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Review Article

Recent Advances on the Molecular Mechanism and Prevention of Cardiotoxicity Induced in Targeted Cancer Therapy

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Abstract

First proposed in 2000, cardio-oncology bears the mission to reduce cardiotoxicity whilst successfully treating cancer. Through two decades of development, substantial progress had been made in determining the specific clinical symptoms, mechanism of action, ways of monitoring, and toxicity reduction of the cardiotoxicity induced by cancer-related treatment. By summarizing the progress in cardiotoxicity induced by targeted cancer therapy in the past two decades, this mini-review aims to give some enlightenment on the fundamental research of cardio-oncology.

Keywords: Cancer treatment; Cardiotoxicity; Mechanism of action; Way of monitoring; Prevention strategy

Abbreviations

ABL: Abelson; Ang II: Angiotensin II; APC: Antigen Presenting Cells; ASK1: Apoptosis Signal-Regulating Kinase 1; ATP: Adenine Triphosphate; Bcl-2: B-Cell Lymphoma-2; BNP: Brain Natriuretic Peptide; CTLA-4: Cytotoxic T Lymphocyte-Associated Antigen-4; eNOS: Endothelial Nitric Oxide Synthase; ESC: European Society of Cardiology; HER-2: Human Epidermal Growth Factor Receptor-2; HER-4: Human Epidermal Growth Factor Receptor-4; Iodine 123-mIBG: *meta*-Iodobenzyl Guanidine; IRE-1: Inositol-Requiring Enzyme-1; JNK: c-Jun N-Terminal Kinase; LVD: Left Ventricular Dysfunction; LVEF: Left Ventricular Ejection Fraction; MRI: Magnetic Resonance Imaging; NO: Nitric Oxide; NRG-1: Neuregulin-1; NT-pro BNP: N-terminal pro-Brain Natriuretic Peptide; PDGF: Platelet-Derived Growth Factor; PD-L1: Programmed Cell Death 1 Ligand 1; PGI_2: Prostaglandin I; PP2A: Protein Phosphatase 2 A; ROS: Reactive Oxygen Species; TKI: Tyrosine Kinase Inhibitor; Tn: Troponin; UCG: Ultrasonic Cardiogram; VEGF: Vascular Endothelial Growth Factor

Introduction

Cancer has always been a major obstacle on the road to human health, and in addition to surgery, chemotherapy, and radiation therapy, novel treatment methods have emerged, such as molecular targeted drug therapy, immunotherapy and so on. Thanks to these diverse treatments, cancer patients are surviving and the survival rates increase steadily. Relatively, however, surviving cancer patients are almost accompanied by heart disease.

As cardiotoxicity induced by cancer-related treatment is gaining more attention, the oncology and cardiology, as two traditionally separate disciplines, gradually integrate into one emerging science in clinical practice. More interestingly, this novel science field has been named as cardio-oncology [1,2], which takes the cardiovascular diseases of patients suffering from malignant tumors, undergoing anti-cancer treatment, or having history of cancer as the research subjects [3]. Not limited to identification and detection of cancer treatment-related cardiovascular diseases, cardio-oncology also sets out to classify patients undergoing anti-cancer treatment as per their risks, to diagnose and deal with the resulting cardiotoxicity, and to trace both short-term or long-term cardiac symptoms during or after cancer treatment [1,3]. The ultimate goal of cardio-oncology is to protect the heart while treating cancer [4].

As revealed by ESC proposal concerning anticancer treatment and cardiotoxicity in 2016, the cardiotoxicity related to anticancer treatment can be divided into nine categories: cardiac insufficiency, arrhythmia, heart valve disease, coronary artery disease, thrombosis, hypertension, pulmonary arterial hypertension, peripheral vascular diseases and stroke, and other cardiovascular complications [5]. The cardiotoxicity of anticancer treatment means other cardiovascular diseases, which are induced in interfering with or removing the cancer

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cells in patients' bodies. Given the increasing cancer survival rate, the studies on cardiotoxicity induced by cancer-related treatment turn to be more and more important. Cancer and cardiovascular diseases share some common risk factors (*e.g.*, age, smoking, alcohol, obesity, sedentariness, diabetes and hypertension), so most cancer patients have clinical or subclinical heart diseases when receiving cancer diagnosis and treatment. Consequently, the therapies containing chemotherapeutic drugs and targeted drugs usually have to be suspended and the patients canonly settle for other suboptimal schemes [6].

