Cardiovascular Toxicity of Molecular Targeted Therapy in Cancer Patients: A Double-Edged Sword

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The annual incidence of cancer has increased over the past 20 years, yet the 5-year relative survival rate for cancer has improved with the increasing availability of advanced therapies, including molecular targeted therapy. Cardiovascular toxicity can develop with this type of targeted therapy, which can cause serious side effects including left ventricular dysfunction, hypertension, hypotension, QT prolongation, thromboembolism, and myocardial ischemia. In many ways, the quality of life primarily depends on the health status of patient cardiopulmonary function. However, risk factor assessment, routine monitoring, and prompt intervention remain the best strategy to deal with these patients with malignancies, to ensure that their cardiopulmonary function is maintained at the highest possible level.

Most previous studies on cardiovascular toxicity have focused on conventional chemotherapy. Molecular targeted therapy is a novel anticancer treatment; however, due to potentially adverse cardiovascular events from this therapy, oncologists and cardiologists need to work together to maximize the benefits. In this review, we focused on target therapy-induced cardiovascular toxicities, in particular cardiac structural, electrophysiological, and vascular effects.

Key Words: Cardiovascular toxicity • Molecular target therapy

INTRODUCTION

Over the past 20 years, there has been a noticeable increase in the annual incidence of cancer. However, the 5-year relative survival rate has also increased from 50% to 68% in all types of cancers, affecting all ethnic groups.[1] Each year, more than a million people are diagnosed with cancer worldwide, and a portion of them will be at risk of treatment-related complications. In contrast to conventional systemic chemotherapy, tyrosine kinase (RTK) or membrane receptor inhibitor monoclonal antibodies that target the intracellular pathways of cancer proliferation or differentiation are thought to be cancer-specific, and cause fewer side effects than chemotherapeutic agents. However, cardiovascular toxicity can develop with this type of molecular targeted therapy (MTT), which can cause serious side effects including left ventricular dysfunction, hypertension, hypotension, QT prolongation, thromboembolism, and myocardial ischemia.[2,3] In this review, we review the current targeted agents with their reported cardiovascular toxicity, focusing on cardiac structural, electrophysiological, and vascular effects.

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PATHOPHYSIOLOGY

The cardiovascular toxicity of MTT results from so-called “on-target” and “off-target” mechanisms.[4] On-target toxicity demonstrates that the target plays a

critical role in tumorigenesis, and also involves hypertrophic responses and survival in cardiomyocytes. For example, a growth factor binds to a RTK, which activates phosphatidylinositol 3-kinase (PI3K), Akt, mammalian target of rapamycin complex 1 (mTORC1), eventually leading to signal intracellular responses of cell growth, protein translation, and angiogenesis. The inhibition of the RTK/PI3K/Akt/mTORC1 pathway, therefore, not only causes cell death in variable types of cancer, but presumably also cardiomyocytes.

Off-target toxicity illustrates that a kinase important to heart survival or function has been unintentionally inhibited. Hasinoff et al. found that among 7 anti-cancer tyrosine kinase inhibitors (TKIs) that they studied, cardiomyocyte damage-related lactate dehydrogenase (LDH) release was correlated to the binding specificity of molecular TKIs.[5] The more specific the TKI, the less damage it caused. Lapatinib, an epidermal growth factor receptor (EGFR)/human epidermal growth factor receptor-2 (HER2) inhibitor, caused non-significant LDH change after 72 hours of treatment at a concentration of 2 micromoles, whereas dasatinib, a multi-target TKI, caused the most LDH change at the same concentration and duration. Kerkela et al. also reported imatinib-treated cardiomyocyte death, which was mediated by endoplasmic reticulum stress response and collapse of mitochondrial membrane potential.[6]

CARDIAC STRUCTURAL EFFECT OF MTT

Left ventricle dysfunction

Those agents that have been most documented to cause cardiotoxicity are anthracycline-like chemotherapeutics such as doxorubicin, daunorubicin and epirubicin. Risk factors have been reported to include cumulative dose, old age, radiation therapy, concomitant chemotherapy, and history of heart disease.[7-11] It is believed that free radical generation resulting from doxorubicin administration causes irreversible subcellular myocardial fibrosis. Trastuzumab, a monoclonal antibody against HER2, has been shown to prolong clinical survival in women with overexpressed HER2 breast cancers.[12] Trastuzumab-related cardiac dysfunction developed in this study group, of whom 27% were given anthracycline, cyclophosphamide, and trastuzumab, 8% were given the same regimen without trastuzumab, 13% were given paclitaxel and trastuzumab, and 1% were given paclitaxel alone. Four of 5 major clinical trials found that the rate of cardiotoxicity in patients receiving trastuzumab as adjuvant therapy ranged from 0.4 to 4.1% compared to 0.06 to 0.8% in patients that did not receive trastuzumab.[13-17] In contrast, Joensuu et al. reported no decrease in left ventricular (LV) ejection fraction (EF) in trastuzumab-treated patients after 36 months of follow-up.[18]

