Review

Cardiotoxicity of Molecular-targeted Drug Therapy

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Abstract. *Cardiotoxicity is a well-known side-effect described in patients receiving various antineoplastic agents. With the abundance of clinical research and a heavy focus on drug development over the past decade, there has been a major shift in the use of non-specific cytotoxic drugs to molecular-targeted drug therapy. However, as a result, it has become clear that these drugs have numerous adverse effects, both on-target and off-target. Small-molecule tyrosine kinase inhibitors and other molecular-targeted agents, including monoclonal antibodies, have been the primary agents associated with cardiotoxicity. As more molecular-targeted therapies are developed, early recognition and management of drug-related cardiotoxicity will be extremely important in order to reduce morbidity and mortality. Pre-treatment evaluation with a surface electrocardiogram, echocardiography, cardiac history, and comprehensive review of concomitant medications are the current mainstay of treatment. However, much is still unknown about the potential cardiotoxic side-effects of these drug and optimal management. In the present article, we aim to review the cardiovascular implications and related cardiotoxicities associated with molecular target-based chemotherapeutic agents, with special emphasis on hypertension, cardiac dysfunction, and QT prolongation. Their implication, mechanism, and management are discussed where possible.*

Cardiotoxicity is a well-known side-effect described in patients receiving various antineoplastic agents. A large body of literature exists describing anthracycline-based chemotherapeutic agents and their association with cardiotoxicity in patients treated for both hematological and solid malignancies (1). Despite markedly increased survival rates with these potent anticancer agents, their cumulative dose-dependent cardiotoxicity has limited their potential antineoplastic use (2). With the abundance of clinical research and a heavy focus on drug development over the past decade, there has been a major shift from non-specific cytotoxic drugs to molecular targeted drug therapy. These agents target upstream cellular signaling to attenuate cell differentiation and proliferation, thus leading to improved survival. However as a result, it has become more apparent that these drugs have numerous on-target and off-target adverse effects (3). One of the major off-target effects is cardiotoxicity, which has emerged as a tremendous major safety concern (3). These agents are described in Table I.

In this article, we aim to review the cardiovascular implications and related cardiotoxicities associated with molecular target-based chemotherapeutic agents with special emphasis on hypertension, cardiac dysfunction, QT prolongation. Their implication, mechanism, and management are discussed whenever possible.

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Hypertension

Molecular-targeted agents that inhibit angiogenesis through the vascular endothelial growth factor (VEGF) or its receptor (VEGFR) have been associated with a common adverse event, hypertension. VEGF plays a key role in maintaining vascular homeostasis through the production of nitric oxide (4). Its vasodilator properties reduce vascular resistance *via* increased vascular dilatation, permeability, and generation of new blood vessels (5). The underlying basis for the antineoplastic use of anti-VEGFs is their target-specific action primarily of inhibiting proliferating tumor endothelium (6). This is achieved by inhibiting the downstream signaling pathways, including phosphatyidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) (3). Attenuation of these signaling pathways leads to decreased production of nitric oxide and consequently disruption of vascular tone, resulting in increased peripheral vascular resistance and, thus, elevated blood pressure (BP) (3).

Table I. *Summary of molecular-targeted agents.*

Name	Target action	Indication	Cardiotoxicity	Risk
Bevacizumab	VEGF	Colorectal cancer, non-squamous NSCLC, renal cell carcionoma, glioblastoma multiforme	Hypertension	Significant hypertension, RR=5.38
Trastuzumab	HER2	Breast cancer	LV dysfunction	Heart failure, RR=2.5
Lapatinib	HER2, EGFR	Breast cancer, GIST	LV dysfunction	Incidence of LV dysfunction, 1.7%
Sunitinib	RTK, VEGFR	Renal cell carcinoma, GIST	Hypertension, QT prolongation, heart failure	All-grade hypertension, RR=22.72, all-grade heart failure, RR=4.1
Sorafenib	RTK, VEGFR	Renal cell carcinoma, Hepatocellular carcinoma, thyroid cancer	Hypertension	All-grade hypertension, RR=1.81
Pazopanib	RTK, VEGFR	Renal cell carcinoma, soft-tissue sarcoma	Hypertension	Incidence of hypertension, 35.9%
Vendatanib	RET inhibitor, VEGFR, EGFR	NSCLC	Hypertension, QT prolongation	Incidence of QT prolongation, 16.4%
Crizotinib	ALK	NSCLC	Bradycardia, QT prolongation	Average decrease in heart rate, 26.1 beats per minute
Imatinib	BCR-ABL	Chronic myelogenous leukemia	LV dysfunction	Overall incidence of LV dysfunction 1.7%

VEGF, Vascular epidermal growth factor; VEGFR, vascular epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; RTK, receptor tyrosine kinase; NSCLC, non-small cell lung carcinoma; GIST, gastrointestinal stromal tumor; BCR–ABL, break point cluster region–Abelson murine leukemia; ALK, anaplastic lymphoma kinase.

