

New progress in elucidating the relationship between cancer therapy and cardiovascular toxicity

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SUMMARY Onco-cardiology is an emerging field linking cancer with cardiovascular injury. Understanding the mechanism of cardiac injury helps improve the quality of life of cancer survivors. A series of studies on adverse reactions to cancer or oncological treatments has indicated that adverse cardiovascular events related to cancer treatments may occur over a longer period of survival, and even years after therapy has concluded. Current cancer therapies, including chemotherapy, radiotherapy, targeted therapy, and immunotherapy, have been found to have latent cardiovascular toxicity. These toxic effects are often progressive and irreversible and ultimately lead to cardiovascular events such as heart failure, hypertension, coronary heart diseases, arrhythmia, and thromboembolism. Therefore, more emphasis should be placed on revealing the mechanism of cancer treatment-related cardiovascular toxicity. This would help to guide prevention, diagnosis, and treatment of CVDs in cancer survivors.

Keywords onco-cardiology, cardiovascular toxicity, cardiovascular diseases, cancer

1. Introduction

Cardiovascular diseases (CVDs) and cancer are the two leading causes of death worldwide. Mortality from cancer has been steadily declining over the past few decades, largely because of early detection strategies, improved surgical approaches, and advances in cancer therapeutics. However, recent data have indicated that CVDs are becoming the second leading cause of long-term morbidity and mortality among cancer survivors. This is largely due to the following reasons: *i*) Cancer and CVDs involve many common risks and pathologic factors, like smoking, diabetes, and aging (1-3); *ii*) Various cancer treatments cause direct or indirect damage to the cardiovascular system. According to previous investigations, over 60% of patients were prescribed cardiovascular risk drugs during cancer treatments (4,5). Conventional chemotherapy and targeted therapies are associated with an increased risk of cardiac damage including heart failure (HF), hypertension, arrhythmia, thromboembolism, and ischemic cardiomyopathy (CM), and may be life-threatening in some instances.

Oncologists puzzled by the necessity of cardiovascular assessment and monitoring when dealing with patients with tumor. The field of onco-cardiology

has developed in response to a fusion of relevant theories in cardiology and oncology to optimize care for patients with cancer. Thus, further studies on the epidemiology and pathophysiology of cardiovascular damage & dysfunction in cancer survivors need to be promptly conducted to identify screening, preventive, and therapeutic approaches.

2. Epidemiology: Cancer treatments and CVDs

The overall incidence of cancer increases steadily with age for over 80% of patients between the ages of 60 and 80. The International Agency for Research on Cancer (IRCA) has reported that there were approximately 19.3 million new patients with cancer worldwide and nearly 10 million deaths in 2020 (6). In China, there were close to 4.57 million new cancer cases in 2020, accounting for about a quarter of new patients with cancer worldwide. The number of patients found to have cancer is estimated to increase by 60% in 2030.

As a result of continued advances in cancer treatments, the survival rate has increased significantly. About 75% of cancer survivors suffer from one or more chronic diseases, and the leading cause of death for these survivors is CVDs (7-9). The largest cohort analysis of

cancer and CVDs in China reported that 18% of patients with cancer have at least one cardiovascular risk factor and that 5% of patients with cancer have CVDs (4). Patients with cancer and CVDs have a higher mortality risk than patients without CVDs. In addition, a 2008 study by Menna, Salvatorelli, & Minotti (in *Chemical Research in Toxicology*) found that many decades after diagnosis and treatment, patients with cancer had a 15-fold higher rate of HF, a 9-fold higher rate of stroke, and a 10-fold higher incidence of coronary atherosclerosis (10,11). Within 5 to 10 years after cancer treatments, more than 50% of survivors have subclinical signs of heart and blood vessel damage (12,13).