Ewer et al. demonstrated the reversibility of LV dysfunction in patients who received adjuvant trastuzumab after doxorubicin.[19] Twenty-five of 32 patients were re-challenged with trastuzumab, and 88% of them did not have a recurrence of a decreased LV EF. The mean time to recovery of LV function was 1.5 months after discontinuation of therapy, and right ventricular endomyocardial biopsies showed no evidence of typical anthracycline-related ultrastructural changes. On-target toxicity to the HER2 or ErbB2 signaling pathway has been suggested to cause LV dysfunction in animal models.[20-23] Other therapeutic agents reported to have cardiotoxicity to congestive heart failure or LV dysfunction are presented in Table 1.

Risk factors that make trastuzumab-treated patients vulnerable to cardiac dysfunction include concurrent or prior anthracycline exposure, age in excess of 50 years, and baseline LV dysfunction.[24] The diagnosis of heart failure is made by thorough history and physical examinations. The 2005 American College of Cardiology and American Heart Association guidelines for adults with chronic heart failure defined stage A heart failure as those patients at an increased risk of developing cardiac dysfunction.[25] Patients involved in high-risk planning to receive these agents should have their baseline LV function measured, and be followed at regular intervals.

LVEF measurement by multigated radionuclide angiography is regarded as the “gold standard” for monitoring drug-related cardiotoxicity, and a decline in LVEF by more than 10% and an absolute LVEF value of less than 50%, or LVEF value of less than 44% alone, is commonly used as the criteria for drug discontinuation.[26-28] However, this underestimates cardiac damage, and several strategies to early detect subclinical cardiac dysfunction have been proposed. The modalities of LV assessment

Table 1. Cardiotoxicity related to congestive heart failure or LV dysfunction

Compound	Frequency of cardiac dysfunction	Proposed mechanism	Reference
Anthracyclines	+++	Generation of reactive oxygen species by iron-anthracycline complex, leading to mitochondria-related apoptosis	24-26
Mitoxantrone	++		
Cisplatin	++		
Cyclophosphamide (high dose)	++	Direct endothelial injury, resulting in myocardial damage, interstitial hemorrhage, and edema; myocardial ischemia due to microemboli or coronary spasm	27
Mitomycin C	++	Superoxide free radical formation	25
All-trans-retinoic-acid	++		
Bevacizumab	++	Hypertension, inhibition of angiogenesis leading to reduction of myocardial capillary density, cardiac fibrosis and global contractile dysfunction	27
Trastuzumab	++	Block HER2 or ErbB2 signaling pathway, which repairs the oxidative damage caused by anthracyclines	23
Imatinib	+	c-ABL signal inhibition and induced stress response that may be responsible for the mitochondrial damage	6
Sorafenib	+	Mitochondrial damage and cardiomyocyte apoptosis; KIT inhibition, which impairs mobilization of endothelial progenitor cells to the site of myocardial injury	28,29
Sunitinib	+±		

Frequency: +, rare; ++, relatively infrequent; +++, frequent. KIT: stem-cell-factor receptor.

and monitoring for early or late cardiac damage include echocardiography, biochemical cardiac markers, or cardiac magnetic resonance imaging.[29] In particular, myocardial strain and strain rate measured by tissue Doppler imaging and speckle tracking show early significant differences between patients with or without trastuzumab-induced cardiomyopathy with regular follow-up.[30,31] The predictors of an early detection of LV dysfunction include global longitudinal and radial strain, high-sensitivity cardiac troponin I,[32] and systolic annular velocity of the LV lateral wall (S').[26] The onset of these changes developed 3 months after initiation of trastuzumab, whereas the LVEF decreased after 6 months. In contrast, N-terminal B-type natriuretic peptide failed to predict LV dysfunction by either change or absolute level.[26,32]

