Focus on anticancer therapy-induced cardiotoxicity from the perspective of oncologists

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To the Editor: Cancer and cardiovascular (CV) disease are associated with the largest morbidity and mortality in the world, and they are related to each other through some common risk factors.[1] The incidence of cardiac toxicity during anticancer treatment will continue to increase as the survival time of cancer patients is prolonged, the population ages, the incidence of chronic underlying diseases related to CV diseases increases, and a large number of new drugs are introduced.[1] Cardio-oncology is a new interdisciplinary research field focusing on the screening, prevention, detection, monitoring, and treatment of CV toxicity related to anticancer treatment, and the development of rational management strategies for cancer patients is within its research scope.[1]

The incidence of CV injury induced by anticancer therapy varies widely and depends on the type of drug used, its duration of use, and underlying patient comorbidities.[2] Many kinds of CV drugs can cause one or more forms of cardiac toxicity, including most chemotherapy drugs, a large number of new targeted therapeutic drugs, immune checkpoint inhibitors (ICIs), and radiation.[1,3,4]

Chemotherapeutic agents, represented by anthracyclines, mostly cause type I cardiotoxicity, and their pathophysiology is related to cell loss, which is irreversible. Most targeted drugs, represented by trastuzumab, cause type II cardiotoxicity, the pathophysiology of which is cellular dysfunction (mitochondrial and protein alterations). The manifestations of CV damage caused by chemotherapy or targeted therapy drugs include congestive heart failure (HF), cardiomyopathy, arrhythmia, QT interval prolongation, thrombosis, hypertension, etc. ICI-related cardiotoxicity is caused by non-specific activation of the immune system, and the symptoms vary slightly, with myocarditis being the most common symptom. Although the incidence is not high (approximately 0.09% for a single drug and 0.3% for a combined drug), the mortality rate is very high (approximately 50%),[5] and toxicity is followed by various arrhythmias, myocardial pericarditis, cardiomyopathy, acute coronary syndrome, and sudden cardiac death. Radiation exposure has potentially profound effects on vascular structures, valves, the pericardium/myocardium, the conduction system, and the autonomic nervous system, and symptoms are dominated by the clinical manifestations of these lesions.[1,6] However, although CV events among cancer patients are diverse, the long-term clinical consequences mainly include left ventricular dysfunction and HF.[3] At present, the most commonly used definition of chemotherapy-induced cardiotoxicity is a left ventricular ejection fractions (LVEF) decrease greater than 10% compared with the LVEF at baseline, and an absolute value below 50% or 53% (various among different guidelines).[3,6]

In general, the initial stage of cardiotoxicity is more insidious and may be characterized by only subclinical symptoms or some very subtle signs, such as a decreased exercise ability and resting tachycardia.[6] However, cardiac function is often damaged continuously with treatment progression until symptomatic cardiac insufficiency occurs after a certain trigger.[2] The schematic diagram of disease progression for cardiotoxicity was shown in Supplementary Figure 1, http://links.lww.com/CM9/B28. Even if the symptoms are relieved after treatment, the LVEF cannot recover before the onset of toxicity, resulting in irreparable long-term heart damage.[2]

Careful baseline assessment of patients' health status and CV risk factors is always the first step before any anticancer

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000002133

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Chinese Medical Journal 2022;135(17)

Received: 16-05-2021; **Online:** 2-8-2022 **Edited by:** Ningning Wang and Lishao Guo

