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PRIMERS IN CARDIO-ONCOLOGY

The Evolving Immunotherapy Landscape and the Epidemiology, Diagnosis, and Management of Cardiotoxicity

JACC: CardioOncology Primer

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ABSTRACT

Immune checkpoint inhibitors (ICIs) are newer therapies being applied to an increasing number of patients with cancer. Data suggest that up to 36% of cancer patients may be eligible for immunotherapy and, in late 2019, there were more than 3,362 clinical trials initiated to evaluate the effectiveness of immunotherapy, either as single agents or in combination with other immunotherapy, targeted therapies, or traditional cytotoxic or radiation therapy. With the combination of both immune and non-immune treatment approaches, the complexity in making the diagnosis of cardiotoxicity related to an ICI will increase substantially. Here, we summarize the published data on the epidemiology, diagnosis, and management of cardiotoxicity of ICIs. This is a rapidly evolving field, and as our understanding continues to evolve, previously considered hypotheses may not prove to be entirely correct. Research and continued collaborations are urgently needed to provide evidence-based cardiovascular care for this rapidly expanding and vulnerable cohort of patients. (J Am Coll Cardiol CardioOnc 2021;3:35–47) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

LANDSCAPE OF IMMUNOTHERAPY

The landscape of oncology has dramatically changed over the last decade with the advent of immunotherapy. Immunotherapy is any type of cancer treatment that leverages the immune system to fight cancer. There are many types of immunotherapy, including cytokines to influence downstream immune cell activity (interferon, interleukin-2), immune checkpoint blockade with monoclonal antibodies to unleash T cell responses, adoptive cell therapies using components of the immune system to recognize cancer (chimeric antigen receptor-T cell therapy and natural killer cell therapy), vaccines to

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ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