In 2007, Suter et al. reported cardiac monitoring in trastuzumab-treated patients based on the HERA trial.[15,16,27] To apply the recommendations to all patients receiving trastuzumab, the United Kingdom National Cancer Research Institute reviewed the existing trastuzumab cardiac guidelines, and made recommendations on the basis of the latest published data and expert experiences in 2009 (Figure 1).[33] If the LVEF recovered, re-challenge with trastuzumab could be safely administered in most patients.[19,33] Prevention of chemotherapy-induced cardiomyopathy by enalapril and carvedilol is currently under investigation in a prospective study.[34]

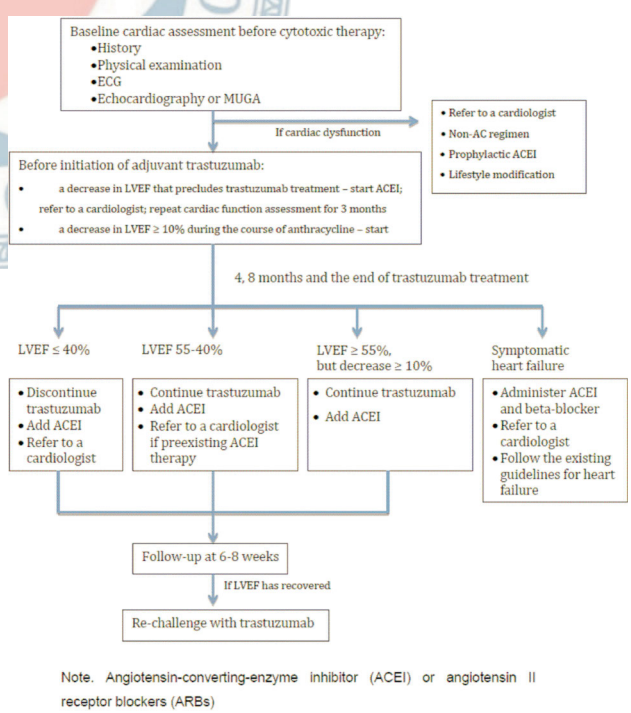

Figure 1. *Management of cardiotoxicity in trastuzumab-treated patients.*

ELECTROPHYSIOLOGICAL EFFECT OF MTT

It is difficult to determine whether arrhythmias are derived from the cancer itself or chemotherapeutic drugs.[37] Most clinical trials have reported arrhythmias to be an adverse drug reaction, not in a controlled fashion. In addition, usually more than one drug is administered in the typical anti-cancer treatment regimen. Specific types of arrhythmia are also hard to differentiate because most arrhythmic events are reported by non-cardiologists.

Cardiac arrhythmia and QT prolongation

The most common drug-associated arrhythmia is asymptomatic sinus bradycardia, which requires no specific treatment. Symptomatic bradycardia prompts drug discontinuation, dose reduction, or pacemaker implantation.[35] Atrial fibrillation is associated with the use of anthracycline, ifosfamide, gemcitabine, melphalan, cisplatin, docetaxel, 5-fluorouracil, and etoposide, or with high doses of corticosteroids.[36]

Anthracycline, taxol, and arsenic are associated with widening of the QRS complex.[37] Doxorubicin was found to have a reversible effect of QRS prolongation in a rat model.[38] Anthracycline-induced cardiomyopathy caused significant QRS prolongation (4.3 ms vs. 3.9 ms in the control group) in the 8th week of administration in a rabbit model.[39] ST-T change, ventricular arrhythmia, and sudden death have been reported in patients receiving 5-fluorouracil (5-FU), which are thought to be complications of myocardial ischemia. Among MTTs, trastuzumab, sunitinib, cetuximab, rituximab, and alemtuzumab are associated with atrial fibrillation (Table 2).[40-44]

QT interval or QTc can be measured to evaluate QT prolongation.[45] It is associated with an increased risk of syncope and sudden death due to ventricular tachyarrhythmia (e.g. Torsades de pointes).[46] Arsenic is well-known to be associated with QT prolongation and is taken by 38.4% of patients, 26.5% of whom develop a QTc of > 500 ms.[47] Risk factors for QT prolongation include electrolyte abnormalities, congenital long QT syndrome, concomitant use of anti-arrhythmic agents, high cumulative anthracycline dose, female gender, old age, bradycardia and a history of myocardial ischemia.[35] The possible mechanism is via blockade of the rapid component of delayed rectifier potassium current (I_{Kr}) or the slow component of the potassium current (I_{Ks}) and activation of the adenosine triphosphate-sensitive potassium current (I_{KATP}).[37]

Most arrhythmic effects are reversible after discontinuation of the causative agents. Routine monitoring of cardiac rhythm is indicated in high-risk patients, and in those patients using antiemetic agents or antidepressants that prolong QT interval. Interruption of the treatment course and a shift to a new drug may be considered if significant arrhythmia develops.

