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Research Article

THE INTERSECTION OF ONCOLOGY AND CARDIOLOGY: UNDERSTANDING THE CARDIOVASCULAR RISKS OF CANCER THERAPIES

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Abstract

Cancer therapy, including chemotherapy, radiation therapy, and targeted therapies, plays a vital role in cancer treatment but can also induce cardiovascular complications. Chemotherapy, such as anthracyclines, generates reactive oxygen species (ROS) that contribute to myocardial damage and cardiomyopathy. Radiation therapy, often used in thoracic and breast cancers, leads to endothelial dysfunction, accelerated atherosclerosis, and increased incidence of ischemic heart disease. Targeted therapies, such as tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs), can induce hypertension, left ventricular dysfunction, and an elevated risk of cardiovascular events. Patients with pre-existing cardiovascular conditions require careful management to ensure the safe administration of cancer treatments. Regular cardiovascular monitoring, including electrocardiograms (ECGs), echocardiography, and cardiac biomarkers, is crucial for early detection and intervention in therapy-related cardiotoxicity. These assessments help differentiate between inflammatory and non- inflammatory dysfunctions, guiding appropriate treatment strategies. Personalized management approaches and novel anticancer treatments that minimize cardiovascular impactare emerging priorities in cardio-oncology. The goal is to balance the effectiveness of cancer therapy with reducing adverse cardiovascular outcomes, ensuring improved quality of life for patients. In summary, cardio-oncology aims to address and manage cardiovascular complications associated with cancer treatments, focusing on early detection, tailored treatment plans, and thedevelopment of anticancer therapies that are less harmful to the cardiovascular system. Future advancements in this field will likely play a pivotal role in optimizing both cancer and cardiovascular care for patients.

Keywords: Cancer Therapy, Cardiovascular Complications, Chemotherapy, Anthracyclines, Radiation Therapy, Targeted Therapies, Cardiotoxicity, Cardio-oncology, Personalized Management, Early Detection, Novel Treatment.

INTRODUCTION

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to otherparts of the body. Sometimes this orderly process breaks down, and abnormal or damaged cells grow and multiply when they shouldn't. These cells may form tumors, which are lumps of tissue. Tumors can be cancerous (malignant) or not cancerous (benign) [1]. Various cancer therapies have evolved for different type of cancers all over the world. Many cancer patients are getting treated through these therapies but what are the further complications they are facing? One of the major complications faced by these patients are cardiovascular complications. The field of cardio-oncology has emerged to address these cardiovascular complications associated with cancer treatments, The intersection of cancer and cardiovascular diseases has led to the emergence of cardio-oncology as a specialized field within medicine.[2] Cardio- oncology focuses on elucidating the mechanisms underlying cardiovascular toxicities associated with cancer therapies and developing tailored strategies to mitigate these risks. This multidisciplinary approach involves close collaboration between oncologists, cardiologists, and other healthcare providers to optimize cancer treatment efficacy while safeguarding cardiovascular function [3].

Mechanism of cardiovascular damage by cancer treatments

Cancer treatments exert cardiovascular damage through diverse mechanisms, each contributing to distinct clinical manifestations and long-term health implications [4].

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Chemotherapy, particularly anthracyclines like doxorubicin, induces myocardial injury by generating reactive oxygen species (ROS) and disrupting cellular homeostasis. These oxidative stress pathways can lead to cardiomyocyte apoptosis and subsequent development of cardiomyopathy, a condition characterized by impaired cardiac function and potentially progressing to heart failure [4]. Radiation therapy, commonly employed in the treatment of thoracic and breast cancers, poses significant cardiovascular risks due to its detrimental effects on endothelial cells and surrounding vasculature. Chronic inflammation and fibrosis within the radiation field contribute to endothelial dysfunction, predisposing patients to accelerated atherosclerosis and increased incidence of ischemic heart disease[6]. The delayed onset of radiation-induced cardiovascular complications underscores the importance of long-term surveillance and preventive measures in cancer survivors [7]. Targeted therapies, including tyrosine kinase inhibitors (TKIs) and monoclonal antibodies, have revolutionized cancer treatment by targeting specific molecular pathways essential for tumor growth and proliferation [8]. However, these therapies can inadvertently disrupt physiological signaling pathways in the cardiovascular system, resulting in adverse cardiac events such as hypertension, left ventricular dysfunction, and thromboembolic events. The evolving landscape of immunotherapy, characterized by immune checkpoint inhibitors, introduces unique challenges with the potential for autoimmune myocarditis and immune-mediated cardiotoxicities [9].