3. Mechanism of cancer treatment-related cardiovascular toxicity

Direct compression or infiltration of the heart by tumor, cytokines and growth factors secreted by tumor cells, and endocrine factors released by tissues surrounding tumors degrade the normal structure and function of the heart. The control of primary disease is the best way to alleviate these effects. However, mounting evidence has suggested that cancer treatments, such as drugs, surgery, and radiation (Table 1), induce cardiovascular impairment that may be related to cardiomyocyte apoptosis, mitochondrial damage, oxidative stress, proinflammatory response, and endothelial cell damage (Figure 1).

3.1. Cardiac toxicity

The structure and electrical behavior of the myocardium are the two leading components that maintain the normal physiological function of the heart. Various cancer treatments disrupt normal cell, tissue, and organ function, degrading cardiac function and ultimately leading to CVDs.

3.1.1. Structural dysfunction of the myocardium

Cardiomyocyte apoptosis has been reported to be a key mechanism of cancer treatment-induced cardiotoxicity, and it is frequently accompanied by oxidative stress and mitochondrial injury. Some evidence suggests that anthracyclines, one of the most widely used chemotherapeutic agents, induce apoptosis of cardiomyocytes. Anthracycline exposure reduces the number of mesenchymal progenitor and circulating cells, and thus reduce cardioreparative capacity when the heart is exposed to stress (14). In addition, anthracyclines act on topoisomerase-II, which has been found to be one of the direct target molecules of cardiotoxic drugs. Dysfunction of topoisomerase II exacerbates the breakage of DNA, mitochondrial DNA damage, and oxidative stress, it prevents ligase repair, and it up-regulates the expression of MAPK,

Table 1. Mechanism of cardiovascular toxicity induced by cancer treatments

Mechanism	Cancer treatments	Related CVDs
Cardiac apoptosis	<ul style="list-style-type: none"> • Anthracyclines • Antimetabolites • PKIs • Radiation • Topoisomerase II inhibitors 	HF Arrhythmia Heart valve disease
Endothelial damage	<ul style="list-style-type: none"> • Alkylating agents • Anthracyclines • PKIs • Taxanes • Proteasome inhibitors • Radiation • Platinum • VEGF inhibitors 	CAD Hypertension Thromboembolism
Mitochondrial injury	<ul style="list-style-type: none"> • Anthracyclines • TKIs 	HF Arrhythmia CAD
Oxidative stress	<ul style="list-style-type: none"> • Alkylating agents • Anthracyclines • Antimetabolites • Mitomycin C 	HF Pericarditis CAD
Proinflammatory response	<ul style="list-style-type: none"> • Anthracyclines • Antimetabolites • Interferon-α 	HF Pericarditis Arrhythmia CAD
Cytokine release syndrome	<ul style="list-style-type: none"> • Alkylating agents • Anthracyclines • Antimetabolites • Monoclonal antibodies • Amsacrine • Platinum • Melphalan 	Thromboembolism Arrhythmia HF CAD
Abnormal Ca^{2+} homeostasis	<ul style="list-style-type: none"> • Anthracyclines • Arsenic trioxide • Taxanes 	Arrhythmia

Abbreviation: PKIs, protein kinase inhibitors; TKIs, Tyrosine kinase inhibitors; HF, heart failure; CAD, coronary atherosclerosis; VEGF inhibitors, vascular endothelial growth factor inhibitors.

JNK, p38, and protein kinase B. Thus affecting Ca^{2+} -regulating proteins or Ca^{2+} channels and leading to events such as Ca^{2+} overload and cardiac remodeling (15-17). Another anti-cancer agent involved in apoptosis is imatinib, which produces a dose-dependent collapse of the mitochondrial membrane potential that damages cardiomyocyte mitochondria. At the subcellular level, a lack of functional mitochondria causes a decrease in intracellular ATP content, an endoplasmic reticulum stress response, and increased release of cytochrome C into the cytoplasm, thus accelerating cardiomyocyte apoptosis (18).

