Cardiotoxicity In The Era Of Immuno-Oncology

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Abstract : The rise of immune-oncology (IO) has transformed modern cancer therapy, especially through the development of immune checkpoint inhibitors (ICIs) such as anti–PD-1, anti–PD-L1, and anti–CTLA-4 agents. These therapies have shown exceptional success by strengthening the immune system's capacity to recognize and eliminate malignant cells. However, alongside their therapeutic benefits, ICIs have also introduced a spectrum of immune-related adverse events (irAEs). Among these, cardiotoxicity, although uncommon, has become a clinically significant and potentially fatal complication. Cardiotoxic effects linked to IO therapies encompass myocarditis, pericarditis, arrhythmias, and heart failure. Myocarditis is of particular concern due to its rapid progression and high mortality, making timely detection and immediate treatment essential. The pathogenesis is thought to stem from immune-mediated inflammation, where activated T cells target cardiac tissues because of shared antigens between tumors and the myocardium, resulting in unintended immune cross-reactivity. Although the overall incidence of IO-related cardiotoxicity remains lower than that of other irAEs, its severity warrants careful attention. Patients with pre-existing cardiovascular disease appear to be at greater risk, highlighting the growing importance of cardio-oncology, a field dedicated to managing cardiovascular complications in cancer patients. Current strategies to reduce cardiotoxic risk include routine cardiovascular assessments, early use of corticosteroids to control immune inflammation, and close collaboration between cardiologists and oncologists to ensure integrated care. As IO therapies continue to advance, a deeper understanding of cardiotoxic mechanisms is essential. This review examines the pathophysiology, clinical presentation, and management approaches for IO-associated cardiotoxicity while emphasizing the urgent need for predictive biomarkers and safer therapeutic strategies.

Keywords: Cardiotoxicity; Myocarditis; Immune System; Arrhythmia; Cancer Immunotherapy; Cardiovascular Toxicity; Cardiooncology

1. INTRODUCTION:

With the increasing survival rates of cancer patients, the long-term adverse effects of chemotherapy—particularly cardiovascular complications—have become a major concern. In fact, the occurrence of cardiac injury, cardiotoxicity, and hypersensitivity reactions now exceeds the rate of tumor recurrence in many cases. Despite this growing issue, the identification of individuals at high risk for immunotherapy-related cardiac effects and the optimal strategies for managing these complications remain unclear. This highlights the urgent need for deeper exploration of the immune mechanisms linking cancer therapy and cardiovascular disease. The use of immune checkpoint inhibitors (ICIs) combined with immune-stimulating agents holds promise for enhancing anticancer efficacy while potentially reducing toxicity. However, administering immunotherapy to patients who have already experienced cardiovascular damage remains difficult. Conventional cardiotoxic agents, such as anthracyclines, may strengthen antitumor immune responses but simultaneously increase the risk of cardiac complications. Recent scientific progress has underscored the close relationship between immune processes and cardiovascular function, with inflammation emerging as a key contributor to heart disease. New insights—such as those involving clonal hematopoiesis—may pave the way for improved risk assessment and targeted interventions. Although the CANTOS trial demonstrated encouraging cardiovascular benefits, the lack

of regulatory approval for canakinumab highlights the challenges of translating experimental success into routine clinical use. Over recent decades, oncology research has significantly advanced our understanding of the molecular pathways driving tumor growth, treatment resistance, metastasis, and immune evasion. This has led to the development of numerous innovative therapeutic agents, with many more progressing through clinical pipelines. Among these, immunotherapy has emerged as one of the most promising systemic treatment strategies.

Alongside treatment efficacy, managing therapy-related adverse effects remains a critical priority. While various organs may be affected by anticancer drugs, cardiovascular toxicities are among the most serious, directly influencing patient survival and quality of life. The cardiotoxic effects of established therapies, such as anthracyclines and radiotherapy, are well documented and continue to be areas of intensive study.Advances in cancer therapy have improved patient survival, making early detection of therapy-related cardiotoxicity crucial. There are two types of cardiotoxicity: Type 1, associated with anthracyclines (e.g., doxorubicin), which can cause permanent myocardial damage, and Type 2, linked to targeted therapies like trastuzumab, which may recover after drug withdrawal.