Cardio-oncology has made a lot of research progress in the relationship between cancer and heart disease in past two decades. Many scholars have summarized the underlying cardiotoxicity of targeted cancertherapy,but most of them focus on the clinical perspective, and there is a lack of discussion on the specific mechanism of cardiotoxicity induced by targeted drugs. This mini-review places special emphasis on the mechanism of cardiotoxicity and discuss the methods of preventing cardiotoxicity and is hoped that it could shed light on the clinical treatment of cancer and the prevention of cardiotoxicity.

Mechanism of Cardiotoxicity Induced by Targeted Drugs

Targeted drugs underwent a development by leaps and bounds during the last decade. Exerting treatment on specific targeted sites, targeted agents are theoretically safer than traditional chemotherapies. Nevertheless, present clinical practice indicates targeted agents are also perplexed by extensive cardiotoxicity (Table 1). The following is a summary of the mechanism of cardiotoxicity induced by targeted drugs (Figure 1).

Monoclonal antibody can inhibit HER-2 signal transduction pathway to downregulate Bcl-xl, which leads to the decrease of

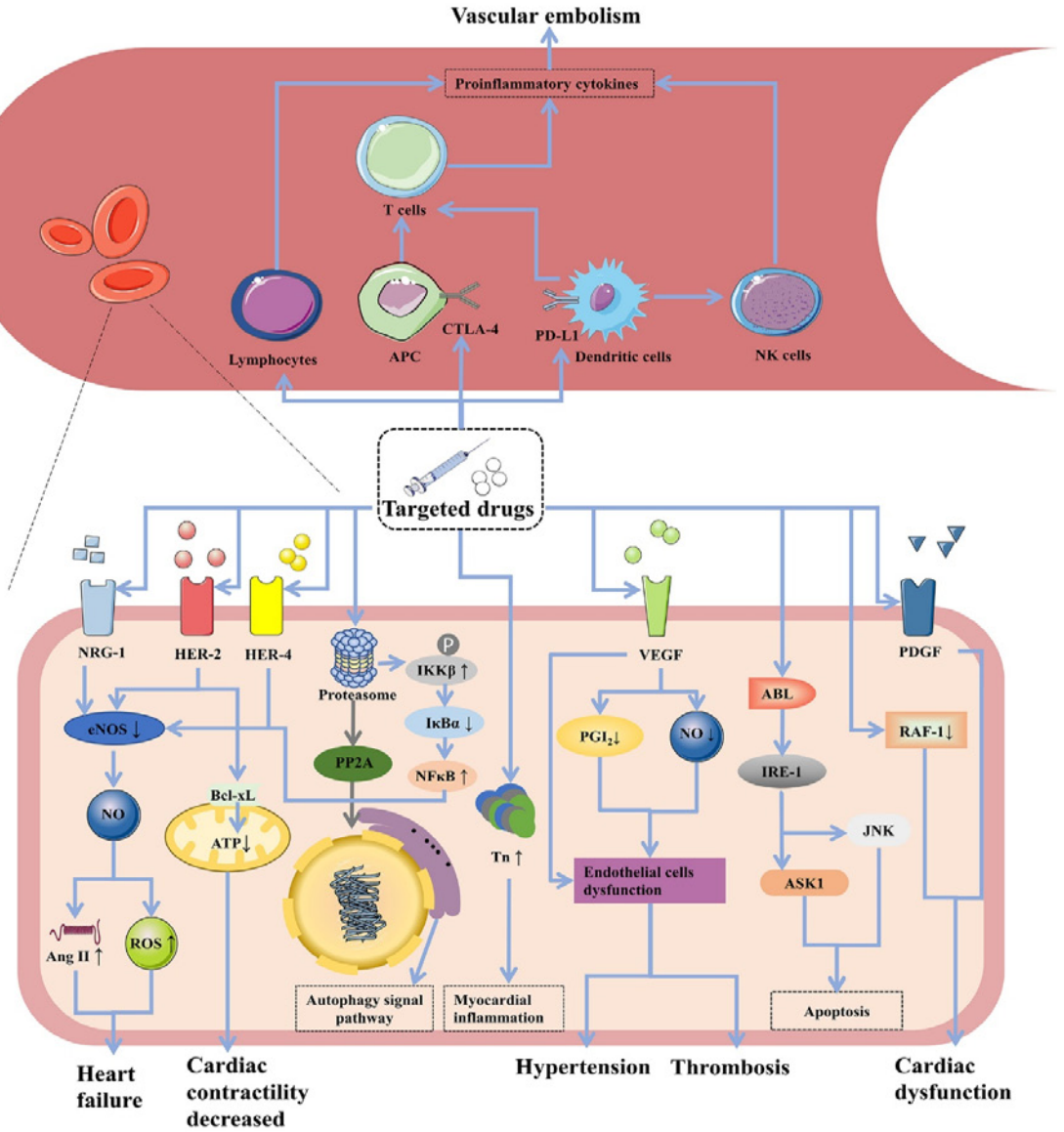

Figure 1: Mechanism of cardiotoxicity caused by targeted drugs.

membrane potential of mitochondrial andcause dysfunction, also consume adenosine triphosphate to cut down the presence of effective ATP, leading to the decrease in the contractility of heart [7]. As reported, monoclonal antibody can also interfere with NRG-1 and HER-2 or HER-4 in cardiomyocytes, which will reduce the expression of eNOS and block the biological function of NO, then, facilitate the generation of Ang II and ROS, and cause cardiac cell injury and eventually heart failure [8,9]. Monoclonal antibody can also inhibit VEGF and lead to the decrease of endothelial cells activity, eventually resulting in platelet aggregation and thrombosis [10-12].

TKI can directly act on endothelial cells, and thus cause endothelial dysfunction and damage, induce higher level of vascular oxidative stress, and inhibit endothelial cell proliferation [9]. TKI can inhibit the signal pathway of VEGF, reduce the production of NO and PGI_2 by vascular endothelial cells, decrease vascular permeability and vasodilation, increase blood flow, and finally lead to hypertension [13]. As reported, TKI also can inhibit PDGF and the activity of RAF-1, cause systemic vasoconstriction, which directly cause mitochondrial damage and cardiomyocyte apoptosis, result in cardiac dysfunction [14-16]. In addition, they can also suppress ABL and activate the endoplasmic reticulum stress response through IRE-1 which could activate apoptotic signals ASK1 and JNK, raise the release of cytochrome C and synchronically inhibit the generation of apoptotic gene Bcl-2. Consequently, mitochondrial dysfunction and cell death are caused [17].

