

Progress in prevention and treatment of myocardial injury induced by cancer therapy

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Abstract

Objective: This article aims to present a brief profile of the advances in prevention and treatment of myocardial injury in cancer therapy based on relevant literature or reports.

Data sources: The data cited in this review were obtained from articles indexed in PubMed and China National Knowledge Internet (CNKI) up to June 2019.

Study selection: Articles were selected with the following keywords “Anti-cancer therapy,” “Myocardial injury,” “Breast cancer,” “Echocardiography,” and “Chemotherapy.”

Results: Due to the rapid development of novel cancer therapeutic approaches, the life expectancy of tumor patients has been prolonged continuously. Meanwhile, a large number of studies have found that among patients benefiting from precise management, some medications have exerted direct or indirect side effects on the cardiovascular system, leading to the occurrence of myocardial injury. Because there are many common risk factors between breast cancer and cardiovascular disease, and there is a special anatomical position between breast and heart, the cardiology related to breast cancer patients is relatively unique in onco-cardiology.

Conclusions: Heart function monitoring is critical during anti-cancer therapy so that we can early identify cardiac abnormalities and actively adopt measures to prevent myocardial injury.

Keywords: Myocardial injury; Anti-cancer therapy; Tumor

Introduction

Due to the rapid development of oncotherapy methods, such as surgery, radiotherapy, chemotherapy, targeted therapy, endocrine therapy, and immune therapy, the life expectancy of patients with cancer has been prolonged continuously. Meanwhile, a large number of studies have found that among patients benefiting from cancer therapy, these therapeutic methods have exerted direct or indirect side effects on the cardiovascular system, leading to the occurrence of many types of cardiovascular side effects. Cardiovascular side effects induced by cancer therapy include aggravation of original heart-related disease, occurrence of potential heart-related disease among high-risk patients, and heart diseases caused by the direct damage to the structure and function of heart. The intention of the establishment and development of cardio-oncology is to reduce the mortality associated with cardiovascular disease caused by cancer therapy while maximizing the benefit of the cancer therapy itself.

Additionally, cardio-oncology aims to prolong the life expectancy of tumor patients and improve their life qualities.

Currently, breast cancer has become the most common malignant tumor among females. Because there are many common risk factors between breast cancer and cardiovascular disease, and there is a special anatomical position between breast and heart, the cardiology related to breast cancer patients is relatively unique in onco-cardiology. Therefore, heart function monitoring is critical during anti-cancer therapy so that we can early identify cardiac abnormalities and adopt measures to deal with myocardial injury actively. This article aims to present a brief profile of the advances in prevention and treatment of myocardial injury in cancer therapy based on relevant literatures or reports.

Malignant tumor and cardiovascular disease

Currently, malignant tumor and cardiovascular disease are the two leading causes of death worldwide. A multicenter,

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retrospective study on the death spectrum among elderly inpatients during the past 10 years shows that the number of patients with malignant tumor and hypertension has been rapidly increasing in recent years.^[1] Moreover, refractory hypertension can cause cardiovascular and cerebrovascular diseases through the mechanism of target-organ impairment and atherosclerosis promotion.^[1] The relationship between malignant tumor and cardiovascular disease is multifaceted and complex. A lot of common risk factors between malignant tumors and heart disease are found: (1) Diabetes mellitus is one of the major risk factors of cardiovascular disease. In addition, diabetes mellitus has an impact on breast cancer. For instance, among patients with type II diabetes, insulin resistance promotes the release of estrogen and testosterone. These steroids may explain why diabetes is a risk factor of breast cancer. (2) Post-menopausal females are more likely to develop obesity and hyperlipidemia. In addition, hyperlipidemia, especially the elevated level of low-density lipoprotein, is another explicit risk factor of atherosclerosis. (3) Genetically, mutation in *BCRA1* and/or *BCRA2* among patients with breast cancer is also an important risk factor, but original *BCRA* genes are related to the protection of cardiac function. Therefore, abnormalities in these genes may increase the organism susceptibility to cardiovascular injury.^[2] Meanwhile, chronic inflammation, oxidative stress, smoking, unhealthy diet, and lack of physical exercise are also common risk factors of cancer and cardiovascular disease. At the same time, the occurrence of heart-related disease also affects or limits the application of anti-tumor drugs and treatment approaches. Therefore, oncocardiology refers to diagnosis stratification, prevention and therapy of malignant tumor aiming at a series of risk factors of cardiovascular disease throughout a patient's lifetime. Oncocardiology involves all aspects of tertiary prevention of cardiovascular disease among malignant tumor patients, including screening and early intervention in order to maximize the protective effects on cardiac function.