Many agents are implicated as causing hypertension. Bevacizumab is a monoclonal antibody that binds to circulating VEGF and blocks its binding to the VEGFR (7). It is currently Food and Drug Administration (FDA)-approved for metastatic colorectal carcinoma; non-squamous, non-small cell lung carcinoma; metastatic renal cell carcinoma (RCC), and glioblastoma. In a meta-analysis of over 12,000 patients treated with or without bevacizumab for advanced solid tumors, it was found that the relative risk (RR) for developing significant hypertension was 5.38 [95% confidence interval (CI)=3.63-7.97] (7). The overall incidence of raised BP events was 24% (95% CI=20-29%) and the incidence of significantly raised BP [defined as more than one drug needed for treatment (grade 3), or life-threatening consequences([grade 4)] was 8% (95% CI=6-10%) (7). See Table II for grading categories. Patients receiving bevacizumab at 5 and 2.5 mg/kg per week exhibited a dose-dependent increased RR of 7.17 (95% CI=3.91-13.13) and 4.11 (95% CI=2.49-6.78), respectively (7). It appears that patients who were being treated for RCC (RR=13.77, 95% CI=2.28-83.15) and breast cancer (RR=18.83, 95% CI=1.23-292.29) at 5 mg/kg per week had a higher risk of developing significant hypertension (7). The association between improved antitumor efficacy and the development of hypertension have been reported and hypothesized but continues to remain controversial (8).

Other anti-VEGF agents classified as small-molecule tyrosine kinase inhibitors (TKIs) have also been implicated as causing hypertension (9). TKIs act by intracellular inhibition of phosphorylation *via* blockade of high-affinity growth factors, cytokines and hormones to transmembrane receptor tyrosine kinases (10). This results in de-activation of downstream signaling events that regulate cellular differentiation, proliferation, and survival. Sorafenib, sunitinib, and pazopanib are small-molecule TKIs that have anti-angiogenic properties and are FDA-approved for the treatment of various neoplasms including metastatic RCC, gastrointestinal stromal tumors, advanced hepatocellular carcinoma, and soft-tissue sarcoma (10). In a meta-analysis by Zhu *et al*., nearly 5,000 patients who received sunitinib for advanced RCC and other malignancies were evaluated; they found that the incidence of all-grade and high-grade hypertension were 21.6% (95% CI=18.7-24.8%) and 6.8% (95% CI=5.3-8.8%), respectively (11). Sunitinib was also associated with a significant increased risk of high-grade hypertension (RR=22.72, 95% CI=4.48-115.29; $p<0.001$) compared to controls (11). Wu *et al*. showed an overall incidence of all-grade and high-grade (grade 3 or 4) hypertension of 23.4% (95% CI=16.0-32.9%) and 5.7% (95% CI=2.5-12.6%), respectively, with sorafinib (12). Sorafinib was associated with a significant increased risk of all-grade hypertension with a RR of 6.11 (95% CI=2.44-15.32; $p<0.001$) compared to controls (12). The risk of all-grade hypertension in patients receiving pazopanib (RR=4.97, 95% CI=3.38-7.30; $p<0.001$) was even higher than for sunitinib (RR=2.20, 95% CI=1.92-2.52; $p<0.001$) and sorafenib (RR=1.99, 95% CI=0.96-1.53; $p<0.001$) (13). The overall incidence of all-grade and high-grade

Table II. *Hypertension grade characteristics adapted by the National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v4.0 available at ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.*

Grade	Description
1	Prehypertension: Systolic BP 120-139 mmHg or diastolic BP 80-90 mmHg
2	Stage 1: Systolic BP 140-159 or diastolic BP 90-99 mmHg or Symptomatic increase in 20 mmHg in diastolic BP or to >140/90 mmHg if previously normal or Requires treatment, monotherapy indicated, recurrent or persistent ≥24 hours
3	Stage 2: Systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg or Requires treatment, more than monotherapy indicated or intensive therapy indicated
4	Evidence of end-organ damage (i.e. malignant hypertension, transient ischemic attack, hypertensive crisis) or Urgent intervention indicated
5	Death