Proteasome inhibitor can inhibit proteasome as the name indicates, cause higher level of IKKβ-dependent phosphorylation and down regulated expression of I-κBα, also activate PP2A and inactivate downstream autophagy signal pathway and destroy intracellular homeostasis [18]. Besides, proteasome inhibitor can activate NF-κβ, promote expression of eNOS uncoupling protein and generation of more ROS. At the same time, by changing the activity of protein and suppressing protein circulation, proteasome inhibitor can cause gathering of ubiquitinated protein to form aggregates of high-order protein, mitochondrial dysfunction, and higher level of endoplasmic reticulum's oxidative stress, and further undermine the cardiac muscle cells [19,20].

Autoantibody against myocardial surface proteins by immune checkpoint inhibitor causes an overall increase in Tn level and directly exerts the cytotoxic effect, leads to lymphocyte infiltration, and finally results in myocardial inflammation and deterioration of cardiac function [21]. These agents can cause the deficiency of CTLA-4 in APC which can destroy immune homeostasis, and lead to spontaneous activation of T cells, increase inflammatory response, and seriously damage myocardium [22]. Immune checkpoint inhibitor can reduce the expression of PD-L1 in vascular dendritic cells, uncontrollably activate T cells and natural killer cells, release massive of proinflammatory cytokines, activate related inflammation, and may affect atherosclerotic coronary artery plaques, trigger fibrous cap rupture, destroy blood vessel walls, and eventually lead to vascular occlusion [23].

Ways of Monitoring Cardiotoxicity

Heart is an important organ for the human body. Since anticancer treatment might impair heart, adverse event of cardiotoxicity should be detected as soon as possible so as to take heart protection strategy, to lower down morbidity and mortality of CVDs, and to prevent an interruption of compulsory anticancer treatment [24,25]. By far, only a few methods have been developed for assessing the cardiac damage arising from anticancer treatment, including imaging diagnosis, biomarkers, nuclear cardiological approaches, and genetic risk analysis.

