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REVIEW

Cardiotoxicity from Immune Checkpoint Inhibitors: Myocarditis

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Importance: Immune checkpoint inhibitors (ICIs) are a class of immunotherapies that have significant clinical efficacy in treating many cancer types, but they are also associated with systemic effects, including myocarditis.

Objective: This review describes potential mechanisms underlying ICI-associated myocarditis; data on epidemiology, including possible risk factors; diagnostic criteria for ICI-associated myocarditis; and recommendations for managing ICI-associated myocarditis.

Review: This paper is a narrative literature review that summarizes existing literature to increase awareness of ICI-associated cardiotoxicities, including myocarditis.

Findings: Reported cardiovascular adverse events include myocarditis, cardiomyopathy, arrhythmias, pericarditis, vasculitis, atherosclerotic cardiovascular events, Takotsubo syndrome, and venous thromboembolism. Myocarditis is associated with the highest risk of morbidity and mortality.

Conclusions: With increasing use of ICIs, there is an urgent need for greater awareness and understanding of ICI-associated myocarditis. Clinicians need to recognize the diagnostic criteria and develop current treatment recommendations for ICI-associated myocarditis given the condition's variable clinical presentation and potential fulminant course.

Keywords: myocarditis, cardiotoxicity, immune checkpoint inhibitors, programmed cell death protein 1, cytotoxic T-lymphocyte-associated protein 4

Immune checkpoint inhibitors (ICIs) represent a major advance in the field of immunotherapy and have changed the standard of care for many cancer types. In 2019, an estimated 44% of patients with cancer in the United States were eligible for treatment with ICIs.[1] Immune checkpoints are regulatory pathways that attenuate the immune response and are upregulated by tumor cells to evade antitumor attack by immune cells.[2] ICIs target immune checkpoints, programmed cell death protein 1 (PD-1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) to promote the antitumor immune response.[2] Although ICIs have led to improved survival of patients with cancer, they are associated with adverse events that affect various organ systems.[3]

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OBJECTIVE

This review focuses on ICI-associated myocarditis, or inflammation of the myocardium.[4] Although cardiotoxicities are not among the most common type of immune-related adverse events (irAEs), ICI-associated myocarditis can be fatal.[5] As the use of ICIs becomes more common, greater awareness, timely diagnosis, and effective management of ICI-associated myocarditis is essential.

REVIEW

This narrative literature review is intended for cardiology providers, oncology providers, and primary care providers who may encounter patients treated with ICI therapies. The literature included in this review was found via a PubMed search and selected based on relevance to the topic and reputation of the journal.

FINDINGS

Immune checkpoints: CTLA-4 and PD-1

In 2018, James P. Allison and Tasuku Honjo were awarded the Nobel Prize in Physiology or Medicine for their seminal work in immune checkpoint pathways. Two central checkpoints, CTLA-4 and PD-1, participate in signaling pathways essential in regulating T-cell activation. These checkpoints inhibit T-cell activation by distinct but potentially synergistic mechanisms.[6] CTLA-4 is a receptor protein predominantly expressed on naïve T cells and constitutively expressed on memory T cells and T-regulatory cells for suppressive functions.[7] CTLA-4 increases the activation threshold of T cells, thus functioning as an essential regulatory pathway in preventing the development of autoreactive T cells at the initial stage of T-cell activation. This process could contribute to autoimmune pathology.[8]

The PD-1 immune checkpoint pathway involves the transmembrane protein PD-1 and programmed death-ligand 1 (PD-L1) and PD-L2.[9] Whereas CTLA-4 expression is confined to T cells, PD-1 receptors are also expressed on B, natural killer, and myeloid cells.[9] PD-1 ligands are expressed on various antigen-presenting cells.[8] Although CTLA-4 regulates the early stages of T-cell activation primarily in the lymph nodes and spleen, the PD-1 pathway also regulates the effector phase in later stages of the immune response in peripheral tissues.[10] In addition to inhibiting the expansion of naïve self-reactive T cells and their differentiation into effector cells, PD-1 restricts self-reactive T-cell effector function.[11]