Two-dimensional echocardiography (2DE) is commonly used to assess cardiotoxicity through left ventricular ejection fraction (LVEF), but it often fails to detect subtle dysfunction and has variability issues. Three-dimensional echocardiography (3DE) and speckle-tracking echocardiography (STE) are emerging as better alternatives, offering improved accuracy and reproducibility in detecting early cardiac changes. LV global longitudinal strain (GLS) derived from STE is particularly effective in identifying subclinical myocardial dysfunction and predicting cardiotoxicity before significant LVEF changes occur. However, limitations include availability and the need for consistent imaging technology.

Cardiovascular dysfunction or cardiac function worsening during chemotherapy might be attributed to chemotherapeutic drugs or to radiation therapy. Indeed, in a recent report concerning patients with left-sided breast cancer who received a higher mean heart dose of radiotherapy, the risk of ischemic heart disease was raised by 6.2% per Gy (gray Units of ionizing radiation dose, hazard ratio1.062, 95% confidence interval 1.01–1.12; p = 0.012)

2. Cardiac Toxicity:

The term **cardiotoxicity** is commonly used in cardiovascular medicine to describe the full spectrum of adverse cardiac effects caused by cancer treatments. When cardiovascular dysfunction persists even after discontinuing the offending therapy, it is classified as cardiotoxicity. **Acute cardiotoxicity** refers to harmful cardiac effects that arise following a single or short-term exposure to a treatment. Ultimately, untreated or progressive cardiotoxic damage can lead to myocardial fibrosis, which requires histological confirmation—an assessment that has not been extensively performed in current clinical practice.

2.1 Myocarditis

Although the complete mechanisms underlying therapy-induced myocarditis remain unclear, available evidence indicates that a heightened immune response plays a central role. Immunotherapy can lead to vigorous proliferation and activation of T cells that recognize antigens shared by both tumor cells and cardiac tissue. Studies have shown that identical T-cell clones can be detected in tumor samples as well as in inflamed myocardial tissue after immunotherapy, supporting a shared antigen-driven response.

Experimental models further demonstrate that immune checkpoint molecules such as **CTLA-4, PD-1, PD-L1, and LAG-3** provide protective signals that shield the heart from immune-mediated injury during stress. When these checkpoints are inhibited by immune checkpoint inhibitors (ICIs), cardiac cells may become more susceptible to immune attack. As a result, the same T-cell activity that contributes to tumor destruction may simultaneously trigger myocarditis.

2.2 Pericardial Disease

Pericardial complications associated with ICIs are believed to arise through mechanisms similar to those driving ICI-related myocarditis. Activation of cytotoxic T cells by immune checkpoint blockade can inadvertently target pericardial tissues, leading to inflammation, effusion, or other forms of pericardial involvement.

2.3 Takotsubo-Like Cardiomyopathy:

The mechanism underlying ICI-associated Takotsubo cardiomyopathy is unknownbut, unlike myocarditis and pericarditis, it seems to be non-inflammatory. ICIs may be directly responsible by causing acute multi-vessel coronary spasms. Alternatively, their damage may be indirect, the result of adrenergic stress during early ICI therapy in the form of a sudden and massive release of catecholamines from the adrenal glands or postganglionic sympathetic nerves in the heart, causing catecholamine-mediated myocardial stunning.

3. Myocardial Infarction:

Several pathophysiological mechanisms for ICI-associated MI have been hypothesized,but none have been definitively demonstrated. There is emerging evidence of a link between T cell activity and atherosclerotic plaque stability; because PD1 levels are elevated inplaque T cells, ICI therapy (e.g., PD1 inhibition) might activate these T cells and thus worsen atherosclerotic disease, potentially leading to cardiac ischemic events.

Moreover, ICI associated inflammation may cause the rupture of the plaque's fibrous cap, resulting in acute MI . Coronary spasm leading to ST elevation following PD1 inhibitor (pembrolizumab) therapy has also been postulated as a mechanism of ICI-associated acute MI.

The precise mechanism of coronary spasm is unknown, but it may be linked to a systemic inflammatory response syndrome. Finally, the direct activation of T-cell-mediated coronary vascul it is in the absence of atherosclerosis is a plausible mechanism of ICI-related acute MI, but this has yet to be reported.