Another important factor causing abnormalities in the structure of the heart is due to cancer treatment-related cardiomyocyte and interstitial fibrosis. Human epidermal growth factor receptor 2 (HER2) inhibitor is a targeted drug to treat breast cancer that interferes with the heterodimerization of ErB2 and ErB4 in cardiomyocytes, thus eliminating the protective effect of neuregulin 1, which helps to repair cardiomyocytes

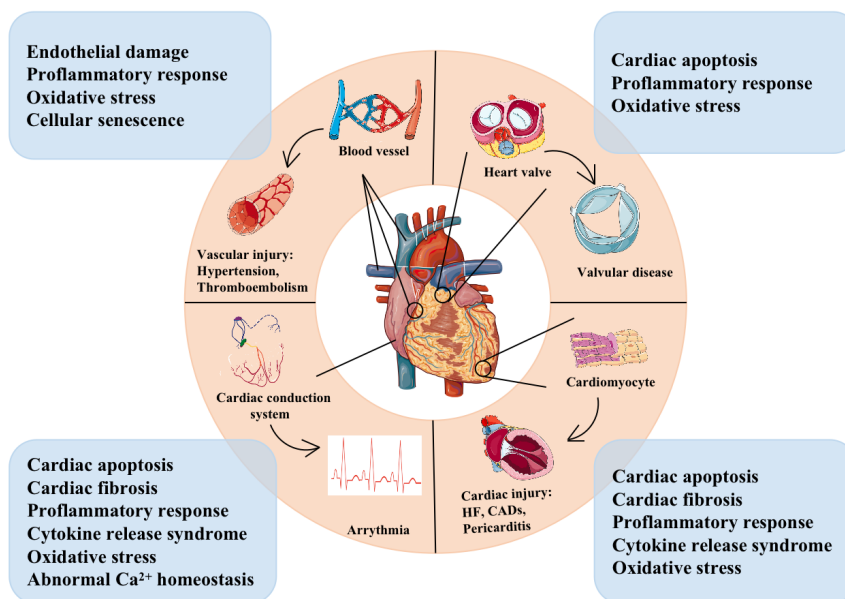


Figure 1. The mechanism of cardiovascular toxicity induced by cancer treatments.

and maintain homeostasis (19,20). In addition to cardiac fibrosis directly caused by drugs, physical therapy also significantly accelerates this process. Radiation therapy continues to advance, and it has become the primary modality for clinical treatment of malignancies. Radiation therapy kills cancer cells and prevents them from returning via a variety of mechanisms. However, it simultaneously kills neighboring normal cells, so the radiation dose and volume exposed must be tightly controlled. Prolonged radiation exposure affects cardiac capillary endothelial cells, leading to their proliferation, damage, swelling, and degeneration, and it significantly reduces the number of capillaries (21). Capillary network damage is associated with decrease in the myocardial blood supply, eventually contributing to the development of myocardial fibrosis. Radiotherapy also induces fibrosis of the heart valves and cusps (22).

In addition to mechanisms mentioned thus far, proinflammatory response and cytokine release syndrome (CRS) often occurs together during immunotherapy and biological treatment. Immune effector cells cross-link with tumor cells, contributing to the release of a large number of cytokines and inflammatory factors. Cytokines are mainly derived from the target cells themselves and immune cells recruited to the tumor. Aggregation of cytokines can lead to excessive activation of immune cells such as macrophages, which create a positive feedback loop that promotes the activation of cytokines such as IL-1, IL-6, IL-8, IL-10, and MCP-1, eventually leading to a cytokine storm and excessive inflammation (23,24).

3.1.2. Myocardial electrical dysfunction

Studies have indicated that cancer treatments regulate

cardiomyocyte ion channels. HER2 inhibitors regulate cardiac sympathetic nerve tension and affect a variety of ion channels, such as I_{to} , I_{K1} , and $I_{K,Ach}$ (3). Arsenic trioxide, which is often used to treat hematologic cancers, blocks I_{Kr} and I_{Ks} and activates $I_{K,Ach}$ (25). An increase in myocyte automaticity and altered expression of ion channels induces prolongation of the QT interval and early post-depolarization and it triggers abnormal cardiac electrical activity.