Blocking immune checkpoints in cancer

Tumor cells have greater genetic instability than normal cells and, therefore, can more easily acquire mutations that upregulate immune checkpoints.[12] This upregulation by malignant cells results in reduced immune cell growth factors and a dampened immune response toward malignant cells.[13,14] This effect enables tumor cells to inhibit T-cell survival and proliferation, induce resistance against lysis mediated by $CD8^+$ T cells, and create a molecular shield to avoid immune attack and tumor-cell apoptosis.[12,13] Development of tumor cells that resist the immune response and selection of these clones through immunoediting give rise to a tumor microenvironment that largely suppresses antitumor immune activity.[8,15]

ICIs, which are monoclonal antibodies (mAbs), alter the tumor microenvironment by blocking the CTLA-4 and PD-1 pathways and activating T cells against cancer cells.[2,15] There are 7 approved ICIs used for cancer therapy, and additional mAbs targeting the CTLA-4 and PD-1 pathways are under preclinical and clinical development.[11] Ipilimumab, an anti-CTLA-4 mAb, was the first approved ICI for treating metastatic melanoma.[13] The remaining 6 ICIs all target the PD-1 pathway. Pembrolizumab, nivolumab, and cemiplimab are mAbs against PD-1; avelumab, durvalumab, and atezolizumab are mAbs against PD-L1 (Table 1).[11] Non-small-cell lung cancer, renal cell carcinoma, Hodgkin lymphoma, and, particularly, metastatic melanoma are the cancer types with the best responses to ICIs.[1] In some malignancies, such as melanoma, combination therapy has greater efficacy than monotherapy with a single ICI agent.[16]

ICI-associated myocarditis

Although ICIs are effective against many cancers, their use is associated with immune-related adverse events. Unfortunately, the T-lymphocyte activation seen with ICIs is not specific to cancer cells, and autoimmune-like adverse events are common and involve various organ systems.[17] Reported cardiovascular adverse events include myocarditis, cardiomyopathy, arrhythmias, pericarditis, vasculitis, atherosclerotic cardiovascular events, Takotsubo syndrome, and venous thromboembolism.[18] Myocarditis is the most feared complication given its high mortality rate.[18]

The exact mechanism underlying ICI-related myocarditis remains unclear, and there are several proposed mechanisms. For example, blocking the PD-1 and CTLA-4 pathways reduces peripheral immune tolerance to the heart.[19] PD-1 and PD-L1 are expressed in cardiomyocytes to protect against autoreactive lymphocytes in the heart.[20] Cytotoxic T-lymphocyte killing of myocardial cells induces secretion of interferon-γ, upregulating PD-1 expression on surrounding myocardial cells to protect against further damage.[21] It is thought that PD-1 mAbs inhibit this upregulation, leading to activation of T cells that target cardiomyocytes.[22] Also, blocking CTLA-4 may result in reduced T-regulatory cells that constitutively express CTLA-4.[22] Two studies examining mouse models found that mice lacking the PD-1 receptor developed a dilated cardiomyopathy.[23,24]

Table 1. ICIs Approved by the Food and Drug Administration

Drug	Target	Indication
Ipilimumab	CTLA-4	Melanoma
Pembrolizumab	PD-1	Melanoma, non-small-cell lung cancer, Hodgkin's lymphoma, squamous cell carcinoma of head and neck, urothelial carcinoma, gastric cancer, Merkel cell carcinoma
Nivolumab	PD-1	Melanoma, non-small-cell lung cancer, Hodgkin's lymphoma, squamous cell carcinoma of head and neck, urothelial carcinoma, gastric cancer, Merkel cell carcinoma
Cemiplimab	PD-1	Non-small-cell lung cancer, locally advanced basal cell carcinoma, cutaneous squamous cell carcinoma
Avelumab	PD-L1	Merkel cell carcinoma, urothelial carcinoma, renal cell carcinoma
Durvalumab	PD-L1	Non-small-cell lung cancer, small-cell lung cancer