4. Arrhythmias and Conduction Disorders:

Inflammation is thought to be the primary cause of conduction disease and ventricular arrhythmias, either locally in the ventricle or His-Purkinje system or systemically. Atrial fibrillation can occur as a result of myocarditis, pericarditis, systemic inflammation, or secondary to another irAE, such as thyroiditis.

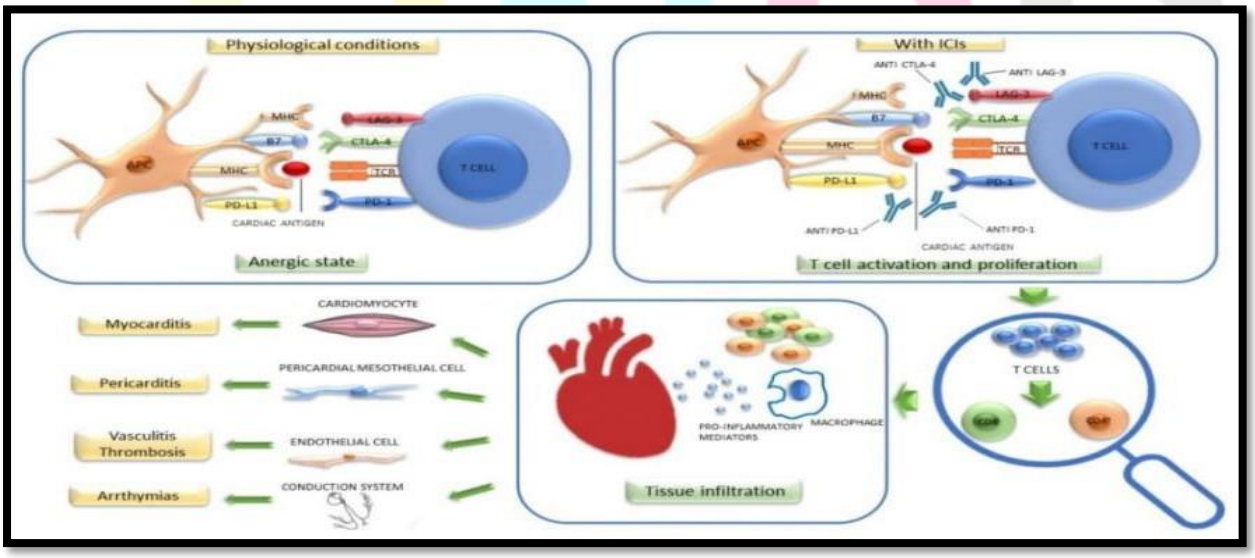

Figure 1 : Potential pathogenetic mechanism of cardiotoxicity induced by immune checkpoint inhibitors (ICIs).

5. Risk Factors And Treatments

The text discusses independent risk factors for cardiotoxicity associated with immune checkpoint inhibitors (ICIs) based on findings from an international registry. Key factors identified include combination ICI therapy, diabetes, obesity, and anti-CTLA-4 therapy, with combination therapy being the most significant, showing a nearly five-fold increased risk of myocarditis compared to monotherapy.

5.1. Ipilimumab:

A fully human CTLA-4 antibody approved in 2011 for cancers like melanoma and lung cancer. Common side effects include fatigue, diarrhea, rash, and colitis. Severe immune-related adverse events (IRAEs) occur in <1%, requiring permanent discontinuation; mild events improve with temporary withholding. Because it boosts immune activity, up to 90% of patients develop IRAEs rather than chemotherapy-type toxicity. Cardiotoxicity is extremely rare, and most IRAEs appear within the first 3 months.

5.2. Pembrolizumab:

A humanized IgG4 PD-1 antibody approved in 2014 for melanoma, lung cancer, and TNBC. It does not induce antibody-dependent cytotoxicity. Up to 70% of patients develop IRAEs, which may affect any organ system. Common effects: fatigue, musculoskeletal pain, low appetite, and GI symptoms. Rare cardiotoxicity (myocarditis, pericarditis) occurs in <1%.

5.3. Nivolumab:

A fully human IgG4 PD-1 antibody (approved 2014) for melanoma and NSCLC. Side effects: fatigue, rash, pruritus, diarrhea, nausea, and musculoskeletal pain. Severe IRAEs may appear even months later due to prolonged PD-1 inactivation (~3 months). Cardiac toxicity occurs in <1%.