Chemotherapy-induced cardiotocixity

This definition is the effect of the chemotherapy on cardiovascular system. Chemotherapy- induced cardiotoxicity

remains a critical concern in oncology practice, particularly with the use of anthracyclines and targeted therapies. These agents exhibit varying degrees of cardiac toxicity, necessitating vigilant monitoring and early intervention strategies to mitigate adverse cardiovascular outcomes in cancer patients [10]. The potential mechanisms underlying chemotherapy-induced cardiotoxicity include: 1) direct cellular toxicity leading to cumulative myocardial injury, resulting in both diastolic and systolic dysfunction; 2) impacts on the coagulation system, leading to ischemic events, thrombogenesis, and vascular toxicity; 3) arrhythmogenic effects; 4) hypertensive effects; and 5) myocardial and/or pericardial inflammation associated with myocardial dysfunction or pericardial sequelae [13]. Several chemotherapeutic drugs induce cardiac toxicity through mechanisms such as rapid apoptosis or necrosis, suppression of angiogenesis, or impairment of repair capacity, affecting both cancer cells and myocardial tissues. Anthracyclines, commonly used in chemotherapy, cause mitochondrial damage, disrupt ATP production, and induce cellular apoptosis. They also increase the production of free radicals, which further damage cellular membranes [14]. Taxanes can induce cardiotoxicity through damage to subcellular organelles or by causing histamine release, which may lead to conduction disturbances and arrhythmias. Trastuzumab, while not inherently cardiotoxic, can potentiate the cardiotoxic effects of anthracyclines by affecting ErbB2 receptors expressed in myocardial tissues, where these receptors play a protective role in cardiac function [16]. 5-Fluorouracil directly affects vascular endothelium, leading to coronary spasm and endothelial-independent vasoconstriction mediated by protein-kinase C [15].

Radiation therapy and cardiotoxicity

Radiation therapy is commonly used as an adjuvant treatment alongside chemotherapy or surgery for various types of cancer, including breast, lung, esophageal cancer, and lymphomas, exposing the heart to the harmful effects of irradiation [11]. Numerous literature reviews have explored potential mechanisms of cardiac toxicity associated with radiation therapy and outlined available treatment options [12]. Another crucial aspect involves the interval between exposure to radiation therapy and the onset of cardiac toxicities, alongside the radiation dosage received by the heart. Some cardiac toxicities may arise shortly after starting radiotherapy, such as pericardial effusion or acute pericarditis, arrhythmic events, and conduction abnormalities, while others, including coronary artery disease, valvular heart disease, chronic pericardial syndromes, and constriction, may manifest years after exposure [8].

Targeted therapies and their impact on heart

Targeted cancer therapies, including tyrosine kinase inhibitors (TKIs), immune checkpoint inhibitors (ICIs), and monoclonal antibodies, have transformed cancer treatment by specifically targeting molecules critical for tumor growth and progression. However, these therapies can inadvertently disrupt cardiovascular homeostasis, leading to cardiotoxic effects that vary in severity and mechanism. For instance, TKIs such as sunitinib and sorafenib, commonly used in renal cell carcinoma andother solid tumors, have been associated with hypertension, left ventricular dysfunction, and increased risk of cardiovascular events [17]. The mechanism underlying TKI-induced cardiotoxicity involves inhibition of vascular endothelial growth factor (VEGF) signaling, which disrupts vascular integrity and promotes hypertension and vascular rarefaction [18]. Immune checkpoint inhibitors (ICIs) like pembrolizumab and nivolumab, which enhance anti- tumor immune responses by blocking immune checkpoints such as PD-1/PD-L1, can lead to immune-related adverse events including myocarditis and pericarditis [19]. These conditions arise from dysregulated immune responses against cardiac tissues, resulting in inflammation and myocardial injury. Monoclonal antibodies targeting HER2, such as trastuzumab, used in breast cancer treatment, have demonstrated significant cardiotoxicity characterized by heart failure and declines in cardiac function [20].