Early detection of cardiac muscle tissue, impaired myocardial blood flow, involvement of heart and pericardium, and thrombogenesis has been successfully realized by using UCG strain imaging as well as conventional cardiac MRI [26]. The two methods appear quite sensitive to the changes in LVEF which is considered as a basis for diagnosing cardiac dysfunction. Generally speaking, when LVEF drops by over 10% to an absolute value of lower than 50%, a cardiotoxicity event will be assumed [26].

Cardiac troponins I and T in plasma are two established markers for determining acute and chronic myocardial damage [27]. An increase of troponins in serum indicates the risk of cardiac toxicity rises. Similarly, BNP and NT-pro BNP in serum are also recognized as two common indicators for cardiac failure [28], as they can be used to evaluate myocardial load/stretching.

Nuclear cardiology remains highly sensitive to LVD. Indium 111-antimyosin is a specific marker of myocyte necrosis uptake which is negatively related to LVEF; while iodine 123-mIBG can manifest the distribution of sympathetic nerves [26].

Genetic risk analysis can be used to partly reveal the heterogeneity of cardiotoxicity induced by anticancer schemes. For example, carbonyl reductase 3G allele can detect the probability of post-cancer treatment cardiomyopathy among children [29]. Modern detection and analysis results like single nucleotide polymorphism [30] can assist genetic risk analysis in cardiotoxicity monitoring. Now Genetic risk analysis is not mature yet and demands further research work.

Ways of Preventing or Reducing Cardiotoxicity

By far, researchers have offered several approaches for relieving cardiotoxicity, including dose restriction, applying lipid formulation, dexrazoxane, and neurohormone antagonist, and these approaches have achieved certain effects in clinical practice.

Dosageand rate: Keep in mind that the dose of the drugs used during treatment should not be too high, and the flow rate of drip should not be too fast.

Neurohormone antagonists: β receptor inhibitors can reduce the generation of intracellular free radicals, some of which will also serve to resist oxidation and dilate the vessels [31]. Angiotensin converting enzyme inhibitor and angiotensin receptor blocker may reduce the occurrence of oxidative stress, regulate calcium ion concentration, and improve mitochondrial functions within the cells [32]. As reported, angiotensin converting enzyme inhibitor, β receptor inhibitor and angiotensin receptor blocker can resist cardiotoxicity [33-35] and effectively cope with reduced LVEF or cardiomyopathy without cardiac failure syndrome [36].

Statins: Occasional use of statins can lower down the occurrence

Table 1: Targeted drugs-related to cardiotoxicity.

Targeted Drugs	Examples	Type of clinical cancer therapy	Cardiotoxicity	Risks
Monoclonal antibody	Abciximab, Adalimumab, Alefacept, Alemtuzumab, Basiliximab, Belimumab, Bevacizumab, Bezlotoxumab, Cetuximab, Canakinumab, Cetuximab, Nimotuzumab, Trastuzumab, Pertuzumab, Ramoruximab, Rituximab	Breast cancer, Cervical cancer, Ovarian cancer, Gastric cancer, Kidney cancer, Lung cancer, Colon cancer, Rectal cancer, Squamous cell carcinoma, Head and neck neoplasm, Glioblastoma, Sarcoma, Leukemia, Stem cell transplantation	Arrhythmia, Cardiomyopathy, Hypertension, Heart failure, Left ventricular dysfunction, Thromboembolism	**1.**Underlying medical conditions: coronary heart disease, arrhythmia, cardiomyopathy, hypertension, thromboembolism, myositis, myasthenia gravis, hepatitis, thymoma, obesity, diabetes, hyperlipemia, high or low body mass index, smoking, drinking, electrolyte disturbance, hyperpyrexia and advanced cachexia. **2.** Female patient. **3.** Age: aged below 5 or over 65. **4.** Combined therapy: combined with chemotherapeutic drugs. **5.** Left ventricular ejection fraction decreased. **6.** Dosage: too high dose. **7.** Rate: rapid infusion rate. **8**. Before treatment: previous drug exposure, previous chest radiotherapy.
Tyrosine kinase inhibitor	Apatinib, Axitinib, Cediranib, Dasatinib, Imatinib, Lapatinib, Nilotinib, Sunitinib, Sorafenib, Pazopanib, Ponatinib, Regorafenib, Trametinib, Vandetanib	Acute Lymphoblastic Leukemia, Chronic Eosinophilic Leukemia, Colorectal cancer, Dermatofibrosarcoma Protuberans, Gastrointestinal Stromal Tumor, Leukemia, Liver cancer, Myelogenous leukemia, Renal cell carcinoma, Sarcoma, Thyroid cancer	Arrhythmia, Heart failure, Hypertension, Ischemic heart disease, Left ventricular insufficiency, Prolonged QT interval, Thromboembolism	
Proteasome inhibitor	Bortezomib, Carfilzomib, Ixazomib	Multiple myeloma, Lymphoma, Mantle Cell Lymphoma	Arrhythmias, Cardiac death, Cardiomyopathy, Hypertension, Heart failure, Ischemic heart disease, Pulmonary hypertension, Thrombotic events	
Immune checkpoint inhibitor	Atezolizumab, Camrelizumab, Duvalizumab, Ipilimumab, Nivolumab, Pembrolizumab, Sintilimab, Tislelizumab	Breast cancer, Bladder cancer, Cervical cancer, Colorectal cancer, Head and neck cancer, Liver cancer, Lung cancer, Hodgkin's lymphoma, Melanoma, Non-small cell lung cancer, Prostate cancer, Renal cell carcinoma, Rectal cancer, Skin cancer, Stomach cancer,	Arrhythmia, Angina pectoris, Acute coronary syndrome, Cardiogenic shock, Cardiac arrest, Heart failure, Left ventricular dysfunction, Myocarditis, Pericardial disease	