CMR = cardiac magnetic resonance imaging

CTLA-4 = cytotoxic T-lymphocyte associated-antigen-4

ECG = electrocardiogram

EMB = endomyocardial biopsy

GLS = global longitudinal strain

ICI = immune checkpoint inhibitor

irAE = immune-related adverse event

LVEF = left ventricular ejection fraction

PD-1 = programmed death receptor-1

PD-L1 = programmed death receptor 1 ligand

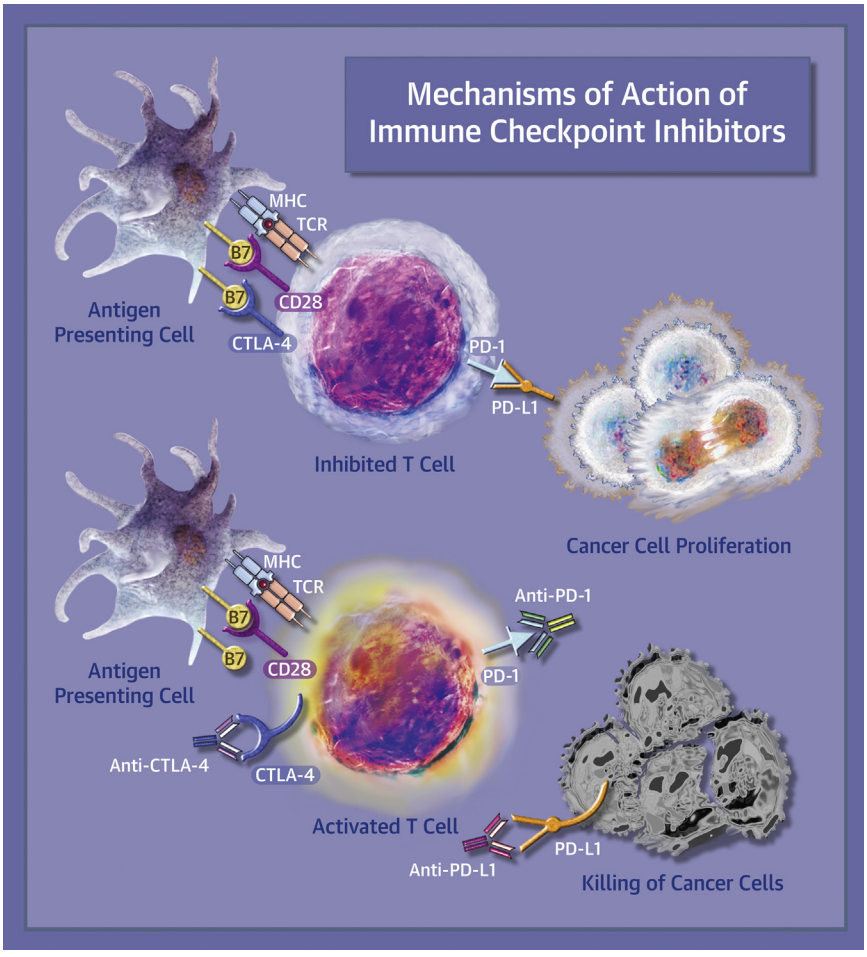
HIGHLIGHTS

- ICIs are novel cancer therapies applied to an increasing number of patients.
- Myocarditis should be a principle diagnosis under consideration in patients on ICIs with new cardiovascular presentations.
- Initial testing should include electrocardiogram, cardiac biomarkers, echocardiogram (with global longitudinal strain) and cardiac magnetic resonance imaging.
- The morbidity and mortality of ICI-associated myocarditis is high.
- The first-line treatment of ICI-associated myocarditis, beyond holding the ICI, is immunosuppression with corticosteroids.
- Data on the value of screening and surveillance approaches are lacking.

elicit immune responses, oncolytic virus therapy (e.g., talimogene laherparepvec) engineered to directly kill the cell, and bispecific T cell engagers to link T cells to target antigens. The concept of using the immune system in cancer treatment was first introduced by William Coley in the late 19th century but did not start to gain traction until more than a half century later when the concept of immune surveillance of cancers was introduced by Thomas and Burnet (1,2). The modern era of immune therapy began in 1985 with the first studies of interferon treatment in melanoma with eventual approval in 1995 (3). However, after the approval of the first immune checkpoint inhibitor (ICI) targeting cytotoxic T-lymphocyte associated-antigen-4 (CTLA-4) in 2011, and subsequently 2 approvals for agents targeting another immune checkpoint, programmed death receptor-1 (PD-1), in 2014, there has been a dramatic change in both the care of patients with cancer and landscape of cancer clinical trials (4–8). These therapies can result in durable and lasting tumor responses, especially for malignancies that were previously difficult to treat (4–8).

ICI FOR CANCER. Malignant cancer cells suppress the immune system to evade detection and escape immune recognition (9). One such strategy is to trigger the overexpression or activation of inhibitor checkpoint pathways (e.g., PD-1 and its ligand [PD-L1]) that suppress the host's ability to mount an immune response against the tumor (**Figure 1A**). ICIs are monoclonal antibodies (e.g., anti-PD-1 and anti-PD-L1) that block this process, thus activating T cells and initiating an adaptive immune response, allowing the immune system to recognize abnormal cancerous cells (**Figure 1B**). Currently, the 3 approved ICIs target pathways include CTLA-4, PD-1, and PD-L1. Numerous randomized clinical trials have shown durable tumor responses and improvement in overall survival of ICI-treated patients, spurring continued ICI development and increased use. In the United States alone, more than 40% of cancer patients are now eligible for ICI therapy with 1 of 7 approved agents: 1 CTLA-4 inhibitor (ipilimumab), 3 PD-1 inhibitors (pembrolizumab, nivolumab, and cemiplimab) and 3 PD-L1 inhibitors (atezolizumab, avelumab, and durvalumab) (10,11). Not all ICI-treated patients will experience a tumor response. Response rates are highly variable and depend on tumor type and the agent used (ranging from 10.9% for single-agent ipilimumab in melanoma to 69% for pembrolizumab in Hodgkin's lymphoma) (10). A subset of patients who initially respond eventually develop resistance to these ICI agents. Although mechanisms are incompletely understood, the most common mechanisms of resistance, or immune escape, are possibly related to genetic/epigenetic alterations (e.g., downregulation of major histocompatibility complex class I, loss of β2-microglobulin that alters neoantigen formation or presentation, alterations in cell signaling that interrupt the T cells or mutations in immune signaling pathways (e.g., JAK1/JAK2 mutation), or noncancerous cells or molecules in the body that create an inhospitable environment (e.g., high level of immune suppressive cells or cytokines) which can foster resistance to immunotherapy and accelerate tumor cell growth (12,13). The process by which a cancer cell defends itself from the antitumor immune response is known as adaptive immune resistance (14). An example of adaptive immune resistance is T cell infiltration into the tumor microenvironment causing secretion of interferon-gamma which can have a protumorigenic role through upregulation of checkpoints (14). To increase the percentage of patients responding to therapy, the preferred treatment strategy in specific instances has shifted from the use of monotherapy ICI to using a combination of agents in search of a synergistic treatment effect. Promising results in patients from the use of ICIs in combination with other immunotherapy agents, chemotherapy, or other targeted therapies suggest that these combined