Cardiovascular diseases induced by cancer therapy include aggravation of original heart-related diseases, occurrence of potential heart-related diseases among high-risk patients, and heart diseases caused by the direct damage to the structure and function of heart. For breast cancer, many early stage cases are already at risk of cardiovascular disease before diagnosis, which increases the risk of cardiovascular injury during relevant adjuvant therapy. A retrospective cohort study of breast cancer and cardio-cerebrovascular diseases among elderly females in the United States showed that patients with breast cancer had a significantly increased risk of cardiovascular disease compared with the general population and that cardiovascular disease was the leading cause of death in patients with early stage post-menopausal breast cancer.^[3]

Radiotherapy is a common therapeutic method. When applying radiotherapy to malignant tumors in the breast region, such as breast cancer and esophageal cancer, cardiotoxicity can be caused by high dose of radiation. The radiation dose to the heart depends on the radiologic technique, laterality, beam energy, and total dose used for radiotherapy.^[4] Radiation-induced heart disease includes

a series of cardiovascular complications, ranging from subclinical microscopic changes to symptomatic heart diseases, such as conduction abnormalities, coronary heart disease, myocarditis, pericarditis, pericardial effusion, cardiac valve injury, and endocardial injury.^[5] Radiotherapy is commonly used as an adjuvant therapy after conservative or radical breast surgery. Due to the different anatomical locations of left and right breast cancer and the different radiologic techniques adopted, the irradiated volume of the heart is different. The different irradiated volume of heart ultimately leads to differences in the morbidity of heart-related diseases. A large number of studies have indicated that the average dose of radiation received by the hearts of patients with left breast cancer is significantly higher than that of those with cancer on the right side. The results of echocardiography showed that significant differences in LVEF before and after a year of radiotherapy only exist in patients with left breast cancer.^[6] For patients with left-sided breast cancer, radiotherapy technique plays an important role in the total cardiac radiation dose. Multi-field intensity-modulated radiotherapy (IMRT) may be the most suitable approach for patients with left-side breast cancer after mastectomy, and in patients receiving post-breast-conserving surgery irradiation, volumetric modulated arc therapy offers certain dosimetric advantages over fixed-field IMRT plans.^[7]

Cardiotoxicity of chemotherapy

Currently, European and American onco-cardiologists tend to sort cardiotoxicity related to chemotherapy into two categories: Type I and Type II^[8] [Figure 1]. It is generally recognized that Type I cardiotoxicity can lead to permanent and irreversible damage to myocardium. The dose-dependent changes in myocardial ultrastructure include obvious vacuolar degeneration, myofibrillar disarray, myocardial necrosis, and fibrosis, which may lead to progressive cardiac dysfunction in the long term. This type of cardiotoxicity is mainly caused by anthracyclines. In contrast, Type II cardiotoxicity is reversible and non-dose-dependent. Moreover, ultrastructural changes, such as cell necrosis, have not been observed. Type II cardiotoxicity is primarily induced by molecular-targeted therapeutic drugs.^[9] The common risk factors involved in this type include dose and administration frequency of chemotherapy drugs, patient age, female gender, hypertension or other complications, pre-existing cardiovascular disease, dose of cardiotoxic drugs the patients have been exposed to, and radiation dose^[8] [Figure 1].