5.4. Atezolizumab:

A humanized IgG PD-L1 antibody approved in 2016 for urothelial carcinoma and TNBC. Common effects: fatigue, nausea, cough, rash. Cardiotoxicity is very rare (<1%), but any such event requires permanent discontinuation. Only one case has been documented so far.

5.5. Durvalumab:

A fully human PD-L1 antibody approved in 2017 for urothelial carcinoma (post-platinum) and NSCLC. Side effects include fatigue, constipation, UTIs, and pneumonitis. Severe reactions—hyperthyroidism, colitis, hepatitis—may require dose adjustment, temporary halt, or permanent discontinuation.

6. Clinical Manifestation of ICI-Associated Cardiac Toxicity

6.1. Myocarditis:

The most serious ICI-related cardiac toxicity, with mortality rates up to 76% in combination therapy. Incidence ranges from 0.09% to 1–2%. Symptoms are often non-specific—chest pain, fatigue, dyspnea, palpitations, or sudden death—and many cases appear within the first 2–3 months of treatment. Risk factors include combination ICIs, prior cardiotoxic therapy, and existing heart disease. Diagnosis relies on elevated biomarkers, ECG changes, cMRI, and endomyocardial biopsy (gold standard). cMRI may show edema or late gadolinium enhancement but can miss early cases. Patients are classified as definite, probable, or possible myocarditis.

6.2. Pericarditis:

The second most common toxicity, presenting as effusion, tamponade, or perimyocarditis. It typically appears around 30 days after starting ICIs and is more common in males (60%). Diagnosis involves echocardiography, cMRI, and 18F-FDG PET/CT. ECG changes may include low QRS voltage, diffuse ST elevation, and tachycardia. Cases of rapid tamponade have been reported with nivolumab, emphasizing close monitoring.

6.3. Arrhythmias:

Arrhythmias may occur with or without myocarditis. Most common: atrial fibrillation (30%), followed by ventricular tachyarrhythmias (27%) and conduction disorders (17%); conduction issues markedly raise mortality. Mechanisms include inflammation of myocardium or conduction tissue, systemic inflammation, QT prolongation, or electrolyte imbalance. Regular ECG monitoring is essential, with early pacing for conduction abnormalities.

7. Diagnosis of ICI-Associated Cardiotoxicity

Routine evaluation during ICI therapy should include symptom review, physical examination, cardiac biomarkers, and repeated ECGs, with TTE used when abnormalities are suspected.

7.1. Electrocardiogram (ECG):

- ECG is sensitive but not specific, as many cancer patients show baseline abnormalities. Findings that raise suspicion for ICI-related cardiotoxicity include new PR prolongation, AV block, atrial or ventricular arrhythmias, ST depression, diffuse T-wave inversion, ST elevation mimicking STEMI, and new Q waves. Nonspecific T-wave changes are the most frequent abnormality in myocarditis.

7.2. Imaging Techniques:

- TTE can detect new global or segmental wall-motion abnormalities, LV systolic/diastolic dysfunction, Takotsubo-like changes, and pericardial effusion. Assessment should include LVEF and global longitudinal strain (GLS), as reduced GLS predicts higher adverse event risk even with preserved LVEF.
- cMRI is the second most useful tool, identifying edema, necrosis, and scar formation in ICI-associated myocarditis.

7.3. Laboratory Tests:

- Guidelines for routine biomarker screening are unclear. Studies suggest monitoring cardiac troponin at baseline or weekly for the first six weeks, though ASCO does not recommend routine serial testing. Natriuretic peptides and echocardiography may be used based on symptoms. Risk assessment should consider age, cardiac history, prior cardiotoxic therapies, and underlying malignancies such as NSCLC. More research is needed to define high-risk groups.

8. Mechanisms of Cardiovascular Toxicity

Cardiovascular disease and cancer share common risk factors such as aging and tobacco use. As cancer survival improves, cardiotoxicity from anticancer therapies has become more evident—especially in long-term survivors who often develop heart failure or arrhythmias years later. These toxicities complicate cancer treatment, particularly in older patients with reduced cardiac reserve. The main mechanisms of cardiotoxicity vary by drug class.

8.1. Anthracyclines:

The earliest known chemotherapy-related cardiotoxicity (Type I), caused by cardiomyocyte death. Damage is linked to oxidative stress from reactive oxygen species and interaction with topoisomerase IIβ in heart cells. Additional pathways include Rac1 and PGC-1α involvement.