FIGURE 1 **Mechanisms of Action of Immune Checkpoint Inhibitors**



(A) Cancer cells escape immune recognition by triggering the overexpression or activation of inhibitor checkpoint pathways (e.g., PD-1 and PD-L1 or CTLA-4) that suppress the host's ability to mount an immune response against the tumor. **(B)** Immune checkpoint inhibitors are monoclonal antibodies (e.g. anti-PD-1, anti-PD-L1 and anti-CTLA-4) that block this process, thus activating T cells and initiating an adaptive immune response, allowing the immune system to recognize abnormal cancerous cells. CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; MHC = major histocompatibility complex; PD-1 = programmed death receptor 1; PD-L1 = programmed death receptor 1 ligand; TCR = T cell receptor.

approaches may be the future of cancer treatment and are likely to increase the complexity of cardiotoxicity. Some successful treatment examples include the use of the combination of 2 ICIs as in the case of metastatic melanoma, renal cell carcinoma, and microsatellite instability-high or mismatch repair deficient colon cancer, combination PD-1 and chemotherapy in lung cancer, or combination PD-1 and targeted therapy such as pembrolizumab/lenvatinib for advanced endometrial carcinoma or axitinib and ICI in renal cell carcinoma (12,13,15–20). Lastly and importantly, recent adjuvant ICI use approvals for melanoma, lung cancer, and non-muscle invasive bladder cancer, now allow for treatment of patients in earlier disease stages (21–23). Independent of the cancer type, stage, or combination, the use of ICIs is rapidly expanding. As of September 2019, there were more than 3,362 clinical trials initiated to evaluate the effectiveness of ICIs either as single agents or in combination with other immune therapies, targeted therapies, or traditional cytotoxic or radiation therapy (24).

GENERAL ADVERSE EVENTS ASSOCIATED WITH ICI. During approval of ICIs, it was anticipated that nonspecific activation of the immune system would lead to off-target immune-related adverse events (irAEs) to every organ system. IrAEs are frequent, with clinically detectable irAEs in 70% to 90% of

patients. The severity of irAEs is classified as low-grade (grades 1 to 2), high grade (grades 3 to 4), and lethal (grade 5) according to the Common Terminology Criteria for Adverse Events, with more severe grades (grade 3 to 4) detected in 10% to 15% (25). These irAEs typically occur within the early phase of therapy (<12 weeks of therapy). Multiple prior reviews discuss mechanisms in depth (26-29). Briefly, there are several suggested potential mechanisms explaining the pathophysiology of irAEs. Firstly, checkpoint blockade causes pre-existing tolerated self-reactive T cells to become deregulated in the periphery. Secondly, there is cross-reactivity between the target of an individual patient's antitumor immune response and normal tissues which share an epitope. Thirdly, it is postulated that T cell receptors target a different but homologous muscle antigen as the tumor antigen such as troponin (30).