Immune checkpoint inhibitors and cardiovascular sideeffects

Immune checkpoint inhibitors (ICIs) are a category of drugs primarily utilized in cancer therapy to augment the body's immune response against cancerous cells. These drugs function by inhibiting certain proteins produced by immune cells, like T cells, as well as some cancer cells. These proteins, referred to as checkpoints, can impede T cells from effectively eliminating cancer cells. By blocking these checkpoints, ICIs enable T cells to better identify and attack cancer cells. The mechanism of action for ICIs involves blocking checkpoint proteins from binding to their corresponding partner proteins. This action prevents the transmission of the “off” signal, thus allowing T cells to destroy cancer cells. One type of these drugs targets a checkpoint protein known as CTLA-4, while other immune checkpoint inhibitors target a protein called PD-1 or its partner protein PD-L1. Certain tumors can suppress the T cell response by producing high levels of PD-L1 [22].

The checkpoints most commonly targeted by ICIs include:

- CTLA-4 (Cytotoxic T-Lymphocyte-Associated Protein 4): Drugs that inhibit CTLA-4include ipilimumab.
- PD-1 (Programmed Death-1): Drugs that inhibit PD-1 include nivolumab andpembrolizumab.
- PD-L1 (Programmed Death-Ligand 1): Drugs that inhibit PD-L1 include atezolizumab,durvalumab, and avelumab.

ICIs have been linked to the onset of various cardiovascular toxicities, such as myocarditis, cardiomyopathy, pericarditis, and arrhythmias. Myocarditis is the most frequently observed cardiovascular toxicity, accounting for 45% of cases [23]. Although ICIs are highly effective intreating cancer, they have unique adverse effects distinct from those seen with cytotoxic chemotherapy, as they directly impact the immune system. Immune-related adverse events (IRAEs) occur in 70–90% of patients receiving ICIs, with severe IRAEs occurring in 10–15%of patients, and these reactions are fatal in up to 1.3% of patients. Signs and symptoms of ICI toxicity can include colitis, hepatitis, thyroiditis, hypophysitis, myocarditis, pericarditis, arthritis, uveitis, pneumonitis, or skin rash. Myocarditis, or inflammation of the myocardial muscle, is the most common and also the most lethal form of cardiotoxicity caused by ICIs, with a mortality rate of up to 50%. Myocarditis can develop as early as two weeks after starting ICI therapy; however, the median time to symptom onset is 65 days, with 81% of patients presenting within three months of initiating therapy. Patients with ICI-associated myocarditis often exhibit symptoms such as shortness of breath, palpitations, and signs of congestive heart failure, including edema, fatigue, weakness, or wheezing [24].

Pre-existing cardiovascular conditions and cancer treatment considerations

Patients with pre-existing cardiovascular conditions pose unique challenges in cancer treatment, as these conditions can impact treatment decisions, efficacy, and safety. This requires careful assessment and management to minimize cardiovascular risks.

- **Influence on Treatment Selection**

Patients with pre-existing cardiovascular conditions may require modifications in cancer treatment regimens. Certain therapies, such as anthracyclines or certain targeted therapies, maypose higher risks of exacerbating cardiovascular conditions or causing new cardiotoxic effects [8].

- **Monitoring and Surveillance**

Rigorous cardiovascular monitoring is essential throughout the cancer treatment course. Baseline assessments of cardiac function, including echocardiograms and cardiac biomarkers, help establish a reference point for detecting any treatment-related changes in cardiac function [21]. Regular follow-up evaluations during is necessary.

- **Cardiovascular Risk Management Strategies**

Implementing cardioprotective strategies is crucial in managing cancer patients with pre- existing cardiovascular conditions. These strategies may include reducing cardiovascular risk factors such as blood pressure, cholesterol levels, and using cardioprotective medications, such as beta-blockers or ACE inhibitors, may be initiated or adjusted to support cardiovascular health during cancer treatment [2].