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Postmortem histological analyses of heart tissue from patients with myocarditis revealed immune infiltrates in the heart, specifically T-lymphocyte infiltration of the myocardium were predominantly $CD8^+$.[25] Histological analysis is a valuable tool for further elucidating mechanisms of checkpoint blockade-induced cardiotoxicities. Understanding the exact mechanism underlying ICI-related myocarditis will be valuable for clinicians and has the potential to improve treatment.[26]

Epidemiology

General irAEs occurred in 60% to 80% of patients treated with ICIs.[18] In 3326 patients who received ICIs, 2.4% experienced cardiovascular irAEs.[27] Several analyses found that 0.02% to 1.14% of patients treated with ICIs develop myocarditis.[28,29] Although the incidence of myocarditis is low, the mortality is exceedingly high. ICI-induced myocarditis has a fatality rate estimated at as high as 50%.[18,30,31] Mahmood et al. found 46% of myocarditis cases resulted in a major adverse cardiovascular event, which includes cardiovascular death, cardiogenic shock, or cardiac arrest.[29] Overall, more than 80% of cardiovascular irAEs are severe, and 17% of ICI-induced deaths are cardiac-related.[32] Overall, both the number and proportion of ICI-associated myocarditis cases compared to all ICI-associated irAE cases have increased since 2012.[30] The true incidence of ICI-associated myocarditis is likely underreported due to the challenge of making the diagnosis, which may not be recognized until histological analysis at autopsy.[33]

Several risk factors exist for developing ICI-associated cardiotoxicity. Combination therapy with 2 immune checkpoint inhibitors is consistently associated with an increased incidence of myocarditis and a higher fatality rate than monotherapy.[30,34,35] Genetic factors may influence the risk of developing myocarditis, but are still largely unknown.[36] A review of 3326 patients treated with ICIs found 3 clinical factors associated with a higher incidence of myocarditis: history of acute coronary syndrome, history of heart failure, and age greater than 80 years.[27] A separate study of patients treated with ICIs found diabetes was more common in patients who developed myocarditis.[29] Further research is needed to develop a more comprehensive risk-prediction model for ICI-associated cardiotoxicities.

Diagnosis

Myocarditis has a wide clinical presentation that ranges from subclinical disease to mild symptoms (eg, fatigue, general malaise, weakness, palpitations, chest pain, dyspnea) to severe symptoms (eg, ventricular arrhythmias, myocardial injury, heart failure with hemodynamic compromise, cardiogenic shock, cardiac arrest).[5,13,18] The initial presentation of ICI-associated myocarditis varies as well. Fulminant myocarditis is characterized by hemodynamic or electrophysiological instability,[37] and it can initially present with a non-dilated left ventricle with increased wall thickness and preserved left ventricular function.[38] Myocarditis must be detected early due to the potential for a more fulminant course.[39]

The median time to myocarditis onset is 17 to 34 days[18]; however, the timing can be variable. One study reported a range of ICI-associated myocarditis onset as wide as 5 to 155 days.[34] Another study reported a case of fulminant myocarditis that developed over 1 year of treatment without any previous symptoms.[40] Overall, most cases occur earlier in the treatment course. One study reported that 76% of ICI-myocarditis cases occurred in the first 6 weeks of ICI treatment, and 64% of patients received 1 or 2 doses of an ICI before myocarditis onset.[34] Interestingly, the onset of cardiotoxicity tends to be earlier in patients treated with ICI combination therapy.[5]

Concurrent irAEs occur in approximately 50% of patients with ICI-associated myocarditis.[41] Myositis and myasthenia gravis are the most common,[34] possibly due to shared antigens in cardiac and skeletal muscle.[32,42] Diagnosing ICI-associated myocarditis in patients treated with concurrent or previous chemotherapy or radiation therapy requires even greater scrutiny. Because other cancer therapies (eg, anthracyclines) can also cause cardiotoxicities,[39] it can be challenging to distinguish which therapy causes the cardiotoxicity.

