicity incidence and molecular mechanism. Trastuzumab was a significant breakthrough in the treatment of breast cancer overexpressing HER2 receptors (~25-30% of breast cancers) (15). Cardiac dysfunction, either asymptomatic (decreased LV ejection fraction) or symptomatic (CHF), has been reported in pivotal phase II and III clinical trials, with a range from 3 to 64% when used alone or as part of combination regimens (Table I) (8,16,17). Trastuzumab significantly increases the incidence of cardiotoxicity when combined with other agents. For example, in clinical trial H0648g, anthracycline and trastuzumab-treated patients experienced cardiac dysfunction at a rate of 27%, compared with a rate of 8% in patients treated with anthracyclines alone (18-20). In the majority of the cases (79%), the cardiac dysfunction improved after receiving treatment for heart failure (18), and reintroducing trastuzumab after recovery from cardiac dysfunction is considered acceptable (21). Trastuzumab is also safe when administered concurrently with postoperative radiotherapy, without an increased risk of cardiac events (22). Although there is no consensus on the onset of cardiotoxicity, it appeared that administering trastuzumab for >6 months was more likely to lead to a decline in the ejection fraction, whereas shorter treatment (≤6 months) did not appear to be associated with an increased risk of heart failure.

Due to the limited biopsy samples, the mechanism of cardiotoxicity caused by trastuzumab treatment is not fully understood; however, inhibition of HER2 in cardiomyocytes may be the main mechanism underlying decreased cardiac function. Selective inactivation of ErbB2 in mouse ventricular myocardium revealed no overt developmental heart phenotype; however, on subsequent analysis, we observed dilated cardiomyopathy and a ≤50% reduction in fractional shortening. Furthermore, isolated neonatal cardiomyocytes from ErbB2 mutants in culture were more sensitive to adriamycin treatment, with apoptosis being more prominent in mutant hearts (23-26). All these data suggest that ErbB2 signaling is required to maintain adult cardiac function. However, the low incidence of cardiotoxicity with lapatinib (dual inhibition of HER2 and epidermal growth factor receptor) and pertuzumab (another HER2 antibody) makes this possibility more obscure and debatable (27-30). Recently, Fedele *et al* reported that their newly synthesized anti-ErbB2 antibody, Erb-hcAb, recognizes a different epitope in HER2 than trastuzumab, without cardiac function alterations in their preclinical trial (31). The downstream targets mitogen-activated protein kinases (Erk1 and Erk2) and Akt activation were preserved in cardiac cell lines when treated by Erb-hcAb, but lowered in trastuzumab- or pertuzumab-treated cells. These findings suggest that trastuzumab causes cardiotoxicity by binding to a unique epitope in HER2 and blocks the Erk/Akt singling pathway (31). Other mechanisms that cause tumors to shrink are as follows: (i) Prevention of HER2 receptor dimerization and inhibition of downstream signaling pathways; (ii) recruitment of immune effector cells and subsequent tumor cell death; (iii) downregulation of the HER2 receptor (32,33).

Bevacizumab

Background. Several types of tumor cells secrete angiogenic molecules, such as vascular endothelial growth factor (VEGF), to promote new vessel formation in order to meet the increased demands on oxygen and nutrients. By blocking VEGF/VEGF receptor (VEGFR) signaling, bevacizumab was the first FDA-approved humanized monoclonal anti-VEGF antibody to treat metastatic malignancies, including metastatic colorectal cancer (34) and non-squamous, non-small-cell lung cancer (35). In addition to bevacizumab, the FDA-approved small molecules that target VEGFR include lapatinib, sunitinib and sorefenib (Table I). The downstream targets of VEGF/VEGFR include phosphoinositide 3-kinase (PI3K)/Akt/protein kinase (PK) B and PKC/Erk, all of which are critical for endothelial cell survival and proliferation (36).

Cardiotoxicity incidence and molecular mechanism. Cardiotoxicity was observed in several clinical trials, although bevacizumab is not as widely used as trastuzumab (Table I). The three most commonly reported cardiovascular adverse effects are hypertension (HTN), CHF and thromboembolism. In rare instances, myocardial infarction was reported (37). The incidence of bevacizumab-related HTN was reported to be 16-47% in several clinical trials (38,39) and it appears to be dose-dependent (40). When bevacizumab was used together with irinotecan, fluorouracil and leucovorin in metastatic colorectal cancer, the incidence of grade 3 HTN increased by 8 points (41,42). HTN associated with bevacizumab may be effectively controlled by an angiotensin-converting enzyme (ACE) inhibitor (43). As a rare adverse effect, CHF was reported in ~1.7-3% of patients following bevacizumab treatment. The incidence of CHF was higher among patients with prior anthracycline treatment, cardiomyopathy, or chest wall irradiation (44-46). Thromboembolism is another severe adverse effect of bevacizumab treatment and the combination of bevacizumab and chemotherapy increases the risk of arterial thromboembolic events (hazard ratio = 2.0, 95% CI: 1.05-3.75, P=0.31) more than chemotherapy alone. Prior arterial thromboembolic events and age >65 years were also reported as risk factors (37). Bevacizumab was also reported to be associated with the development of venous thromboembolism in cancer treatment (relative risk = 1.33, 95% CI: 1.13-1.56, P<0.001). The type of tumor is associated

Table I. Representative tyrosine kinase inhibitors that cause cardiotoxicity.