8.2. HER2/ErbB2 Inhibitors (e.g., Trastuzumab):

Cause a distinct, often reversible cardiotoxicity. Trastuzumab blocks HER2/ErbB2 signaling, which is essential for cardiomyocyte survival. This “on-target” inhibition weakens cardiac stress-response pathways, predisposing patients to LV dysfunction.

8.3. Immune Checkpoint Inhibitors:

By boosting immune activity against cancer, ICIs can trigger autoimmune damage to healthy tissues. Cardiac effects stem from excessive immune activation, leading to myocarditis, pericarditis, and conduction abnormalities.

8.4. VEGF Inhibitors:

Block angiogenesis by inhibiting VEGF receptor tyrosine kinases. Cardiovascular toxicity results mainly from increased endothelin-1, reduced nitric oxide, and microvascular rarefaction, leading to rapid-onset hypertension and LV dysfunction. About half of patients develop hypertension and 4–8% develop symptomatic heart failure.

9. Cardioprotective Drugs

9.1. Dexrazoxane:

Dexrazoxane is the only FDA-approved drug for preventing anthracycline-induced cardiotoxicity. It works by chelating iron, preventing anthracycline-iron complex formation and reducing reactive oxygen species. Evidence shows it significantly lowers the risk of heart failure without reducing anticancer effectiveness, though it may increase leukopenia. ASCO recommends its use in patients receiving high cumulative doses of doxorubicin (>300 mg/m²) who require continued therapy.

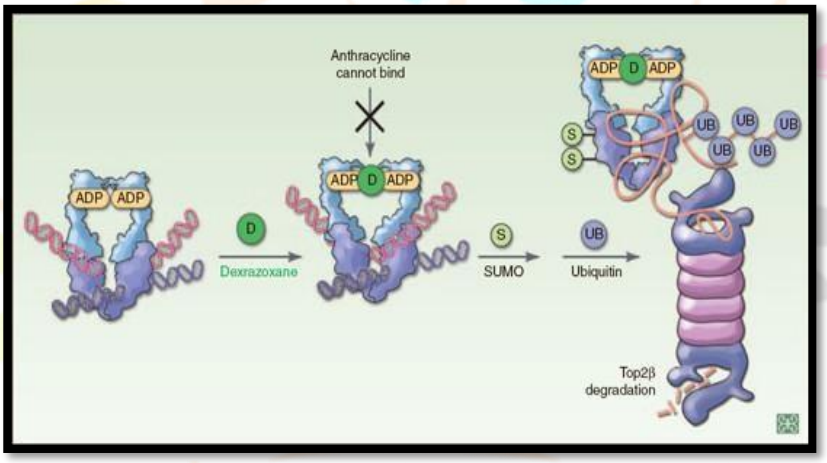

Figure 2 :Mechanisms of Dexrazoxane

9.2. Statins:

Statins exhibit antioxidant and cardioprotective effects. Preclinical studies show that lovastatin reduces doxorubicin-induced cardiomyocyte death and Top2β-mediated DNA damage, suggesting potential benefit in limiting anthracycline-related toxicity.

9.3. β-Blockers:

β-blockers, especially carvedilol, are increasingly used to reduce chemotherapy-related cardiotoxicity. Their cardioprotective mechanisms include antioxidant activity, nitric oxide stimulation, inhibition of harmful signaling pathways, and activation of β-arrestin–mediated protective pathways. They may also modulate SERCA2 to prevent calcium overload and reduce cardiac remodeling.