There is no single test for myocarditis, and the diagnosis relies on integrating findings from physical examination, history, electrocardiogram (ECG), biomarkers, echocardiography, cardiac magnetic resonance (CMR) imaging, and possibly endomyocardial biopsy.[18]

One paper recommended performing a baseline ECG before each ICI dose and again when the patient develops cardiac symptoms.[37] However, this recommendation has not been prospectively validated as a cost-effective strategy. ECG abnormalities found in patients with ICI-associated myocarditis include ST-segment changes and arrhythmias, the latter associated with a poor prognosis.[38] ST-elevation mimicking myocardial infarction can indicate fulminant myocarditis.[37] Although ECG is highly sensitive in detecting cardiac irAEs and is commonly abnormal for myocarditis, ECG lacks enough specificity to be the only test for diagnosing myocarditis.[18,37]

ICI-associated myocarditis is typically characterized by an elevated troponin, which reflects myocardial injury.[38] Troponin is generally regarded the most sensitive biomarker for myocarditis,[5] although it may be initially normal in some cases.[43] An elevated troponin can also indicate myocardial injury from other mechanisms, such as pre-existing cardiovascular disease, cancer progression, or acute coronary syndrome.[44] Additional cardiac biomarkers should also be assessed for abnormalities, including total creatine kinase, creatine kinase-myocardial band, and N-terminal pro-brain natriuretic peptide.[40]

Echocardiography is most often the initial imaging test in cases of suspected myocarditis.[45] Findings that support myocarditis include abnormalities of left or right ventricular systolic function, new-onset diffuse or segmental wall motion abnormalities, changes in the size of cardiac chambers, pericardial effusion, and diastolic dysfunction with preserved ejection fraction.[37,45] Myocarditis may resemble dilated, hypertrophic, and restrictive cardiomyopathy on echocardiography.[45] As with other diagnostic tests, echocardiography alone cannot make the diagnosis as it lacks specificity, and patients with severe myocarditis can have a normal echocardiogram.[18]

Because many patients with ICI myocarditis will present with chest pain, biomarker and/or ECG evidence of myocardial injury is important to exclude non-ICI etiologies, such as coronary artery disease. The threshold for pursuing coronary angiography will depend on the clinical scenario and patient-specific factors. This threshold should be considered given the prevalence of cardiac risk factors and established cardiovascular disease in many patients with cancer.[42]

CMR imaging is the gold standard for the imaging diagnosis of non-ICI-associated myocarditis, relying on the presence of imaging markers of myocardial edema and myocardial injury (ie, late gadolinium enhancement).[39] Importantly, CMR diagnostic criteria have been validated for non-ICI myocarditis, and criteria specific for ICI-associated myocarditis are lacking. Zhang et al. reported that 58% of 77 patients with ICI-associated myocarditis had a normal left ventricular ejection fraction, and only 52% of patients had late gadolinium enhancement.[46] Using the established diagnostic criteria for non-ICI myocarditis (referred to as the Lake Louise Criteria), less than 50% of patients with confirmed ICI myocarditis who presented with a preserved ejection fraction had neither late gadolinium enhancement nor evidence of myocardial edema on standard imaging.[47] These results caution

against an overreliance on non-ICI-myocarditis criteria. Recently, Thavendiranathan et al. reported using the CMR technique to characterize tissue with quantitative parametric mapping (also known as T1 and T2 mapping).[48] Using these parameters led to improved sensitivity and prognostic value in this retrospective registry.[46] Further studies are needed to validate these findings.

Endomyocardial biopsy is still the gold standard for non-ICI myocarditis, though routine use of biopsy is uncommon.[37] In the case of ICI-associated myocarditis, endomyocardial biopsy is important, particularly when the diagnosis is uncertain based on clinical and imaging characteristics. An early and accurate diagnosis is critical to ensure that treatment strategies begin quickly. Moreover, rechallenging patients with an ICI after myocarditis develops is typically avoided due to the risk of recurrent myocarditis.[42] As such, an accurate diagnosis of ICI myocarditis is key when the stakes are so high.