Currently, the most common chemotherapy drugs include anthracyclines, such as doxorubicin and epirubicin; human epidermal growth factor receptor 2 (ErbB2/HER2) inhibitors, such as trastuzumab; and tyrosine kinase inhibitors (TKIs) of the vascular endothelial growth factor (VEGF) signaling pathway, such as sorafenib and sunitinib. The cardiovascular side effects induced by these chemotherapy drugs include diastolic dysfunction, conduction abnormalities, arrhythmia, heart failure (HF), pericarditis, ischemic cardiomyopathy (CM), Q-T interval prolongation, arteriovenous thrombosis, hypertension, and hypotension.^[10]

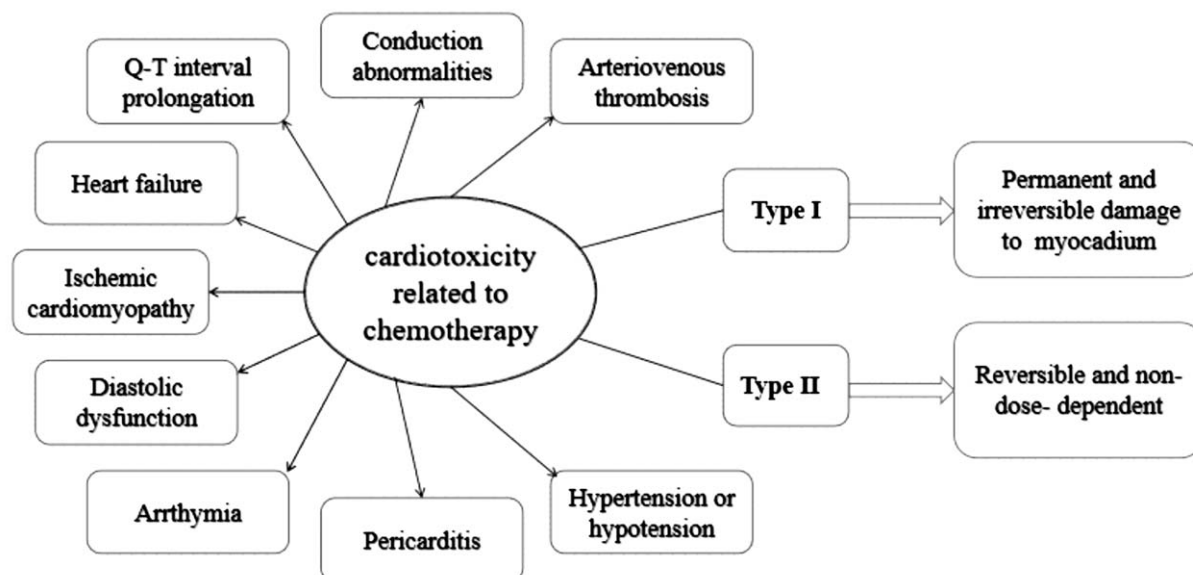


Figure 1: Cardiotoxicity related to chemotherapy.

Heretofore, anthracyclines remains to be one of the most commonly used anti-tumor drugs. However, the exact mechanism of their cardiotoxicity is still unclear. Conventional theories include formation of oxygen radicals, calcium overload, induction of cell apoptosis, DNA damage caused by interaction with topoisomerase II enzyme (Top2), and inhibition of protein synthesis.^[11] The cardiotoxicity of anthracyclines can be classified as acute or chronic. Acute cardiotoxicity usually occurs during or shortly after the beginning of treatment and may manifest as self-limited and transient non-specific electrocardiogram changes, arrhythmias, elevated myocardial enzymes, or transient left ventricular (LV) dysfunction. The most common anthracycline-related chronic cardiotoxicity is HF caused by progressive decline in LV systolic function, which is atypical at onset but can often develop into irreversible dilated CM.^[12]

In recent years, increasing attention has been paid to targeted therapy of breast cancer, but numerous targets of effective targeted drugs are also antigens expressed by certain myocardial cells. Thus, these drugs affect the normal protective pathway of myocardial cells, causing damage to myocardial cells or blood vessels, leading to the development of hypertension, myocardial injury, and other cardiovascular diseases. Among these drugs, trastuzumab, an ErbB2/HER2 inhibitor, is an anti-tumor drug that targets metastatic breast cancer cells with HER2 over-expression.^[13] ErbB2/HER2 is a member of the epidermal growth factor receptor family of tyrosine kinases and is an important mediator that plays crucial roles in abnormal cell growth and proliferation in various cancers. Gene amplification can be found in patients with breast cancer. Moreover, tumor cells with high ErbB2 expression show active proliferation capacity but inhibited differentiation, maturation, and apoptosis. Therefore, tumors with high ErbB2 expression are characterized by high malignancy, a high chance of metastasis and mortality. In addition, breast cancer with HER2 over-expression is prone to be resistant