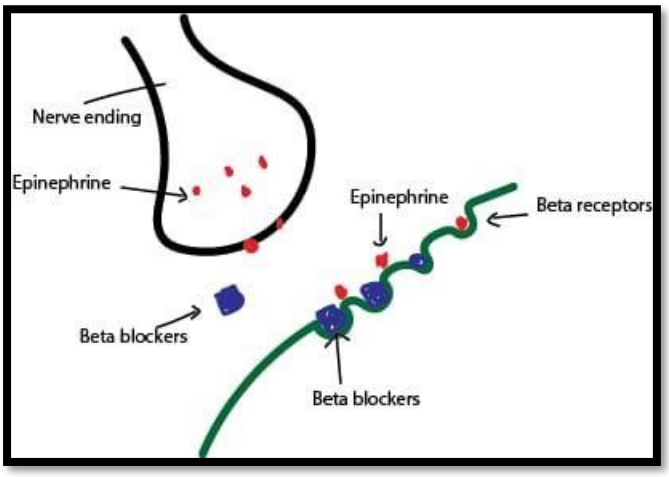

Figure 3 : Mechanisms of β-blockers

9.4. ACE Inhibitors (ACEIs):

ACE inhibitors help prevent anthracycline-induced cardiomyopathy by blocking the renin-angiotensin system. They reduce oxidative stress, limit cardiac fibrosis, decrease apoptosis, and improve mitochondrial function. Experimental data support their role in reducing heart failure risk in patients undergoing chemotherapy.

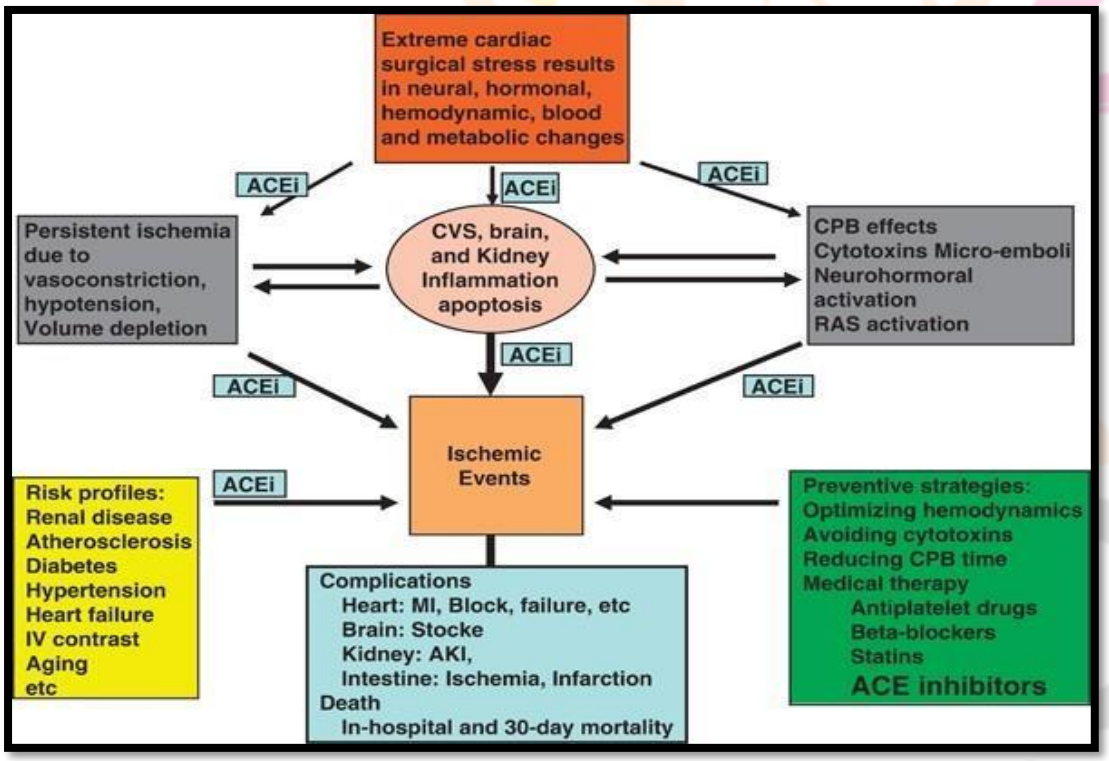

Figure 4 : ACE Inhibitors in cardiac surgery

10. Conclusion:

Immunotherapy has revolutionized cancer treatment, offering improved survival rates and new hope for many patients. However, a significant challenge is the risk of cardiotoxicity, which can lead to heart damage through immune-related adverse events. Understanding the mechanisms of cardiotoxicity is essential, especially for patients with pre-existing cardiovascular conditions or those receiving combination therapies. A proactive, multidisciplinary approach involving oncologists, cardiologists, and primary care providers is crucial for early identification and management, including regular cardiovascular monitoring. Educating patients about symptoms of cardiotoxicity and conducting ongoing research to develop targeted prevention strategies can improve patient outcomes and enhance the effectiveness of immuno-oncology treatments, ensuring safer, more effective cancer care.

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