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Immune-Related Cardiotoxicity of Checkpoint Inhibitors: Mechanisms, Biomarkers, and Emerging Cardioprotective Strategies

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ABSTRACT

Immune checkpoint inhibitors (ICIs), including CTLA-4, PD-1, and PD-L1 inhibitors, have revolutionized cancer therapy by restoring T-cell-mediated anti-tumor immunity. However, their use is increasingly associated with immune-related adverse events (irAEs), including potentially fatal cardiotoxicity. ICI-related cardiotoxicities range from myocarditis and pericarditis to arrhythmias and heart failure, and often present with fulminant onset and high mortality. This review examines the immunopathological mechanisms underpinning ICI-induced cardiotoxicity, including T-cell infiltration, cross-reactivity with cardiac antigens, and the role of cytokine storms. We also explore the challenges of early diagnosis, current and emerging cardiac biomarkers, and the utility of non-invasive imaging. Furthermore, we highlight therapeutic strategies, including immunosuppression, guideline-directed cardiology management, and investigational cardioprotective agents. Improved understanding of this emerging clinical entity is essential to balancing oncologic efficacy with cardiovascular safety in cancer immunotherapy.

Keywords: Immune checkpoint inhibitors, Cardiotoxicity, Myocarditis, Biomarkers, Immunotherapy

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have transformed the landscape of oncology, offering durable responses across various malignancies, including melanoma, lung cancer, renal cell carcinoma, and Hodgkin lymphoma [1]. By inhibiting regulatory proteins such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death-1 (PD-1), and programmed death-ligand 1 (PD-L1), ICIs unleash the immune system to attack tumor cells [2]. However, this immune activation can be nonspecific and may extend to normal tissues, resulting in a broad spectrum of immune-related adverse events (irAEs). Among the most serious and underrecognized irAEs is cardiotoxicity [3]. Although less frequent than dermatologic or gastrointestinal toxicities, ICI-associated cardiotoxicity, particularly myocarditis, carries high mortality rates—reported to be as high as 50 percent in fulminant cases [4]. The true incidence may be underestimated due to lack of systematic screening and variability in clinical presentation. As ICIs gain broader use in combination regimens and earlier cancer stages, the burden of cardiovascular immune toxicity is expected to rise. This review aims to provide a comprehensive understanding of the immune-related mechanisms underlying ICI-induced cardiotoxicity, discuss the current and emerging tools for diagnosis and monitoring, and evaluate treatment and prevention strategies to mitigate cardiovascular complications without compromising oncologic efficacy.

Mechanisms of Immune-Related Cardiotoxicity

Immune checkpoint inhibitors (ICIs) function by releasing the physiological brakes on T-cell activation, thereby enhancing anti-tumor immune responses [5]. However, this immunologic reactivation can breach self-tolerance and provoke autoimmunity, leading to off-target damage in multiple organs, including the heart [6]. Cardiotoxicity from ICIs is most frequently manifested as autoimmune myocarditis, characterized histologically by dense infiltration of cytotoxic CD8+ T cells and CD68+ macrophages in myocardial tissue [7]. This infiltration results in widespread myocyte necrosis and inflammation. The pathogenesis is driven in part by molecular mimicry, wherein tumor and cardiac tissues share antigenic epitopes [8]. Activated T cells may cross-react with myocardial antigens such as α-myosin or troponin, leading to targeted cytotoxicity [9]. Experimental data from PD-1 and CTLA-4

knockout mice demonstrate a predisposition to myocarditis and dilated cardiomyopathy, underscoring the physiological importance of these checkpoints in cardiac immune regulation [10].

In addition, ICIs can trigger a cytokine milieu characterized by elevated IL-6, TNF-α, and IFN-γ, promoting further immune cell recruitment and myocardial injury [11]. These cytokines also enhance antigen presentation and sustain immune activation, exacerbating the autoimmune response [12]. Combination ICI therapy intensifies this effect and is associated with more severe cardiac events.

Clinical Manifestations and Diagnostic Challenges

The clinical spectrum of ICI-related cardiotoxicity is diverse, ranging from asymptomatic troponin elevation to fulminant myocarditis and fatal arrhythmias [13]. Myocarditis is the most frequently reported and feared manifestation [14]. It typically presents within the first six weeks of treatment and may include symptoms such as chest pain, shortness of breath, palpitations, or fatigue. In severe cases, cardiogenic shock or sudden cardiac death can occur [14]. Other cardiovascular irAEs include pericarditis, with or without effusion [15]; arrhythmias, including atrial fibrillation, ventricular tachycardia, and high-grade atrioventricular block [16]; and new-onset or exacerbated heart failure [17]. Importantly, these conditions often overlap with other systemic irAEs such as myositis or myasthenia gravis, indicating a shared autoimmune basis [18]. Diagnosis is complicated by the nonspecific nature of presenting symptoms and the often-normal findings on standard cardiac investigations. While electrocardiogram abnormalities and echocardiographic changes may support the diagnosis, they lack specificity [19]. This makes a high index of suspicion essential, especially in patients receiving combination checkpoint blockade or those with pre-existing cardiac risk factors.