therapy.[3,4,7] For chemotherapy-associated cardiotoxicity, considering the many types of chemotherapy drugs and different mechanisms, the risk factors generally include the following: prior anthracycline-based treatment; combined treatment with trastuzumab and anthracycline or chest radiotherapy; elderly or very young age (>75 or <10 years old); hypertension or diabetes mellitus; smoking exposure; elevated cardiac biomarkers at baseline; and baseline abnormal systolic LV function with a LVEF <0.50.[2] If the most representative anthracycline is taken as an example, the 2016 European Society of Cardiology (ESC) guideline[3] and 2017 American Society of Clinical Oncology guideline[7] provide different recommendations. The risk factors were noted in the two guidelines as follows: (1) Female sex; (2) Young or elderly age; (3) Treatment factors, including high-dose anthracycline (doxorubicin >250 mg/m^2 or epirubicin >600 mg/m^2), lower dose anthracycline in combination with lower dose radiotherapy when the heart is in the treatment field, treatment with lower dose anthracycline followed by trastuzumab, concomitant chemotherapy with alkylating or antimicrotubule agents, and concomitant chemotherapy with immuno- and targeted therapies; (4) High-dose radiotherapy (>30 Gy) when the heart is in the treatment field; (5) Renal failure; (6) The presence of any of the following CV risk factors (>two risk factors): smoking, hypertension, diabetes, dyslipidemia, and obesity; (7) A compromised borderline LVEF at baseline, a history of myocardial infarction, >moderate valvular heart disease at any time during treatment; and (8) Genetic factors. Among targeted drugs, trastuzumab is the most representative drug with CV toxicity, and its risk factors include elderly age, previous exposure to anthracyclines, a short time between anthracycline and anti-HER2 treatment, preexisting arterial hypertension, a low LVEF, elevated baseline troponin, a previous radiotherapy history, a history of arterial hypertension, a low LVEF and obesity.[3] The risk factors for radiation-associated cardiotoxicity include a dose >30 to 35 Gy; a dose per fraction >2 Gy; a large volume of irradiated heart; younger age; concurrent radiation therapy and chemotherapy/endocrine therapy/trastuzumab; and the presence of other CV risk factors (hypertension, diabetes mellitus, dyslipidemia, smoking, etc).[6] The risk factors for ICI-related cardiotoxicity are not clear. The definite risk factors include previous CV diseases and the combined use of immunotherapeutic drugs.[5]

Any anticancer therapy that impacts cardiac safety requires timely and adequate monitoring for the detection and identification of cardiotoxicity.[1,2] Oncologists should comprehensively evaluate CV risk factors before any treatment with potential CV toxicity; at least electrocardiogram (ECG), echocardiography, myocardial marker, and blood lipid spectrum results should be reviewed.[1,3,4,7] For immunotherapy patients, no authoritative guidelines are available for assessment items in baseline examinations, but in addition to the above examination items, total creatine kinase, C-reactive protein, virus titers, and cardiac magnetic resonance (MR) examination are also recommended items for patients who develop new CV symptoms[4,5] However, at present, no consistent detection frequency recommendation is available, and most existing monitoring programs are based on the methodology of clinical trials and expert opinions. For patients under treatment, continuous CV risk assessments including ultrasonic cardiogram (UCG) (LVEF and global longitudinal strain [GLS]), ECG, and myocardial enzymes must be carried out every 1 to 2 cycles of anthracycline use and at least every 3 months during trastuzumab treatment[1-3]; for survivors with normal cardiac function, screening with an LVEF assessment should be considered at 6 to 12 months and possibly 2 years post-treatment, and periodic reassessment can be considered thereafter.[1]

Cardiotoxicity prevention can also be classified as tertiary prevention. Cardio-oncology focuses more on primary prevention and secondary prevention. Primary prevention includes lifestyle interventions and drug interventions. Positive health-promoting behaviors including a healthy diet, smoking cessation, regular aerobic exercise, and weight control should be the first forms of cardiotoxicity prevention and are strongly advised before or during antitumor treatment.[1,2]