VASCULAR EFFECT OF MTT

Hypertension

Hypertension is the most common comorbidity reported in cancer registries, and is associated with agents that block the vascular endothelial growth factor (VEGF) – VEGF receptor pathway.[36] Proposed mechanisms include a decrease in nitric oxide (NO) synthesis in the walls of arterioles resulting from a lack of VEGF stimulation, vascular rarefaction (a functional decrease in the number of arterioles and capillaries) causing increased peripheral vascular resistance, and hypertension secondary to nephrotoxicity.[48] Table 3 lists the agents that have been reported to frequently cause hypertension.[3,49,50]

The risk of cardiovascular mortality doubles with each 20/10 mmHg blood pressure increment.[51] In 2010, the Taiwan Society of Cardiology reported guidelines for the management of hypertension,[52] and suggested that lifestyle changes should be encouraged in all patients and included the following six items: S-ABCDE (Salt re-

Table 2. Cardiotoxicity related to arrhythmia

Compound	Frequency of cardiac arrhythmia	Reference
Trastuzumab	+	41
Sunitinib	++	40
Rituximab	+	44
Cetuximab	+	43
Alemtuzumab	+	42
	Frequency of QT prolongation	
Arsenic trioxide	++++	45
Sorafenib	++	3
Sunitinib	++	3

Frequency: +, rare; ++, relatively infrequent; +++, frequent; ++++, very frequent.

Table 3. Cardiotoxicity related to hypertension

Compound	Frequency of hypertension	Reference
Bevacizumab	+++	49
Sunitinib	+++	50
Sorafenib	+++	64
Cisplatin	++	3
Alemtuzumab	++	3

Frequency: +, rare; ++, relatively infrequent; +++, frequent.

Table 4. Cardiotoxicity related to hypotension[3]

Compound	Frequency of hypotension
Alemtuzumab	+++
Rituximab	++
Cetuximab	+
Interleukin-2	++++
All-trans-retinoic acid	++

Frequency: ++, relatively infrequent; +++, frequent; ++++, very frequent.

striction, Alcohol limitation, Body weight reduction, Cessation of smoking, Diet adaptation, Exercise adoption). When pharmacological management is indicated, physicians should consider the principle of "PROCEED" (Previous experience of the patient, Risk factors, Organ damage, Contraindication or unfavorable conditions, Expert or doctor judgment, Expense or cost, Delivery and compliance) to decide the optimal treatment. Angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin II receptor blockers (ARBs) may be the first line drug of choice because angiotensin II-IV have proangiogenic effects in tumor tissue and upregulate VEGF.[53] Without compelling indication, ACEI or ARB + calcium channel blockers or ACEI or ARB + diuretics are reasonable choices for combination therapy.

Hypotension

The anticancer agents that cause hypotension, anaphylactic shock and even death are involved in allergic hypersensitivity reactions (Table 4).[3] Premedication, fluid supply, or lowering the rate of drug infusion can usually prevent adverse reactions. If hemodynamic compromise develops, airway protection, vasopressor administration, and blood pressure monitoring are warranted.

Thromboembolism

Bevacizumab is associated with an increased incidence of arterial and venous thromboembolism.[54,55] VEGF is critical in maintaining vascular integrity, and blockade of the VEGF signaling pathway leads to apoptosis of endothelial cells and compromise of the intercellular junction.[56] Exposure to the underlying prothrombotic factors activates both primary and secondary hemostatic cascades. In addition, anti-VEGF therapy also interferes with the production of platelet inhibitors such as prostaglandin I-2 and NO.[57]

Several biomarkers (D-dimer, soluble P-selectin, coagulation factor VIII, inflammation markers, and thrombin generation) have been investigated with regards to their capacity to predict primary or recurrent venous thromboembolism, facilitate diagnosis, and assist in clinical management.[58] D-dimer has been found to have a sensitivity of 95% and a negative predictive value of almost 100%. The 2007 guidelines from the American Society of Clinical Oncology, the 2007 clinical practice guidelines of the American College of Physicians and the American Academy of Family Physicians, the 2008 National Comprehensive Cancer Network (NCCN) guidelines, and the 2008 American College of Chest Physicians (ACCP) guidelines favor low-molecular-weight-heparin over oral anticoagulants in patients with malignancy and venous thromboembolism.[59-61]