Biomarkers and Imaging in Detection

Early detection of ICI-induced cardiotoxicity is critical but remains challenging due to a lack of specific and sensitive diagnostic tools. Cardiac troponins (I and T) are currently the most utilized biomarkers, with elevated levels commonly observed in ICI-associated myocarditis [20]. However, elevated troponin may also result from other irAEs or underlying cardiac conditions, limiting its diagnostic specificity [21]. Brain natriuretic peptide (BNP) and NT-proBNP can indicate myocardial stress or volume overload, which may suggest heart failure, but they are also nonspecific [22]. High-sensitivity C-reactive protein (hs-CRP), interleukin-6, and other inflammatory cytokines are under investigation for their utility in detecting subclinical inflammation and stratifying risk [23]. Cardiac magnetic resonance imaging (CMR) has emerged as the preferred imaging modality for suspected myocarditis [24]. It provides high-resolution tissue characterization, revealing myocardial edema, late gadolinium enhancement (LGE), and regional wall motion abnormalities [25]. These findings support the diagnosis and may correlate with disease severity. Endomyocardial biopsy remains the definitive test but is invasive and subject to sampling error, thus reserved for ambiguous or severe cases [26].

Therapeutic Strategies and Cardiac Risk Management

Management of ICI-associated cardiotoxicity involves prompt recognition, withdrawal of the offending agent, and early initiation of immunosuppressive therapy [27]. High-dose corticosteroids, typically methylprednisolone at 1–2 mg/kg/day, are the first-line treatment and have shown the best outcomes when administered early [28,29]. Delayed treatment is associated with poor prognosis, emphasizing the need for rapid clinical decision-making.

For patients unresponsive to corticosteroids, additional immunosuppressive agents such as mycophenolate mofetil, intravenous immunoglobulin (IVIG), abatacept, or infliximab may be considered [30]. These agents have demonstrated some success in case series, but robust evidence from clinical trials is lacking. Supportive cardiac care is also essential and should be guided by standard cardiology protocols. This includes guideline-directed medical therapy for heart failure, arrhythmia management, and consideration of device therapy for life-threatening conduction abnormalities. Some patients may require temporary pacing or implantable cardioverter-defibrillators.

Preventive strategies include pre-treatment cardiac screening with ECG and baseline biomarkers, particularly in high-risk individuals. Emerging research is exploring prophylactic use of beta-blockers, renin-angiotensin system inhibitors, and mitochondrial-targeted antioxidants to mitigate cardiac inflammation without compromising anti-tumor efficacy [31]. Ongoing trials are also evaluating whether dose-modulation or sequential checkpoint blockade can reduce cardiotoxic risk [32].

Future Directions and Research Needs

Despite growing recognition of immune-related cardiotoxicity, many aspects of its epidemiology, pathophysiology, and optimal management remain inadequately characterized. Prospective, multicenter cohort studies and real-world registries are urgently needed to ascertain the true incidence and spectrum of ICI-associated cardiovascular complications. These efforts should also aim to standardize diagnostic criteria, define subclinical disease presentations, and establish validated grading systems for cardiotoxicity severity.

There is significant momentum toward the development of predictive tools based on clinical risk factors, immunophenotyping, and genetic susceptibility. Integrating these variables into machine learning-based algorithms may enable risk stratification before ICI initiation. In addition, longitudinal biomarker profiling—including cardiac

troponins, cytokine panels, and circulating microRNAs—may serve as a foundation for biomarker-guided surveillance strategies that allow early intervention before irreversible myocardial damage occurs.

Therapeutically, novel immune-modulatory approaches are gaining interest. These include strategies aimed at selectively inducing immune tolerance to cardiac antigens, blocking specific inflammatory cytokines such as IL-6 or IFN-γ, and using engineered regulatory T cells or immune checkpoint "decoys" that preserve anti-tumor immunity while mitigating autoimmunity. Furthermore, the feasibility of re-challenging patients with ICIs following recovery from cardiotoxicity remains an area of active investigation, requiring careful patient selection and monitoring protocols.

Collaboration across cardiology, oncology, immunology, and bioinformatics will be essential to advance research in this field and translate discoveries into clinical practice. Emphasis should also be placed on including diverse populations to ensure findings are generalizable and equitable.

CONCLUSION

While immune checkpoint inhibitors represent a major milestone in cancer immunotherapy, they have also introduced new risks in the form of immune-mediated cardiotoxicity. Myocarditis, though rare, carries a high fatality rate and exemplifies the complexity of balancing immune activation with cardiovascular safety. Future progress depends on deeper mechanistic insight, enhanced diagnostic tools, and the development of targeted strategies that preserve oncologic efficacy while protecting cardiac health. A multidisciplinary cardio-oncology approach, coupled with advances in precision immunotherapy, offers the most promising path forward in managing this evolving clinical challenge.

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