of heart failure [37] and prevent thrombosis [38]. Furthermore, they can also relieve intracellular oxidative stress and improve endothelial function [39,40].

Aerobic exercise: aerobic exercise can protect the heart for most people. However, its heart-protecting mechanism for cancer patients is still in doubted [32]. Some reports assume that exercise might reduce drug level within cells as well as generation of apoptotic signals and ROS, and thus protect the heart [41,42]. Improving traditional risk factors and doing aerobic exercise might help to prevent the onset of cardiotoxicity [43].

Discussion

At present, UCG, MRI, biomarker detection, nuclear cardiology and genetic risk analysis are available to monitor cardiotoxicity when patients treated with cancer are detected to have cardiovascular disease. We can prevent or reduce the occurrence of the disease by reducing the adding neurohormone antagonists, using statins, and allowing patients to do aerobic exercise. However, each patient has different potential risk factors, these methods are relative and patients need to be monitored and analyzed specific symptoms.

Targeted drugs excel in treating cancers. When combined with chemotherapeutic or radiotherapeutic regimes, they can not only yield better efficacy but also solve the problem of drug resistance. As more cancers are discovered, the combined anticancer therapies (such as targeted +chemotherapy and targeted + radiotherapy) are increasingly applied to clinical practice, with better effects than single therapy. Unfortunately, a harmful side effect arises from those efficient anticancer therapies—cardiotoxicity, which should never be overlooked. Clinical reports of cardiotoxicity are not so common, and no consensus has been reached about the primary mechanism underlying the cardiotoxicity. Thus, we are expected to explore the acting mechanism of cardiotoxicity arising from combined therapies and determine corresponding pathway or target spot so as to provide basis for precision treatment of cardiovascular diseases among cancer patients.

The probability of cardiotoxicity among cancer survivors is affected by several risk factors. Though this paper has summarized factors frequently reported, there are still many unknown risk factors, especially personal factors concerning genetic gene polymorphism. Patients vary in potential risk factors, thus a comprehensive monitoring and understanding needs to be established for each patient to determine counterstrategies case by case. We think that customized drug therapy should be the best and most comprehensive approach for cancer patients. However, the problem is application of customized drug therapy also requires a thorough understanding of drug-metabolizing enzymes, targeted gene of specific drug, and detection of critical genes. Is there a relationship between the cardiotoxicity induced by targeted drugs and metabolic enzyme gene regulation? This is another issue that we need to pay attention to. There are limited studies examining the gene detection and anticancer-related cardiotoxicity. Compared with imaging and biomarkers which are already quite mature, this field is still emerging. Therefore, in the future, it is quite promising to enhance gene detection to present the probability of adverse events and find corresponding therapies from gene detection results.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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