to various chemotherapy drugs, such as tumor necrosis factor- α , and insensitive to endocrine therapy and radiotherapy, which accelerates disease progression. However, when using trastuzumab to inhibit HER2 signal of tumor cells, heterodimerization of ErbB2 and ErbB4 on myocardial cells can also be interrupted, which affects the protective effect of neuregulin on the myocardium, potentially leading to LV dysfunction or even congestive HF.^[10] However, in comparison with the cardiotoxicity caused by anthracyclines, the damage caused by targeted drugs, such as trastuzumab, is reversible.^[14] Gender, age, anthracycline use, preexisting coronary artery disease, atrial fibrillation, renal failure, and cardiovascular risk factors all affect the development of HF when using trastuzumab.^[2] VEGF antagonists (VSPs) disrupt the VEGF signal cascade reaction, which can lead to severe hypertension and myocardial ischemic events. The most commonly used drugs include bevacizumab, sorafenib, and sunitinib. In addition, sorafenib and sunitinib can be classified as small molecule TKIs.^[15] VSPs lead to enhancement of vasoconstriction through a reduction in nitric oxide production and increase in endothelin-1 synthesis, which eventually causes hypertension. In addition, inhibition of VEGF receptor leads to lower capillary density, which in turn increases peripheral resistance and finally induces hypertension.^[16] VSPs can inhibit the expression of important glomerular proteins that maintain the stability of slit membranes, leading to renal function damage, and can also aggravate the occurrence and development of hypertension.^[9]

There are many clinical researches on anthracyclines- a basic chemotherapy drug. And cardiotoxicity of anthracyclines is primarily related to the cumulative dose of the drug. As early as 1979, clinical studies have confirmed that cardiac damage caused by anthracyclines has a certain relationship with the cumulative dose of the drug.^[17] Doxorubicin-associated cardiotoxicity is the most well-studied example. After four to eight cycles of chemotherapy,

the cumulative dose of doxorubicin, typically reaches 240 to 360 mg/m². At these doses, the incidence of cardiac events is between 0.5% and 1.5%.^[18] As shown in another study, apparent cardiotoxicity of doxorubicin at a dose <300 mg/m² in adults is not common. The incidence of HF is approximately 7% to 26% at 550 mg/m² and increases to 18% to 48% at a cumulative dose of 700 mg/m², and thus, the recommended lifetime maximum cumulative anthracycline dose is 400 to 550 mg/m² for adults. In pediatrics, the dose is 300 mg/m².^[8] In addition, the mode of administration is another factor: intravenous drip of anthracycline can lower the incidence of adult heart injury compared with intravenous injection. The cardiotoxicity of different chemo-therapeutic drugs needs further comparison.^[19]

Monitoring of cardiotoxicity

Currently, the major cardiotoxicity monitoring methods include electrocardiogram, cardiac biomarkers, echocardiography, radioactive nuclide myocardial imaging, angiography, cardiac magnetic resonance imaging, and endomyocardial biopsy.^[20] The most common clinical manifestation of cardiotoxicity caused by cancer therapy are cardiac dysfunction and HF. The increase in troponin or natriuretic peptide or a decrease in LV ejection fraction (LVEF) by more than 10%, which is also below the lower limit of the normal value, are two common indexes used to monitor and identify HF in clinical practice.^[21]