In addition, calcium homeostasis plays a key role in myocardial excitation-contraction coupling, which is involved in the changes in cardiac electrical activity. Studies have indicated that paclitaxel increases the expression of neuronal calcium sensor 1 (NCS-1), it modulates the release of calcium from cells depending on the inositol-1,4,5-triphosphate receptor (InsP3R), and it affects calcium signaling, calcium oscillation, and calcium homeostasis in cardiomyocytes. Thus disrupting the normal electrophysiology of the myocardium (26).

3.2. Vascular toxicity

Cardiotoxicity has received extensive scholarly attention, but vascular toxicity cannot be ignored. Endothelial injury is a key feature of vascular toxicity and it is caused by cell aging, oxidative stress, and pro-inflammatory response.

Cisplatin and carboplatin are platinum-based agents that have been in widespread use for many years to treat several forms of cancer, and platinum-based agents are considered to be vasotoxic. Cisplatin can still be detected in serum several years after treatment, and it continues to affect vascular endothelium (27). Cisplatin exposure activates endothelial cells and then up-regulates intracellular adhesion molecule 1, tissue-

type plasminogen activator, and plasminogen activator inhibitor type 1 in endothelial cells, suggesting an acceleration of atherosclerosis (11,27). After many years of cisplatin therapy, patients have an increased carotid intima media thickness (C-IMT) and aortic IMT (A-IMT). Many other types of anticancer drugs appear to be vasotoxic. 5-Fu and capecitabine are commonly used antimetabolites that promote oxidative stress, causing cellular damage and readily inducing endothelial injury followed by thrombosis (28).

Radiotherapy is known to cause the shortening and dysfunction of telomeres, thus accelerating cellular senescence. Senescence of vascular endothelial cells increases the production of reactive oxide species (ROS) and decreases the vascular protective effect of nitric oxide, contributing to the senescence-induced apoptosis of endothelial cells. Cellular senescence is thought to be a gradual decline in the ability of cells to cope with various stresses that may trigger chronic pathological conditions, including CVDs (29).

4. CVDs associated with cancer treatments

Therapy of a longer duration is considered to involve an increased risk of cardiovascular events such as HF, hypertension, CAD, arrhythmia, thromboembolism, heart valve disease, and pericarditis. These events are common, and they involve a high rate of morbidity and disability. Therefore, the cardiovascular system should be monitored, and cardiovascular events prevented in all patients with cancer.

4.1. HF

HF is one of the most common complications in patients with cancer, and it influences the overall outcomes for those patients, particularly the elderly. Conventional chemotherapeutics, such as anthracyclines, antimetabolites, and cyclophosphamide, can induce permanent myocardial cell injury, leading to left ventricular (LV) dysfunction (LVD) and diastolic and systolic dysfunction and eventually progressing to acute or chronic HF (30). Anthracyclines, especially doxorubicin, are the greatest concern, since they can lead to HF and significantly shorten lifespan. Anthracycline-related LVD has historically been considered to be dose-dependent, cumulative, and progressive; over 50% of patients receiving anthracycline-based chemotherapy have a certain degree of cardiac dysfunction 10-20 years after chemotherapy, 5% have obvious HF, and the mortality rate is close to 60% (31). A study has indicated that myocyte injury may also be reversible if LVD, diastolic as well as systolic dysfunction are detected early, and appropriate HF-based treatment is instituted (32).

Surveillance strategies are currently based on expert consensus. An integrated approach combining cardiac biomarkers as well as imaging data plays a major role in

identification, assessment, and monitoring of antitumor drug-induced cardiotoxicity. Troponins may facilitate the detection of cardiotoxicity in the preclinical phase and help to predict the severity of future LVD in patients treated with antitumor drugs (33,34).