Myocardial ischemia

5-FU has been reported to be associated with myocardial ischemia based on typical chest pain, response to nitrate, and electrocardiographic ischemic change; however, normal coronary arteries are found angiographically.[62,63] Mosseri et al. demonstrated that protein kinase C-mediated vasoconstriction of smooth muscles, in vitro, plays an important role in myocardial ischemia.[64] Typically, myocardial ischemia develops within 2 to 5 days of starting therapy, and lasts for up to 48 hours. High doses and continuous infusion of 5-FU have been reported to be risk factors.[35] Furthermore, recurrent ischemia has been reported to develop after re-challenge of the drug.[3]

Sorafenib has been reported to have an ischemic cardiotoxicity of 3% in patients with metastatic renal cell carcinoma.[65,66] Disrupted angiogenesis responses to pressure overload and hypertension resulting from VEGF signaling blockade are believed to be partly re-

sponsible.[53,66] Patients usually tolerate the re-challenge of sorafenib with the use of cardiovascular medication.[66] Carvedilol and simvastatin may have beneficial effects in such patients because of antioxidant properties and cardiomyocyte protection by NO synthase activation and mitochondrial ATP-sensitive potassium channels, respectively.

The standard treatment for ischemia should be used, including antiplatelet agents, beta-blockers, calcium channel blockers, and nitrates.[67,68] Anticoagulation or thrombolytic therapy is contraindicated in patients with brain metastasis or thrombocytopenia. Percutaneous coronary intervention or coronary artery bypass surgery should be considered if there are indications. However, both the benefits and risks of coronary vascular stents should be considered due to long-term dual antiplatelet therapy over anticancer treatment.[69] Risk factor modification, such as hyperlipidemia, diabetes mellitus, smoking, obesity, hypertension, and physical inactivity are important.

Fluid retention: edema, pleural and pericardial effusion

Patients treated with imatinib or dasatinib have occasionally been reported to experience edema, pleural and pericardial effusion.[6,70,71] The mechanism involves platelet-derived growth factor receptor (PDGFR) and Src kinase.[72] The PDGFR pathway has an effect on interstitial fluid pressure and vascular permeability, and its inhibition results in changes in intratumoral interstitial pressure and fluid homeostasis. Vascular permeability mediated by VEGF is directly dependent on Src. In addition, Src regulates focal intercellular junctions, which may maintain the stability of the pleural epithelium.

Asymptomatic pericardial effusion can be observed clinically without withholding the drug. Symptomatic patients require transient cessation of the drugs, and the use of short-term steroid treatment.[71] Pericardiocentesis, chemical pleurodesis, or pleuroperitoneal shunts are indicated in severely symptomatic patients.

Precapillary pulmonary arterial hypertension

The French pulmonary hypertension registry reported 9 incident cases who were treated with dasatinib at the time of pulmonary hypertension diagnosis.[73] Hemodynamic studies showed an elevated mean pulmonary artery pressure with a normal pulmonary capillary wedge pressure, suggestive of group 1 pulmonary hypertension. Dasatinib, a potent inhibitor of RTK, may induce pulmonary hypertension through blockade of Src tyrosine kinase, which is believed to play a critical role in vascular homeostasis, smooth muscle cell proliferation, and vasoconstriction.

Some studies have reported that pulmonary hypertension is a late complication of dasatinib therapy, occurring after 8 to 48 months of exposure.[74-78] Clinical improvement was generally observed after the withdrawal of dasatinib, although some patients were still symptomatic and had persistent hemodynamic impairment several months after discontinuation. Regular echocardiographic monitoring before and after the use of dasatinib is warranted, and right heart catheterization is indicated in patients who develop symptoms and signs of right heart failure.

CONCLUSIONS

The survival of patients with cancers has been significantly prolonged in the era of MTT (in addition to conventional systemic chemotherapy), however it may be accompanied by unintended cardiovascular toxicity. In general, the patients' quality of life mainly depends on cardiopulmonary function. Risk factor assessment, routine monitoring, and prompt intervention remain the best strategies to address these patients with malignancies. Molecular targeted therapy is a powerful but potentially harmful tool, and both oncologists and cardiologists need to work together to maximize the beneficial effects.

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