ICI-ASSOCIATED MYOCARDITIS

Myocarditis is an inflammatory disease of the heart muscle cells. Pathologically, it is defined as histologic evidence of inflammatory infiltrates within the myocardium with or without myocyte degeneration and necrosis of nonischemic origin (31). Myocarditis from ICIs was first noted in case reports and phase II and III clinical trials of ICIs, and later in case series (32-39). Histopathologic examinations of myocardial specimens from patients with suspected ICI-associated myocarditis have revealed the typical findings noted in non-ICI myocarditis with a diffuse T cell predominant lymphocytic infiltration in the myocardium with a predominance of CD3+, CD4+, CD8+ T lymphocytes, CD68+ macrophages, rarely CD20+ B lymphocytes, typically with myocardial necrosis or fibrosis (36,40,41). However, borderline grades of myocarditis have been noted with infiltration without necrosis (42). Other reported findings include the presence of eosinophils. ICI-associated myocarditis and the pathologic findings are often considered to be similar to cardiac allograft rejection, and this perceived similarity has been used as evidence for treating patients with ICI-associated myocarditis with medications that have been successful in the setting of cardiac allograft rejection. In cases of ICI myocarditis where there remains a persistent clinical suspicion after negative noninvasive testing, a biopsy should be pursued. The clinical manifestations of myocarditis are heterogeneous, ranging from asymptomatic states with vague signs and symptoms to severe myocardial destruction yielding cardiogenic shock and arrhythmias. Paralleling the range of clinical manifestations, the diagnosis of myocarditis may also be equally challenging. As detailed below, our insight into the epidemiology, diagnosis, and treatment of myocarditis associated with ICIs is evolving (26).

INCIDENCE AND OUTCOME. There is a wide range in the reported incidence of ICI-associated myocarditis. However, the reporting of myocarditis has increased (43). In an analysis of the Bristol Myers Squibb corporate safety database, Johnson et al. (36) reported that among 20,594 patients, myocarditis was observed in 0.06% of patients who received nivolumab alone, and 0.27% of patients who received combination therapy. In a single-center study, among 964 patients who received ICIs either as monotherapy or combination therapy, ~1% developed myocarditis (38). In a meta-analysis of 22 clinical trials involving single-agent PD-1 or PD-L1 inhibitors in non-small cell lung cancer, incidence rates of 2% for heart failure, 1% for cardiac arrest, and 0.5% for myocarditis were reported (44). In an analysis of the WHO's Global Individual-Case-Safety-Report database, a significant overreporting of myocarditis in patients on immunotherapy (vs. full database), in patients on combination ICI therapy (vs. monotherapy), and in patients on anti-PD-1 (vs. anti-CTLA-4) was noted (45). There are additional data reporting adverse cardiovascular outcomes with ICI therapy (38,45-49). For example, in 1 registry, 40% of 103 myocarditis cases experienced at least 1 major adverse cardiovascular event (41). In a study of 30 patients with ICI cardiotoxicity, which included left ventricular (LV) systolic dysfunction, Takotsubo syndrome-like appearance, atrial fibrillation, ventricular arrhythmia, and conduction disorders (thus not limited to myocarditis), Escudier et al. (37) reported a case fatality rate of 27%. In an analysis of a pharmacovigilance database, a cardiovascular mortality rate of 39.7% was noted (49); studies were noted to have a modest follow-up. For context, among 670 patients admitted with non-ICI myocarditis, a major cardiac event occurred in 15% of patients and death occurred in 4% of patients during a median follow-up time of 4.7 years (50).