The left ventricular ejection fraction (LVEF) is the most commonly used parameter of cardiac function that independently predicts short-term and long-term mortality from cardiovascular events. The Clinical Practice Guidelines of the American Society of Clinical Oncology (ASCO) recommend assessment of LVEF prior to and during exposure to known cardiotoxic agents in high-risk patients (35). Recent improvements in imaging technology have led to more sensitive and precise assessment of cardiac function. New techniques, including spot tracking and measurement of strain, make up for the technical shortcomings of conventional ultrasound (36). These imaging technologies have enabled early detection of structural injury to the heart and cardiac injury as a result of cancer therapy.

The primary goal of treating cancer treatment-related HF is maintaining the LVEF and limiting myocardial remodeling. There is growing evidence suggesting that several agents, such as β -blockers, angiotensin antagonists, statins, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs), play a cardioprotective role in preventing cancer treatment-induced cardiotoxicity. However, patients receiving anthracycline-based chemotherapy have a significant increase in adverse reactions to ACEIs/ARBs, such as a dry cough, hypotension, hyperkalemia, and angioedema (37). For these patients, carvedilol is a better choice to reduce HF.

4.2. Hypertension

Hypertension is a common comorbidity in patients with cancer. Nearly 70% of patients with prostate or bladder cancer develop hypertension. Moreover, the toxicity of anticancer drugs accelerates the development of hypertension. Monoclonal antibodies (such as bevacizumab), TKIs, and vascular endothelial growth factor (VEGF) signaling pathway (VSP) inhibitors disrupt endothelial cell receptor signaling, which affects the activity of nitric oxide synthase, nitric oxide levels, and endothelin synthesis. Increased vasoconstriction capacity and decreased peripheral angiogenesis induce hypertension. In addition, alkylating agents, taxanes, platinum-based agents, and neuroendocrine drugs can also cause hypertension.

The primary goal of treating patients with hypertension is to minimize damage to target organs including the brain, kidneys, and heart by standard management of blood pressure (BP). Effectively lowering BP reduces morbidity and mortality. The European Society of Cardiology recommends a target systolic BP (SBP) < 140 mmHg and a diastolic BP (DBP) < 90

mmHg for patients taking a VSP inhibitor (7). BP should be actively monitored throughout treatment, with weekly assessments during the first cycle of treatment and assessments at least every 2 to 3 weeks during the remaining cycles. In addition, the target BP should be adjusted to < 130/80 mmHg for patients with multiple pre-existing risk factors for adverse consequences of high BP, such as chronic kidney disease (38).

Specific classes of antihypertensives have not been recommended for patients with cancer treatment-related hypertension. ACEIs or ARBs, calcium channel blockers (CCBs), and β -blockers are the treatment of choice. However, non-dihydropyridine calcium channel blockers (non-DHP CCBs), such as verapamil and diltiazem, should be avoided in patients receiving sunitinib or sorafenib due to underlying drug interactions (7). Multi-agent antihypertensive therapy is the preferred treatment for patients with cancer and poorly controlled BP. However, clinical guidelines for the management of hypertension recommend the temporary withdrawal of anticancer drugs if BP cannot be controlled and hypertension-related adverse events occur (39).

4.3. Coronary artery diseases (CADs)

The coexistence of CAD and cancer is largely driven by common risk factors (such as aging, smoking, obesity, and diabetes) and the increasing use of cancer treatments. CAD is triggered by anti-cancer reagents in cancer patients due to increased low-density lipoprotein levels, platelet activation, endothelial damage, and vasospasms (40). The combination of bevacizumab, bleomycin, and vinblastine increases the long-term risk of CAD and myocardial infarction by 1.5- to 7-fold (41). Moreover, radiotherapy has also been found to have negative effects: coronary events occur within 5 years after initial exposure to radiation, lasts up to 30 years post-exposure, and they increase linearly with an increase in the radiation dose (42).