Echocardiography is a non-invasive assessment approach known for its ease of operation and accuracy. It can be used to evaluate the structure and function of the heart simultaneously and therefore has become the preferred mode of cardiac function monitoring and evaluation in clinical practice. However, due to the special properties of tumor patient pathophysiology, conventional ultrasound indexes, such as two-dimensional LVEF, LV shortening fraction, and tissue Doppler imaging, are of low sensitivity, making it difficult to identify early heart impairment.^[22] LVEF is the most commonly used indicator to monitor LV systolic function. However, it is limited by many other factors in tumor patients in addition to some technical defects, such as uncertainty of image acquisition and variability in image analysis.^[22] The other factors are listed as follows: (1) Changes in cardiac load induced by intravenous drugs during chemotherapy may lead to changes in measured values. (2) If the intimal display is not sufficiently clear, ventricular volume will be underestimated. Therefore, for patients undergoing chemotherapy, the endocardium is often unclearly displayed due to the presence of interruption, which is particularly obvious in patients with breast cancer after radical mastectomy and chest wall radiotherapy.^[23] In recent years, new technologies, represented by speckle tracking imaging (STI), have been found to make up for the deficiencies in conventional echocardiography. These technologies can detect subclinical structural and functional changes in the heart related to anti-cancer therapy more sensitively and accurately in the early stage of therapy.^[24] Compared with conventional ultrasound, STI is independent of angle. It can automatically and continuously track the spatial track of acoustic spots in the myocardium during the cardiac cycle and provide quantitative evaluation of the displacement, strain

rate, rotation angle, and velocity. Thus, trajectories between two particles can be calculated and processed to synthesize radial, longitudinal, and circumferential motions of the myocardium. Then, we can perform a comprehensive evaluation of the overall, systolic, and diastolic functions of each segment according to the index listed above. Therefore, the specificity and sensitivity for cardiac function evaluation are high.^[20,25] Overall, compared with conventional ultrasound and other imaging examinations, the new ultrasound technology based on STI has shown advantages in monitoring, identification, diagnosis, risk stratification, and prognosis evaluation of myocardial injury in cancer therapy.^[25]

Medical therapy and prevention

Clinical data on therapy and prevention of tumor-related cardiovascular disease are limited. Currently, it is recognized that angiotensin-converting enzyme inhibitors (ACEIs) and β -receptor blockers can be used for therapy or prevention of cardiac dysfunction related to cancer therapy. A large amount of research evidence is about enalapril and carvedilol. Some evidence shows that drugs such as trimetazidine or candesartan combined with a low dose of carvedilol can significantly reduce the cardiac injury that occurs in patients with breast cancer after anthracycline chemotherapy and can improve cardiac remodeling, myocardial systolic and diastolic functions. The cardiotoxicity of anthracyclines is related to oxidative stress caused by the formation of reactive oxygen species through multiple pathways.^[26] Carvedilol has antioxidant effects apart from its α , β -adrenergic receptor blocking activity. Therefore, carvedilol has the potential to be an ideal drug to prevent chemotherapy-induced myocardial dysfunction. In addition, drugs such as acetylcysteine, vitamins, erythropoietin, endothelin-1 receptor antagonists, and lipid lowering drugs may also be beneficial to cardiovascular system for tumor patients.^[9] Statins and ACEIs can reduce myocardial injury in radioactive heart disease animal models,^[5] and long-chain ω -3 polyunsaturated fatty acids, which are an essential nutrient derived from food, can protect the heart by reducing triglyceride and operate anti-inflammatory, anti-myocardial fibrosis, and anti-arrhythmia effects.^[27] However, we need to conduct further clinical studies to confirm the prevention and treatment effects on myocardial injury in patients with tumor.

Conclusions

Many problems still exist in the development of oncocardiology. For example, reasonable risk evaluation methods can be established so as to realize the early intervention of tumor patients who are likely to develop acute or chronic heart diseases. More importantly, we need to trade off anti-cancer therapy and its cardiotoxicity, aiming to maximize the benefits for cancer patients. For tumor patients, the tumor therapy has already imposed a great financial burden on their family. If too many inspections monitoring cardiovascular side effects were added as routine inspections, it will bring much more burden to their family. Therefore, we are in urgent need to set up standards to screen out high-risk patients in need of

long-term follow-up or early intervention. And in this way, we can reduce the mortality of heart-related diseases in tumor patients while avoiding unnecessary economic burden on patients and other side effects caused by intervention drugs. The development of onco-cardiology depends on the multidisciplinary collaboration among cardiology, oncology and nursing. In addition, with the growing understanding of tumor development and drug-resistance mechanism, a large amount of new drugs featured by stronger effects and lower toxicity will be developed.

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Conflicts of interest

None.

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