Target no.	Agent (trade name)	Class	Targets	Malignancies	Cardiotoxicity incidence	First FDA approval	Molecular mechanism
Single	Trastuzumab (Herceptin)	mAb	ErbB2 (HER2)	$HER2^+$ breast cancer	LVD: 3-7% as a single agent and ≤64% in combination regimens (>6 months administration)	1998	LVD: inactivation of HER2/Erk/Akt pathway in cardiomyocytes; prevention of HER2 receptor dimerization; tumor cell death; downregulation of HER2 receptor
	Bevacizumab (Avastin)	mAb	VEGF	mCRC, nsNSCLC, mRCC, GBM	LVD: 1.7-3%; HTN: 16-47%	2004[a]	HTN: inhibition of VEGF-eNOS to weaken vasodilation; overproliferation of vascular SMCs Thrombosis: increased platelet aggregation and proinflammatory gene expression in endothelial cells
Multiple	Imatinib (Gleevec)	Small molecule	ABL1/2, KIT, PDGFR α/β	CML, RCC, GIST, HES	HF: 0.5-1.7%	2001	HF: inhibition of ABL causes cardiomyopathy, increased apoptosis and ER stress
	Sunitinib (Sutent)	Small molecule	VEGFRs, PDGFR α/β, KIT, FLT3	RCC, imatinib resistant GIST	HF: 2.7-11%; HTN: 5-47%	2006	HF: abnormal mitochondrial biogenesis, increased apoptotic cell death, inhibition of AMPK and PDGFRs

[a]Approved for breast cancer and revoked in 2011. FDA, Food and Drug Administration; mAb, monoclonal antibody; HER2, human epidermal growth factor receptor 2; LVD, left ventricular dysfunction; mCRC, metastatic colorectal cancer; nsNSCLC, non-squamous non-small-cell lung cancer; mRCC, metastatic renal cell carcinoma; GBM, glioblastoma multiforme; VEGF, vascular endothelial growth factor; eNOS, endothelial nitric oxide synthase; HTN, hypertension; SMC, smooth muscle cell; PDGFR, platelet-derived growth factor receptor; VEGFR, VEGF receptor; CML, chronic myelogenous leukemia; GIST, gastrointestinal stromal tumor; HES, hypereosinophilic syndrome; HF, heart failure; ER, endoplasmic reticulum; FLT-3, Fms-like tyrosine kinase 3; AMPK, AMP-activated protein kinase.

with venous thromboembolism and the dose of bevacizumab is another potential risk factor (47).

The molecular mechanisms through which bevacizumab causes these cardiovascular adverse effects are not well understood, but inhibition of the VEGF signaling pathway may play an important role. VEGF exerts a vascular protective effect in the adult vasculature; it may inhibit vascular smooth muscle cell (SMC) proliferation and promote endothelial cell survival. In addition, VEGF upregulates the expression of endothelial nitric oxide synthase (eNOS). Bevacizumab-induced HTN is possibly caused by: (i) Weakened vasodilation due to lowered NO production; and (ii) increased vascular resistance due to overproliferation and/or hyperplasia of vascular SMCs (48,49). According to preclinical findings, VEGF has the ability to inhibit platelet aggregation by increasing NO and prostacyclin production, and chronic exposure to VEGF may decrease proinflammatory gene expression in endothelial cells, such as cyclooxygenase 2 and E-selectin (50-52). This may explain the arterial or venous thromboembolic events during bevacizumab treatment. Although the mechanisms underlying the development of CHF are not clearly understood, the elevated mean arterial blood pressure during bevacizumab treatment may predispose to CHF, particularly in those patients who had prior anthracycline treatment, cardiomyopathy, or chest wall irradiation. Furthermore, Izumiya *et al* reported that, in an animal model, a decoy VEGFR promoted LV dilatation and contractile dysfunction in the presence of pressure overload (53).