Table III. *Chemotherapy-related cardiac dysfunction. Adapted from Ewer et al. (18).*

Characteristic	Type I myocardial injury	Type II myocardial injury
Chemotherapeutic agent	Anthracycline-based *e.g.* doxorubicin	Targeted therapy *e.g.* trastuzumab
Clinical course	Injury often permanent and irreversible, although may stabilize over time	Reversible with good prognosis
Dose effects	Cumulative	Often not dose-related
Mechanism	Free radial injury and oxidative stress	ERBB2 inhibition
Ultrastructure	Vacuoles, myofibrillar disarray, and necrosis	None
Cardiac echocardiography	Depressed LVEF with global hypokinesis	Depressed LVEF with global hypokinesis
Effect of re-challenge	High probability of recurrent dysfunction	Often safe after re-challenge, more data needed
Effect of late sequential stress	High probability of cardiac dysfunction	Low probability of cardiac dysfunction

hypertension in patients receiving pazopanib were 35.9% (95% CI=31.5-40.6%) and 6.5% (95% CI=5.2-8.0%), respectively (13). Interestingly, the risk of pazopanib-induced high-grade hypertension (grade 4) was similar to that for sorafinib (RR=0.98, 95% CI 0.75-1.30; p=0.90) and sunitinib (RR 0.81, 95% CI=0.62-1.06; p=0.12) (13).

In response to this growing concern, the Investigational Drug Steering Committee of the National Cancer Institute recommends pre-treatment evaluation, screening, and monitoring BP before and during therapy (14). It is also recommended to target BP to <140/90 mmHg for most patients and even lower (<130/90 mmHg) in higher risk patients, *i.e.* those with diabetes, chronic kidney disease, and coronary artery disease (14). Treatment should be initiated when the BP reaches above 140/90 mmHg or a 20 mmHg increase in diastolic BP over baseline (14). Oral anti-hypertensive agents such as verapamil and diltiazem should be avoided when treating patients on TKIs (*e.g.* sorafenib and sunitinib) that undergo cytochrome *P450* metabolism (15). However, optimal BP management has not been clearly defined and remains an ongoing area of research.

Cardiac Dysfunction

Cardiotoxicity resulting in ventricular dysfunction has become increasingly relevant as cancer survivorship vastly improves (16). Anthracylines are well known for causing irreversible, dose-dependent cardiotoxicity, resulting in type I chemotherapy-related cardiac dysfunction (17). Type I chemotherapy-related cardiac dysfunction is myocardial injury characterized by myofibrillar disarray, necrosis, and vacuoles on microscopy (18). Oxidative stress *via* free radical formation is the mechanism proposed for myocardial injury resulting in a decrease in ejection fraction with global hypokinesis (18). In contrast, type II chemotherapy-related cardiac dysfunction has been implicated with molecular-targeted drug agents such as trastuzumab, or agents that target human epidermal growth factor receptor-2 (HER2)

(18). Unlike type I cardiac dysfunction, type II cardiac dysfunction results in no changes on ultrastructure, is not dose-dependent, and is reversible, with a favorable prognosis (18). These characteristics are compared in Table III.

Trastuzumab is one of the most well-known targeted agents associated with cardiotoxicity. It is a monoclonal antibody that selectively inhibits HER2, and is indicated in early and metastatic breast cancer with HER2 expression (19). It is thought to down-regulate HER2 receptor expression, activate complement-mediated tumor cell lysis, and augment chemotherapy-induced cytotoxicity (19, 20). Although the mechanism of cardiotoxicity remains elusive, studies have demonstrated expression of HER2 in human cardiac tissue, with implications for embryonic cardiogenesis and cardiac hypertrophy (19, 21, 22). This was evaluated in animal models by Chien, who demonstrated dilated cardiomyopathy with impaired contractility and relaxation in *erbB*-2 knockout mice (23). However, conflicting evidence that demonstrated no overexpression or gene amplification on cardiac tissue biopsy in patients with depressed left ventricular function previously treated with trastuzumab argues for other possible mechanisms (24).