The wide variation in incidence reporting is likely due to the difficulty in establishing the diagnosis and lack of any standardized assessment protocols. Presentations can vary from no symptoms with an abnormal biomarker to nonspecific symptoms such as fatigue, to fulminant presentations with hemodynamic compromise (51). Protocols are challenging as current noninvasive tests may lack sensitivity; a relatively normal electrocardiogram (ECG), lack of major symptoms, absence of late gadolinium enhancement (LGE), or a normal left ventricular

ejection fraction (LVEF) is not sufficient to rule out ICI-associated myocarditis (38,41). Additionally, subclinical myocarditis likely occurs in some as shown by a recent case of a metastatic melanoma patient treated with ipilimumab and nivolumab; cardiac involvement was clinically unapparent, but patchy fibrosis and diffuse mononuclear infiltrates of myocardium was found in postmortem autopsy (52).

TIME OF ONSET. Data suggest that ICI-associated myocarditis typically presents early after starting treatment (37,38,43). Escudier et al. (37) reported that the median time to presentation of cardiotoxicity was 65 days from the start of treatment (equivalent to three ICI cycles), but with a wide variation of 2 to 454 days. Moslehi et al. (43) reviewed 101 cases of ICI-associated myocarditis from the WHO's VigiBase; 64% of myocarditis occurred after the first or second ICI dose, and 76% occurred within the first 6 weeks of treatment (53). Mahmood et al. (38) reported a median time from the first ICI dose to the onset of myocarditis of 34 days and 81% of cases presented within 3 months of the first dose. However, this is not the only paradigm as it is important to recognize that late-onset ICI-associated myocarditis also occurs in a small percentage of patients, in some cases up to several months and years after starting ICI therapies (47,54). It is unclear whether these late-onset cases represent the late diagnosis of myocarditis that had begun much earlier, delayed development of myocarditis after ICI administration or a cardiomyopathy due to persistent systemic immune activation and inflammation.

RISK FACTORS. Consistent data suggest that patients receiving combination ICI therapies have an increased incidence of myocarditis as compared to monotherapy (36,38). For example, leveraging the U.S. Food and Drug Administration Adverse Event Reporting System, Zamani et al. (55) showed that reporting rate of myocarditis was higher in patients receiving combination ICI (odds ratio [OR]: 1.93; 95% confidence interval [CI]: 1.19 to 3.12; $p = 0.008$). Other additional risk factors noted in that study were female sex (OR: 1.92; 95% CI: 1.24 to 2.97; $p = 0.004$) and age (patients 75 years or older OR: 7.61; 95% CI: 4.29 to 13.50; $p < 0.001$). However, whether patients with underlying autoimmune disease, pre-existing cardiovascular disease, obesity, and diabetes mellitus are at increased risk in unclear (26,27,38,46,56). ICI-associated myocarditis can occur with noncardiac irAEs, or in isolation (37,38,43). Concomitant myositis may be found in 25% of patients (37,43). Moslehi et al. (43) reported that myasthenia gravis occurred in 11 of 101 patients with myocarditis. In another report describing 10 patients with immune-related myositis, 4 patients also had evidence of myocarditis (39). The overlap syndrome with myositis and myocarditis has also been reported to be associated with worse outcomes. An analysis of 180 cases of ICI-associated myositis from a pharmacovigilance reporting system detailed the additive morbidity and mortality associated with the overlap between myocarditis and myositis (51.7% mortality versus 14.9% in patients without myocarditis, $p < 0.0001$) (57). These data suggest that patients with ICI-related myositis or myasthenia should undergo an evaluation to exclude cardiac involvement. In reverse, it is also important to assess ptosis, diplopia, dysphagia, dysarthria, weakness, or shortness of breath in patients presenting with myocarditis to determine further workup for inflammatory or noninflammatory muscle syndromes.