As is true for all patients with a heart condition, non-invasive stress testing, ECG, CTA, and coronary angiography represent important modalities for the assessment and management of cancer survivors with CAD (43,44). ECG and cardiac biomarkers are recommended for initial diagnosis of symptoms suggestive of an acute coronary syndrome (ACS). Clinical practice guidelines recommend the temporary withdrawal of chemotherapy if ECG from patients receiving pyrimidine analogue indicates acute myocardial ischemia, such as ST segment changes or T wave inversion.

In patients with angina that fails to respond to optimal medical therapy or in patients with a high TIMI score, invasive evaluation and treatment should be considered. Percutaneous coronary intervention (PCI) is the gold standard for ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial

infarction (NSTEMI)/unstable angina (40). After surgery, patients receive routine anticoagulation therapy for at least 12 months. For patients with cancer and a high risk of bleeding, the European Society of Cardiology (ESC) recommends triple therapy [dual anti-platelet therapy (DAPT) and an oral anticoagulant (OAC)] for one month. Patients should subsequently receive antiplatelet drug and OAC for 11 months. If the risk of bleeding is extremely high, administration of an antiplatelet drug and an OAC for 12 months should be considered, and then OAC can be taken alone (45).

Other important recommendations for patients with cancer and CAD are control of symptoms, prevention of the progression of atherosclerosis, and prevention of the development of acute coronary syndrome via active medical treatment, and particularly with statins and β -blockers.

4.4. Arrhythmia

Kravchenko et al. reported that 28.6% of patients with lung cancer had arrhythmia, including those who received chemotherapy or radiotherapy (46). In general, cancer therapy-related arrhythmias can be differentiated into bradycardia and tachycardia such as atrial fibrillation (AF), ventricular tachycardia (VT), long Q-T syndrome, and heart block.

Cardiac arrhythmias were first found to occur with paclitaxel, which mainly induces episodes of asymptomatic bradycardia. All other rare paclitaxel-induced arrhythmias, including supraventricular tachycardia and premature ventricular, are self-limiting and resolve 48h after treatment is stopped. Radiation therapy is another classic cancer treatment that produce different forms of bradycardia, up to a grade III atrioventricular block. Exposure to radiation causes fibrosis in the conduction system, including the sinus node, atrioventricular and His bundle, and bundle branches.

QTc prolongation and related VT has been noted with arsenic trioxide and various TKIs. These effects are attributed to an increase in the inward current and a decrease in the outward current in the ventricle.

AF is the most frequent sustained arrhythmia in clinical practice, and its prevalence increases with age. Initially, reported risk factors for AF were neoplastic infiltration, mechanical pressure on the heart, or a complication of oncological thoracic surgery. The association between cancer therapy and AF was subsequently identified. During prolonged treatment, the release of proinflammatory cytokines, abnormalities in calcium homeostasis, direct myocardial damage, and an increase in vagal and adrenergic tones can interfere with the electrical conduction system of the heart and serve as major risk factors for AF.

ECG is gold standard for diagnosis of arrhythmia. Clinicians should investigate the QT interval with a

routine 12-lead ECG and calculate the QTc (heart rate-corrected QT interval) both before and after cancer treatments (47). During treatment, discontinuation or adjustment of the anti-cancer regimen should be considered for patients with a QTc > 500ms, QTc prolonged more than 60ms, or new arrhythmia. In addition, 24-hour continuous Holter recording is helpful in diagnosing suspected arrhythmias, and establishing their frequency, relating them to symptoms, and assessing the response to therapy (48).

Management and prevention of arrhythmia in oncology patients have the same goals as in the general population. Amiodarone and β -blockers are used as first-line treatments. Ca^{2+} channel blockers (CCBs) are recommended to reduce the heart rate, but recent studies have indicated that ibrutinib increases the plasma levels of CCBs, amiodarone, and digoxin (47,48). Therefore, caution is recommended when these drugs are combined to manage tachyarrhythmia.