3. Small-molecule TKIs

The concept that ATP analogues may block the catalytic site of receptor tyrosine kinase (RTK) in cancer cells has been applied to design small-molecule TKIs, all of which exhibit very high affinity for the ATP pockets of the TK, so that the substrate protein cannot get access to the kinase site or be phosphorylated. The risk of TKI-associated cardiotoxicity is relatively low and well tolerated (54). We herein discuss two representative drugs, namely sunitinib and imatinib. Small molecules are tentatively considered as type II agents, due to the reversibility of the adverse effects and lack of cumulative dose-dependent effects. However, more biopsy data are required to confirm this classification (8). On-target cardiotoxicity is considered to be the main mechanism underlying imatinib-induced cardiotoxicity. On-target cardiotoxicity occurs when the therapeutic drug functions on the intended target, while off-target cardiotoxicity is observed when the TKI inhibits kinases other than the intended target (55). The representative drug of off-target cardiotoxicity is sunitinib (56).

Imatinib mesylate

Background. BCR-ABL is present in >90% of chronic myeloid leukemia (CML) cases (57,58). ABL is a non-receptor TK, and a fusion product, BCR-ABL, increases the TK activity of ABL. In CML cells, BCR-ABL activates a variety of signaling pathways, such as RAS, PI3K-Akt and signal transducer and activator of transcription 5A, to promote proliferation and prevent apoptosis (59). Imatinib is a revolutionary drug for the treatment of CML by targeting ABL (60); it efficiently inhibits BCR-ABL$^+$ CML cells, blocks phosphorylation and induces apoptotic cell death. Anti-apoptotic factors, such as B-cell lymphoma 2 (Bcl-2) and Bcl-xL, are inhibited. Although imatinib cannot cure CML, it converts CML into a manageable, chronic disease. The best known imatinib targets are ABL, KIT and PDGFRs (α and β).

Cardiotoxicity incidence and molecular mechanism. Imatinib has been approved by the FDA as an oral drug for the treatment of CML, gastrointestinal stromal tumors (GISTs) and hypereosinophilic syndrome. Overall, imatinib is well tolerated. Although the incidence of edema and dyspnea are reported to be as high as 66 and 16%, respectively (57), LVD was overlooked during the first few years that imatinib was in the market (60,61), until Kerkela *et al* reported 10 new-onset CHF cases in their study (57). Atallah *et* (62) reviewed 1,276 patients with hematological malignancies who were receiving imatinib, and found that 22/1,276 (1.7%) had CHF symptoms; however, only 8 cases were considered possibly associated with imatinib treatment. Several other groups revealed the similarly low incidence of this adverse effect, with a range of 0.5-1.7% (62,63). Overall, imatinib-induced cardiotoxicity is a very uncommon adverse event. For those with a prior history, cardiac function should be closely followed up. Beta blockers, ACE inhibitors and diuretics may be used in the management of CHF (62-66).

Kerkela *et al* (57) reported that heart biopsy samples from 2 of 10 CHF patients exhibited dilated sarcoplasmic reticulum with membrane whorls, and abnormal mitochondria with effaced cristae using transmission electron microscopy, which is usually seen as pathological changes in toxin-induced myopathies, as opposed to ischemic myopathy. Biopsies from imatinib-treated mice exhibited similar pathological changes. Since ABL protects against apoptosis, terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay was performed on mouse cardiomyocytes. In *in vivo* as well as *in vitro* experiments, the TUNEL assay revealed an increase in apoptosis. However, in imatinib-treated cell cultures, pronounced cytosolic vacuolization and loss of sarcolemmal integrity were observed, both of which are considered the hallmark of necrotic cell death, strongly suggesting that, besides apoptosis, necrotic death also plays an important role in this event (57,60).

Further investigation using imatinib-treated cardiac cells revealed that, by inhibiting ABL, imatinib induced endoplasmic reticulum stress by activating PK RNA-like ER kinase, PKCδ and inositol-requiring enzyme 1 pathways. All these events caused release of Bcl-2-associated X protein and were followed by mitochondrial depolarization, ATP depletion, cytochrome *c* release and eventually resulted in necrotic and apoptotic cell death (57). To circumvent ABL-induced cardiotoxicity, Fernández *et al* (67) modified imatinib by suppressing BCR-ABL inhibition and maintained its inhibition on c-Kit kinase. This new agent maintains the selective anticancer effects on GIST cells *in vivo* and *in vitro*, with a reduction of cardiotoxicity (67,68). In addition, imatinib may affect cardiac progenitor cells in the human heart by blunting c-Kit, which is preserved in this cell group (69).

Sunitinib

Background. Sunitinib is a multiple TK inhibitor, with >50 known targets, including VEGFR 1-3, PDGFR α and β and RET (70). Sunitinib is the first TKI approved by the

FDA to be used in two different cancers, namely GIST and metastatic renal cell carcinoma (mRCC), with significant survival benefits (71). The antitumor mechanism of sunitinib is as follows: In tumor cells, sunitinib simultaneously inhibits the VEGFR/PI3K/mammalian target of rapamycin signaling pathway, RET, KIT, Fms-like tyrosine kinase 3 and their mutual downstream target, signal transducer and activator of transcription 3, to induce tumor cell apoptosis and growth arrest. Angiogenesis was also found to be inhibited by blocking the autocrine and paracrine effects of PDGFR in breast cancer cell lines (72-74).