DIAGNOSIS. Patients can present with an asymptomatic troponin elevation, fatigue, dyspnea, orthopnea, myalgia, palpitation, chest pain, lower extremity edema, lightheadedness, syncope, or change in mental status (38,58). Severe fulminant cases can present with cardiogenic shock, complete heart block, intractable ventricular arrhythmias, or cardiac arrest (38). Contributing to the diagnostic challenge is that ICI are relatively new medications, with emerging cardiotoxicities, which can be easily overlooked by health care providers who may be less familiar. In addition, more common cardiac conditions such as acute myocardial infarction and ischemic heart failure can present similarly to fulminant myocarditis and are only differentiated with further diagnostic testing. As the range of presentations is broad, any relevant alerting symptoms should trigger immediate testing with subsequent referral to cardiology/cardio-oncology specialists if necessary (38). Because of its potentially fulminant course, a prompt and accurate diagnosis is critical so that ICIs are immediately discontinued and effective treatment can be initiated (38,47). Commonly used diagnostic testing for ICI-associated myocarditis includes an ECG, an echocardiogram, biomarkers, cardiac magnetic resonance (CMR) imaging, and endomyocardial biopsy (EMB).

Electrocardiogram. An ECG is an inexpensive and widely available test which should be performed immediately upon presentation. ECG findings can vary from normal to a range of conduction abnormalities and atrial or ventricular arrhythmias, but is typically abnormal (37,59). In a cohort of 35 ICI-associated myocarditis patients, the ECG was abnormal in 89% of patients (38). Although ECG

abnormalities such as tachycardia, conduction abnormalities, ST-segment/T-wave abnormalities, QT prolongation, presence of Q-waves, or atrial or ventricular arrhythmias are nonspecific, their appearance should trigger further investigation. It is also important to recognize that a normal ECG does not rule out myocarditis. As patients with ICI-associated myocarditis frequently develop tachyarrhythmias and bradyarrhythmias, clinically suspected patients should be admitted and closely monitored with cardiac telemetry.

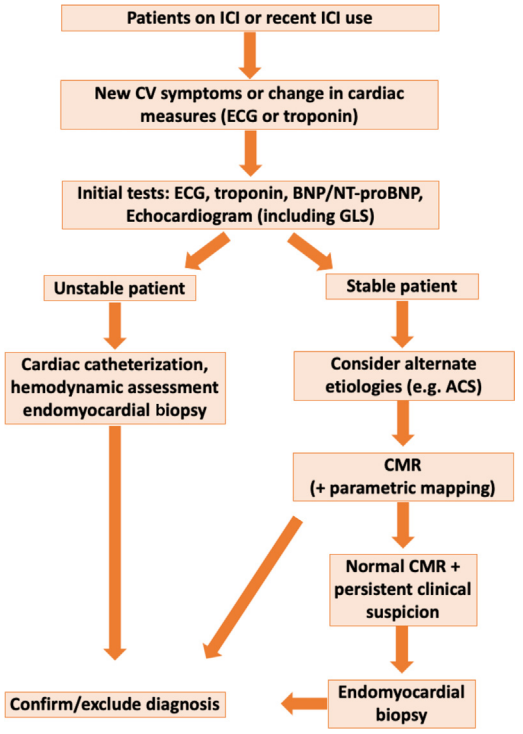
Biomarkers. Troponin levels and B-type natriuretic peptide (BNP) are helpful in the diagnosis and prognosis of myocarditis. Mahmood et al. (38) noted that >90% of patients with ICI-associated myocarditis had an elevated troponin and 66% had an elevated N-terminal-pro-BNP, with data suggesting that both admission and peak troponin levels were associated with subsequent adverse cardiac events. These data suggest value to measurement of serum cardiac biomarkers in suspected cases. However, many cases may present with a minimally elevated troponin. In this situation, a baseline troponin measurement before ICI initiation would be of important value.