Overall, the diagnosis of ICI-associated myocarditis remains challenging and requires a combination of clinical, ECG, laboratory, imaging, and possibly histologic data (Table 2). Increased awareness of ICI-associated myocarditis is an important step toward early detection and treatment. In patients who present with cardiovascular symptoms while on ICIs, there should be a low threshold to pursue further testing and involve cardiovascular specialists given the high risk of morbidity and mortality.

Management

Early diagnosis of ICI-associated myocarditis is critical to initiate management, which involves discontinuing ICI therapy and immediately administering corticosteroids.[20,39] For most grade 1 non-cardiac irEAs, continuing ICI treatment with careful monitoring is standard care; however, for all grades of cardiac irAEs, ICI treatment must be discontinued due to the more severe course.[49] Standard corticosteroid treatment involves systemic prednisone or methylprednisolone at 1 to 2 mg/kg/day for 4 to 6 weeks.[18,39,49] Mahmood et al. found a higher initial dose of methylprednisolone was associated with fewer major adverse cardiac events and a lower final serum troponin level.[29] Troponin levels should be monitored serially to assess the patient's response to the steroids.[42] Myocarditis may worsen despite an initial improvement from corticosteroid therapy.[42] If the patient is unresponsive to initial corticosteroids or their condition worsens, higher doses of corticosteroids can be tried (1 g methylprednisolone/day).[3] If there is a limited response to steroids, then additional immunosuppressants should be considered, such as abatacept,[26] alemtuzumab,[50] mycophenolate mofetil, and infliximab.[39,49] Infliximab should be used cautiously because of the risk of worsening heart failure; a lower dose of 5 mg/kg instead of 10 mg/kg is advised for patients with acute decompensated heart failure.[42] High-dose infliximab is also contraindicated in patients with left ventricular dysfunction.[43] In terms of other treatments, reports have suggested using antithymocyte globulin and tacrolimus.[32] [32] Intravenous immunoglobulin, plasmapheresis, and immunoadsorption therapy may also be considered in steroid-refractory cases.[19,42] There is limited consensus and lack of a large evidence base to guide treatment after starting corticosteroids. Consultation with dedicated cardio-oncologists is recommended if available.

CONCLUSIONS

This review highlights that ICI-associated myocarditis remains a challenging diagnosis due to its variable clinical presentation and requires a high index of suspicion in the early phase.

Early diagnosis is critical given the potential fulminant course that is associated with a high mortality rate. There is a need for more comprehensive diagnostic criteria and for effective screening strategies. Also, future research on risk factors is essential to help generate a more robust risk-prediction tool. The true incidence of ICI-associated myocarditis is likely higher than described in the literature and highlights the need for additional epidemiological studies. In terms of treatment, there is a need for research on optimal treatment pathways, such as randomized controlled trials examining corticosteroid dosages/duration or efficacy of various additional immunosuppressants in steroid-refractory cases. As use of immune checkpoint inhibitors increases, a better understanding of ICI-associated cardiotoxicities is paramount.

Conflicts of Interest: None

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Table 2. Summary of Diagnostic Tools in ICI Myocarditis

Diagnostic tool	Potential findings	Utility
Electrocardiogram	• ST-segment changes • Arrhythmias	Low specificity
Echocardiogram	• Abnormal systolic function • Wall-motion abnormalities • Pericardial effusion • Cardiac chamber size abnormalities	Low specificity
Cardiac magnetic resonance imaging	• Lake Louise Criteria for myocarditis showing: o Myocardial edema o Myocardial injury	No criteria specific for ICI myocarditis
Endomyocardial biopsy	• Characteristic pathology findings	Gold standard
Laboratory studies: • Cardiac troponin • NT-proBNP • CK-MB • CK	• Elevated values indicate cardiac injury	Low specificity

Abbreviations: CK, creatine kinase; CK-MB, creatine kinase-myocardial band; ICI, immune checkpoint inhibitor; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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