Cardiotoxicity incidence and molecular mechanism. Sunitinib is overall well-tolerated and its adverse events are considered as manageable. The most common adverse events in sunitinib-treated patients are HTN and CHF. The incidence of sunitinib-associated CHF ranges from 2.7 to 15% (16,17,75). Motzer *et al* (76) investigated 750 patients with mRCC in a phase III trial of sunitinib; the incidence of grade 3 reduction in LV ejection fraction was similar in the two groups (2 and 1%, respectively). In another research study on imatinib-resistant GIST, 8 of the 75 (11%) patients receiving imatinib had a cardiovascular event and 6 of the 75 (8%) patients had CHF (16); furthermore, 12 (18%) had elevated troponin levels. This incidence is higher compared with that reported by other groups, possibly because patients in this study had received prior anticancer treatment (all their patients had been priorly treated with imatinib and 15 of the 75 patients had an anthracycline treatment history). Furthermore, the blind observation of time-to-CHF in the Chu *et al* study (16) was longer compared with that in Demetri *et al* study (77), namely 33.4 vs. 10 weeks, respectively. This may also explain the discrepancy between these two groups and suggests that a longer exposure to sunitinib may be required for patients to develop CHF (16,76,76). Abnormal mitochondrial biogenesis was observed on transmitted electron microscopic examination, including membrane whorls and efface cristae in sunitinib-treated mice (16). In sunitinib-cultured neonatal rat ventricular myocytes, cytochrome *c* was released, caspase-9 was activated and apoptotic death was detected by the TUNEL assay (16). Kerkela *et al* (56) reported an off-target mechanism of inhibition of AMP-activated protein kinase (AMPK). AMPK is a cellular energy generation switch. When cellular energy levels decrease, AMPK is activated to stimulate ATP production through catabolic pathways, while inhibiting energy-consuming pathways. Similar mitochondrial abnormalities, such as swollen mitochondria and effaced cristae, were observed in sunitinib-treated RCC patients and sunitinib-treated mouse hearts. Sunitinib induces myocyte loss in animal models. Loss of myocytes may be prevented by gene transfer of a constitutively active mutant AMPK, suggesting it was directly inhibited by sunitinib and results in energy compromise (56).

Cell surface RTKs-PDGFRs are important factors regulating cell proliferation and cell differentiation. PDGFRs are also expressed in cardiomyocytes and are unregulated in response to mechanical stress. PDGFRs are known sunitinib targets and inhibition of PDGFRs has been reported to play a protective role in hearts exposed to ischemic injury (78). However, PDGF/PDGFR signaling functions were investigated by treating cardiac tissue or post-myocardial infarction tissue with exogenous PDGF-B. However, the direct PDGFRs functions have not been elucidated. Chintalgattu *et al* (79) selectively blocked PDGFR-B in mice hearts and reported that, in PDGFR-B mutant mice, cardiac function was compromised and angiogenesis was impaired. These results demonstrated that PDGFR-B is required to maintain cardiac function in response to mechanical stress, and also for stress-induced cardiac angiogenesis. PDGFR-B regulates the heart and plays a positive role in maintenance; it is also required for angiogenesis and preservation of cardiac function in the presence of stress overload (79). This may be an off-target effect of sunitinib.

HTN is another cardiovascular toxicity associated with the administration of sunitinib. The incidence of this adverse event is ~17-43%. Of note, HTN was found to be a biomarker of efficacy in patients with mRCC treated with sunitinib. Patients with mRCC and sunitinib-induced HTN had better outcomes compared with those without treatment-induced HTN (80). The mechanism underlying the development of HTN has not been fully elucidated.

4. Conclusion

Targeted cancer therapy inhibits specific key molecules in tumors and is associated with fewer severe adverse effects. However, cardiotoxicity induced by this type of agent is not uncommon in clinical practice. To the best of our knowledge, there is no relevant literature investigating the survival benefit of targeted anticancer agents that cause cardiotoxicities. Although there is no consensus or guideline for evaluating or monitoring cardiac dysfunction, the cardiac function of high-risk patients who are scheduled for intermediate/high-risk surgery should be thoroughly investigated according to the American College of Cardiology/American Heart Association guidelines (81). New imaging technologies, such as three-dimensional echocardiography and speckle tracking imaging are emerging and may be used as surveillance of patients who are predisposed to cardiac dysfunction. As the application of targeted therapies in the treatment of cancer is on the increase, extensive research is required to understand in detail the mechanisms underlying the development of cardiovascular toxicities and promote the design of optimal drugs.

Acknowledgements

The authors would like to thank Ms. Chandler Carroll for the revision of the manuscript and the valuable suggestions.

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