In a meta-analysis that evaluated over 10,000 patients with HER2-positive breast cancer, Moja *et al*. confirmed a significant increased risk of severe heart failure (2.5% *vs*. 0.4%; RR=5.11, 90% CI=3.00-8.72) and a reduction in left ventricular ejection fraction (LVEF) (RR=1.83, 90% CI=1.36-2.47) in patients treated with trastuzumab *vs*. non-trastuzumab-based adjuvant or neoadjuvant chemotherapy (25). The risk of cardiotoxicity also increases with previous exposure to anthracycline-based chemotherapeutic drugs. In a retrospective cohort study, Bowles *et al*. evaluated over 12,500 women with invasive breast cancer who received no chemotherapy, anthracycline-based chemotherapy, trastuzumab-based therapy without an anthracycline, anthracyline plus trastuzumab, or other chemotherapy and found that there was a high incidence of heart failure/cardiomyopathy among patients who received both trastuzumab plus an anthracycline (cumulative incidence 20.1% at five years) (26). The incidence of heart failure/cardiomyopathy was much lower among women who received non-trastuzumab-containing chemotherapy and women who received other non-anthracycline chemotherapy (cumulative incidence at 5 years of 4.3% and 4.5%, respectively) (26).

Other molecular-targeted therapies that have been implicated with cardiotoxicity are small-molecule TKIs lapatinib, sunitinib, sorafinib, and imatinib. Lapatinib is currently FDA-approved for metastatic breast cancer in combination with capecitabine (27). Lapatinib belongs to the family of small-molecule TKIs that affect both HER2 and epidermal growth factor receptor. In a pooled analysis that evaluated more than 3,500 patients, Perez *et al*. prospectively evaluated the cardiac safety of lapatinib and found treatment with previous anthracyclines, trastuzumab, or neither were associated with 2.2%, 1.7%, and 1.5% incidence of cardiac events, respectively (28). The decline in LVEF was rarely severe, often asymptomatic, and reversible (28). Similar rates were seen in patients who received previous either anthracycline or trastuzumab. (28). Sunitinib, an angiogenesis inhibitor, is associated with increased risk of congestive heart failure (CHF) (29). In a study by Richards *et al*., the overall incidence for all- and high-grade CHF in sunitinib-treated patients was 4.1% (95% CI=1.30-3.50%; $p<0.001$) and 3.30% (95% CI=1.29-8.45; $p=0.01$), respectively (29). The RR of all- and high-grade CHF in sunitinib-treated patients were 1.81 (95% CI=1.3-2.50; $p<0.001$) compared to placebo 3.30 (95% CI=1.29-8.45; $p=0.01$) (29).

Limited data are available for cardiac dysfunction in patients who receive sorafinib. In a small study by Schmidinger *et al*., evaluating 86 patients who were treated with either sunitinib or sorafenib, 33.8% experienced a cardiac event (30). All patients, however, recovered after treatment and were eligible for TKI continuation (30). Imatinib, a well-known TKI use for the treatment of Philadelphia chromosome-positive (BCR–ABL) translocation in chronic myelogenous leukemia has also been reported to cause left ventricular dysfunction (31). In animal models, the mechanism of cardiotoxicity was thought to be alterations and damage to mitochondrial cardiomyocytes by upstream activation of the endoplasmic reticulum response, leading to release of cytochrome c and cellular ATP reduction resulting in apoptosis and cell death (31). However, the overall incidence for systolic dysfunction resulting in symptoms remained relatively low (1.7%) in patients treated with imatinib over a median time of 162 (range=2-2045) days (32). It is unclear what the long-term effects of imatinib on cardiac dysfunction and their overall clinical significance are.

Management for cardiac dysfunction involves pre-treatment evaluation and screening for cardiovascular risk factors that may precipitate potential cardiovascular complications. A baseline multigated acquisition scan scan or transthoracic echocardiogram and electrocardiogram (ECG) should be obtained in select patients to achieve a baseline assessment of LVEF before they receive potential cardiotoxic targeted agents (33). A heightened awareness of depressed LVEF regardless of symptoms should consider cardiology consultation and initiation of treatment with angiotensin-converting enzyme inhibitors/angiotensin receptor blocker, or beta-blocker therapy based on current American Heart Association/American College of Cardiology guidelines (33, 34). Discontinuation of drug treatment should be individualized with a focus on overall risk and benefits of therapy.

QT Prolongation

QT prolongation is a major clinical concern because of its increased risk for ventricular tachyarrhythmias (VT). If not recognized and corrected promptly, QT prolongation has

been associated with torsade de pointes, a deadly polymorphic VT that can lead to sudden cardiac death (35). Because its duration is influenced by heart rate, many mathematical models have incorporated the heart rate as a correction factor that adjusts for the interval (QTc) (36,37). Both intervals been used as clinical markers for increased risk for fatal arrhythmia (38). On a surface ECG, the QT interval correlates to ventricular depolarization and repolarization. A proposed mechanism that interferes with the ventricular repolarization and thus the QT interval is the interruption of the human ether-a-go-go subunit of the delayed rectifier K+ channel (39). This translates to prolongation of the action potential duration of phase 2 to 3 of the action potential (39).