For drug interventions, dexrazoxane is currently the most convincing protective agent against anthracycline-induced cardiotoxicity. Dexrazoxane has been recommended as a cardioprotectant in patients who have already received more than 300 mg/m^2 of doxorubicin.[2] Angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs) are also considered to have cardioprotective effects. For chemotherapy, candesartan and enalapril have demonstrated cardioprotective effects.[8,9] Although controversy remains regarding ACEI/ARB prevention of cardiotoxicity caused by trastuzumab, perindopril and lisinopril are believed to have cardioprotective effects based on clinical studies.[10,11] In most studies, β-blockers have been shown to promote ventricular recovery through inhibition of adverse remodeling and to preserve the LVEF through adrenergic and neuroendocrine dysregulation mechanisms.[12] β-blockers such as carvedilol[11] and bisoprolol[10] have been concluded to achieve cardioprotective effects on cancer patients during antitumor treatment. However, neither carvedilol[13,14] nor metoprolol[8] showed positive results. Prophylactic treatment with ACEIs/ARBs or β-blockers alone or in combination has shown equivocal results. Positive results were shown for enalapril combined with carvedilol therapy in the OVERCOME study,[15] while negative results were shown for candesartan combined with metoprolol therapy in the PRADA clinical study.[8] Combination therapy may be more appropriate for people at a high risk of cardiotoxicity.[12] Other drugs, such as statins, have been shown to reduce the decrease in the LVEF during antitumor treatment.[16] Some drugs originally considered to have potential cardioprotective effects, such as coenzyme Q10, L-carnitine, N-acetylcysteine, and antioxidants (vitamin C and vitamin E), were found to have no significant protective effects after meta-analysis. The detailed information of prospective clinical studies involved were shown in Supplementary Table 1, http://links.lww.com/CM9/B28. Studies have shown that implantable cardioverter defibrillators (ICDs) or cardiac resynchronization defibrillators are beneficial for the prevention of sudden cardiac death for patients with a life expectancy >1 year and a good general condition.

Secondary prevention mainly includes early detection and diagnosis of cardiac toxicity in cancer patients and timely treatment. Some early signs of heart injury require our attention, such as an impaired exercise capacity, resting tachycardia, increased myocardial markers, and decreased GLS. For patients who already have cardiotoxicity, a clinical trial confirmed the efficacy of enalapril ± carvedilol treatment,[17] and this protocol is also recommended by several guidelines.[1,3] The ESC also recommends using ICDs to reduce the risk of sudden death in patients who have recovered from ventricular arrhythmia causing hemodynamic instability and who are expected to survive for >1 year with a good functional status. For the choice of treatment length, the ESC recommends that HF treatment should be continued indefinitely unless normal systolic blood pressure function remains stable after HF treatment cessation and no further anticancer treatment is planned. Since cardiac dysfunction caused by trastuzumab is usually reversible, these patients can consider discontinuing HF therapy after their LVEF returns to normal.[1,3]

In summary, regarding preventive drugs for cardiotoxicity, the preventive effect of dexrazoxane is relatively clear. Although controversies remain, most studies still agree on the effects of β-blockers and ACEI/ARB drugs on preventing and treating cardiotoxicity.[1,2,4] The treatment strategies discussed in this article will be applicable to most patients. Nevertheless, in the era of individualized care, a doctor's clinical judgment is important.[1]

In the future, cardio-oncology must be a patient-centered, multidisciplinary, collaborative, and innovative discipline. The cardio-oncology team can use existing risk prediction models to determine a patient's individual risk of CV events and use existing evidence to support anticancer treatment and CV drug selection to reduce the risk of CV disease. Prevention of antitumor drug cardiotoxicity, better identification of high-risk factors for cardiotoxicity, and optimization of the diagnosis and treatment processes in clinical practice are problems that must be solved. With close cooperation among experts in the field of cancer and CV disease, the individualized health management of cancer patients can be realized.

Funding

This work was supported by grants from Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Sciences (CIFMS, 2021-I2M-1-014) and National Natural Science Foundation of China (No. 82172875).

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How to cite this article: Liu B, Wang Y, Lyu D, Ma F. Focus on anticancer therapy-induced cardiotoxicity from the perspective of oncologists. Chin Med J 2022;135:2122–2124. doi: 10.1097/CM9.0000000000002133