Strategies for cardiovascular monitoring and management during cancer therapy

Regular cardiovascular monitoring during cancer therapy might include ECGs, cardiac biomarkers, and echocardiography. In cases of left ventricular dysfunction, cardiac magnetic resonance (CMR) imaging is crucial for diagnosing the underlying etiology and distinguishing between inflammatory and non-inflammatory dysfunctions, which have different treatment options and implications in cancer therapy. Cardiovascular monitoring of select cancer patients receiving cardiotoxic treatments, who are at higher risk, is a rational clinical strategy for the early detection of cardiac dysfunction. This approach allows for the implementation of cardioprotective strategies to enable the continuation of effective cancer therapies safely. The optimal monitoring strategy for each cancer treatment should include determining which modalities (imaging, biomarkers, or a combination) to use and the frequency of monitoring, with the goal of improving both cancer and cardiovascular outcomes [25].

The introduction of new cancer treatments, such as immunotherapies and kinase inhibitors, underscores the necessity of a specialized approach to cardiovascular care for cancer patients. Survivors frequently contend with cardiovascular issues that can compromise their overall health and quality of life, such as heart failure, hypertension, and atherosclerosis. Alkylating agents, antimetabolites, and anthracyclines have significantly advanced cancer pharmacotherapy. However, the cardiotoxic effects of anthracyclines, like doxorubicin, have introduced a new dimension to the relationship between cancer and cardiovascular health. The emergence of cardiovascular problems, such as hypertension, heart failure, and thrombosis, necessitates a sophisticated strategy for managing the cardiovascular health of cancer patients. Breast cancer survivors who undergo treatment with anthracyclines and HER2-targeted therapies face specific cardiovascular risks that differ from those of patients with othertypes of cancer.

Monitoring techniques and biomarkers

Echocardiography and cardiac MRI are non-invasive imaging techniques used to assess the structure and function of the heart. Cardiac troponins and natriuretic peptides are commonly employed biomarkers that indicate damage to the heart muscle and strain on the cardiac system. Dexrazoxane is a cardioprotective drug administered alongside anthracycline chemotherapy toreduce the risk of developing cardiomyopathy. The use of angiotensin-converting enzyme (ACE) inhibitors and beta-blockers has shown potential in preventing chemotherapy-induced cardiotoxicity. Cardiac MRI is particularly beneficial for oncologists and cardiologists as it provides detailed insights into the effects of cancer treatments on the heart [26].

Future directions in minimizing cardiovascular complications of cancer

Cardiovascular disease (CVD) in cancer patients is complex, necessitating personalized management and treatment plans. The field of cardio-oncology encompasses not only the prevention, detection, monitoring, and treatment of cardiovascular toxicity related to anticancertherapy but also the development of novel anticancer treatments that minimize the impact on cardiovascular health. Close collaboration among oncologists, cardiologists, and allied health professionals ensures the delivery of optimal care for cancer patients without compromising cardiovascular health. Implementing surveillance strategies in cancer survivors helps prevent potential long-term cardiovascular morbidity and mortality associated with oncological treatments. Educating healthcare providers, particularly the next generation of cardiologists and hematologists-oncologists, as well as patients, on the importance of cardiovascular health in conjunction with anticancer treatment, should lead to better cancer and cardiovascular clinical outcomes [27].

Conclusion

Balancing cancer treatment efficacy with cardiovascular safety

It is crucial to implement lifestyle adjustments to reduce cardiovascular risk in cancer patients. Promoting a heart-healthy lifestyle, which includes regular physical activity, a balanced diet, and smoking cessation, significantly enhances overall cardiovascular well-being. Lifestyle therapies for cancer survivors aim to manage cardiovascular risk factors and improve overall quality of life and health. Managing modifiable cardiovascular risk factors, such as hypertension, diabetes, and dyslipidemia, proactively and using pharmacological interventions as necessary, helps reduce

cardiovascular risk and can potentially enhance the safety of cancertreatments [26].

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