Multiple agents have been associated with QT prolongation, particularly the small-molecule TKIs sunitinib, sorafenib, vendatanib, and crizotinib (3). In prior clinical trials, sunitinib was associated with rare events of QT prolongation (2/387 patients with QTc ≥500 ms) (40). However, the changes in QT interval from placebo compared to baseline-adjusted QTc (ΔΔQTcF) of 9.6 ms (90% CI=4.1-5.1) on day 3 and 15.4 ms (90% CI=8.4-22.4) on day 9 appear to be substantial (40). In addition, sunitinib has also been shown to have a dose-dependent effect on the QT interval (41). It is unclear if this prolongation translates to a clinical significance and even less so with sorafenib (40).

Vendatabnib, a TKI FDA-approved for the treatment of metastatic medullary carcinoma of the thyroid is associated with QT prolongation, torsades de pointes, and sudden death (42). In a meta-analysis by Zang *et al*., the risk of QTc prolongation was evaluated in over 2000 patients who were treated with vandetanib (42). They found that the overall incidence of all-grade QTc prolongation was 16.4% (95% CI=8.1-30.4%) with an increase risk of 5.70 (95% CI=3.09-10.53) in patients being treated for thyroid cancer and 7.26 (95% CI=4.36-12.09) for those treated for non-thyroid cancer (42).

Crizotinib is FDA-approved for the treatment of anaplastic lymphoma kinase-positive non-small cell lung carcinoma (43). However, its association with bradycardia was demonstrated by Ou *et al*. who showed that there was an average decrease of 26.1 beats per minute (bpm) from pre-treatment heart rate (HR) among all patients on crizotinib (44). Patients who were at risk for sinus bradycardia were older (55.8 *vs*. 47.8 years, p=0.0336), had lower pre-treatment HR (mean 77.9 bpm *vs*. 100.6 bpm, p=0.002) and longer duration of treatment (52.9 weeks *vs*. 24.6 weeks, p=0.0250) (44). In addition, other clinical trials have demonstrated an association with significant QT prolongation (4/306 with QTc ≥500 ms and ΔQTc ≥60 ms in 10/289) (40). Its clinically significant cardiotoxicity should be closely monitored in patients with prior prolonged QT intervals and discontinued in patients with an interval prolongation of 500 ms or more (45).

As with all molecular-targeted antineoplastic agents, a pre-treatment surface ECG should be maintained in all patients. A baseline QT interval of 450 ms or greater should alert to the initiation of drug therapy, especially in patients undergoing treatment with vendatanib (46). Because of the numerous medications that have been associated with QT prolongation, a thorough review of medications should be initiated before, during, and after therapy (3). Moreover, electrolytes should be closely monitored and aggressively replaced when appropriate. Ultimately, the QT assessment will be a balance between the perceived risk of cardiotoxicity and the expected therapeutic benefit of drug therapy, with focus on improved quality of life and survival.

Summary

Over the past decade, there has been a major shift from non-specific cytotoxic drugs to molecular-targeted drug therapy. It has become more apparent that these drugs have numerous adverse effects, including cardiotoxicities associated with hypertension, cardiac dysfunction, and QT prolongation. Small-molecule TKIs and other molecular-targeted agents, including monoclonal antibodies, are the primary agents associated with cardiotoxicities and will be the future of chemotherapeutic drug therapy. As more molecular-targeted therapies are developed, early recognition and management of drug-related cardiotoxicity will be extremely important to reduce morbidity and mortality. Pre-treatment evaluation with a surface ECG, echocardiography, cardiac history, and comprehensive review of concomitant medications are the current mainstay of treatment. Careful monitoring of symptoms of heart failure throughout the treatment course with the addition of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or beta-blockers should be considered in patients with depressed left ventricular function. Moreover, a comprehensive review of QT-prolonging agents should be carefully evaluated to prevent fatal ventricular arrhythmias such as torsade de pointes. In conclusion, molecular drug therapy is the future of chemotherapeutic drug therapy. Initiation, maintenance, and discontinuation of treatment should be individualized, with benefits of treatment outweighing the overall risk, in order to optimize patient management.

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