Adequate anticoagulation therapy is the cornerstone of AF treatment, but it must be carefully administered to patients receiving cancer therapies. CHADS₂ (CHA₂DS₂-VASc) and HAS-BLED scoring standards are currently the general methods for assessing AF. However, neither consider cancer and cancer treatment-induced hypercoagulability. Thus, both the score and the patient's condition need to be considered when determining whether to administer anticoagulant therapy.

4.5. Thromboembolism

Hypercoagulability associated with cancer seems to be a major problem leading to thrombosis. Thromboembolism can be divided into venous thrombosis and arterial thrombosis. Venous thrombosis often occurs in patients with advanced cancer; it poses a huge burden and has a poor prognosis (49). Arterial embolism is mainly evident as acute coronary syndrome, acute ischemic stroke, or peripheral vascular disease. Coronary thrombosis is the most common form of acute coronary syndrome. Cancer treatments accelerate thrombosis due to injury to the vascular endothelium and disruption of normal coagulation (50). Anti-angiogenic drugs or TKIs lead to arterial thrombosis such as thrombosis or embolism; thalidomide or lenalidomide are major causes of venous thrombosis, which manifests as deep vein or pulmonary embolism.

Excellent tumor control is associated with a decreased risk of thromboembolism. Therefore, anti-cancer drugs are not considered to be absolutely contraindicated. Given a high risk of arterial embolism, VEGF should be avoided and aspirin or clopidogrel should be used to prevent thromboembolism. Warfarin and low molecular weight heparin (LMWH) are recommended to treat patients with an increased risk of venous thrombosis (51). A point worth mentioning is that deep vein thrombosis is a serious complication after surgery for cancer, regardless

of the type of cancer or the patient's age or sex. Khorana scoring can be used to predict the risk of chemotherapy-associated VET. In high-risk patients undergoing surgery, bleeding and the risk of an embolism should be assessed preoperative and anticoagulants should be administered to prevent embolism.

4.6. Other CVDs

Pericarditis, myocarditis, and heart valve disease are seen in patients with cancer, and especially those undergoing radiotherapy (21). Acute radiation pericarditis typically occurs within days to a few weeks after treatment and gradually develops into chronic pericarditis, which manifests as pericardial effusion or constrictive pericarditis. Mitral valve dysfunction is the main feature of radiation-related heart valve disease, and the degree of damage is correlated with the radiation dose.

The main methods of monitoring pericarditis, myocarditis, and heart valve disease include ECG and echocardiography. Cardiac ultrasound is generally the method of choice for monitoring pericarditis and heart valve disease, and it can be used to evaluate the structure and function of the heart valves and pericardium (34). A conventional 12-lead ECG is recommended as an initial diagnostic test for patients suspected of having myocarditis.

Clinical data on the prevention and treatment of cancer treatment-related pericardial and valvular disease are limited. As in patients who do not have cancer, conventional surgical resection and interventional valve replacement are indicated for patients with cancer treatment-related pericardial or valvular disease. Due to the potential adverse effects of radiotherapy, a lower radiation dose or new techniques to precisely locate and expose less of the heart are crucial to reducing valvular and pericardial injury.

5. Conclusion

Improvements in cancer diagnosis and treatment have led to a significantly increased survival rate for patients with cancer. Long-term quality of life after therapy has become a topic of increasing interest for both cancer survivors and experts. Cancer therapies cause short-term and long-term adverse reactions involving the heart and circulation and they exacerbate existing CVDs. Therefore, large-scale prospective studies need to be conducted and the mechanism of cancer treatment-related cardiovascular toxicity needs to be understood further to improve guidelines on appropriate monitoring, prevention, and treatment of cancer treatment-related cardiovascular events.

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