Echocardiography. An echocardiogram is the first-line noninvasive imaging test in the assessment of ICI-associated myocarditis because of its widespread availability, portability, and ease of performance. The LVEF has been shown to be preserved in >60% of ICI-associated myocarditis patients and severe LV dysfunction (LVEF ≤35%) is much less common (37,38,48). Myocardial strain assessment has been applied in the monitoring of traditional chemotherapy-associated cardiotoxicity (60). In a study from Awadalla et al. (48), global longitudinal strain (GLS) was worse among myocarditis patients at presentation with myocarditis with either a reduced or preserved LVEF. GLS remained preserved in patients who were on ICIs but did not develop myocarditis. In follow-up, the risk of adverse events was higher with a lower GLS among myocarditis patients regardless of LVEF where, after adjustment for LVEF, each percent reduction in GLS was associated with a 1.5-fold increase in cardiac morbidity and mortality among patients with a reduced LVEF and a 4.4-fold increase with a preserved LVEF (48). Additional data are needed to validate these findings. The use of GLS may be dependent on operators' experience and may be vendor-dependent; therefore, dedicated training, quality assurance and using consistent vendors for longitudinal comparison are essential in the application of GLS. Wall motion abnormalities, indices of diastolic function, pericardial effusions, and valvular function in ICI-associated myocarditis have not been extensively investigated and represent important topics of future research. Pericardial effusions have been reported in 7% to 17% of patients with ICI-associated myocarditis (37,38).

CMR imaging. CMR is the gold-standard imaging test for the diagnosis and risk prediction of myocarditis of other etiologies (50,61). There are established Lake Louise Criteria for the CMR diagnosis of myocarditis from other etiologies which use advanced tissue characterization, LGE, and the presence of myocardial edema (61). Escudier et al. (37) reported that LGE was present in only 23% of patients in their cohort with ICI cardiotoxicity. In a retrospective study of 103 patients with ICI-associated myocarditis, LGE was present in only 48% of patients and elevated T2-weighted short-TI inversion recovery (qualitative edema) was present in 28% of patients (41). In comparison, LGE is present in approximately 80% of cases of non-ICI myocarditis (62,63). A moderate correlation was found between LGE and pathological fibrosis (35%) and between elevated T2-weighted STIR signal and lymphocytic infiltration (26%). The presence of LGE, LGE pattern, and elevated T2-weighted STIR were not associated with subsequent adverse cardiac events (41). In addition, positive LGE does not indicate whether it is active myocarditis or a remnant of prior inflammation. These data suggest caution in reliance on an LGE or qualitative T2-STIR-only approach for the exclusion of ICI-associated myocarditis (41). Alternative CMR techniques such as T1 and T2 mapping and the calculation of the extracellular volume may offer improved diagnostic and prognostic value (64,65). However, there are no published systematic data on the use of these techniques in ICI-associated myocarditis and such studies are needed.

EMB. EMB remains the gold-standard test for the diagnosis of myocarditis. There are established criteria using right ventricular (RV) biopsy to diagnose myocarditis (31), and when 5 or more samples are available the accuracy is increased (66,67). An EMB should be performed by experienced operators in specialist centers under imaging guidance after weighing the benefit of diagnostic clarification against the inherent risks of EMB. However, because of its invasive nature and potential complications (overall rate 1% to 6%), EMB is rarely pursued as the first-line test (68). There are limited data on EMB in ICI-associated myocarditis. In their study of ICI cardiotoxicity, Escudier et al. (37) reported that 89% (8 of 9) of patients had lymphocytic infiltration. In 56 pathology-proven patients, a lymphocytic infiltration was seen in 55 patients (98.2%), among whom 21 patients (38.2%) had LGE and 14 patients (25.5%) had

FIGURE 2 Proposed Diagnostic Algorithm for Immune Checkpoint Inhibitor-Associated Myocarditis



We propose the following diagnostic algorithm. The **arrows** represent steps forward in the diagnosis. An electrocardiogram (ECG), troponin, B-type natriuretic peptide (BNP), and echocardiogram including global longitudinal strain (GLS) should be obtained as the initial tests. Unstable patients should undergo cardiac catheterization. Stable patients should rule out acute coronary syndrome (ACS) and obtain cardiac magnetic resonance (CMR) imaging with parametric mapping. If patients with persistent clinical suspicion despite a normal CMR, endomyocardial biopsy (EMB) is recommended to confirm the diagnosis. CV = cardiovascular; ICI = immune checkpoint inhibitor.

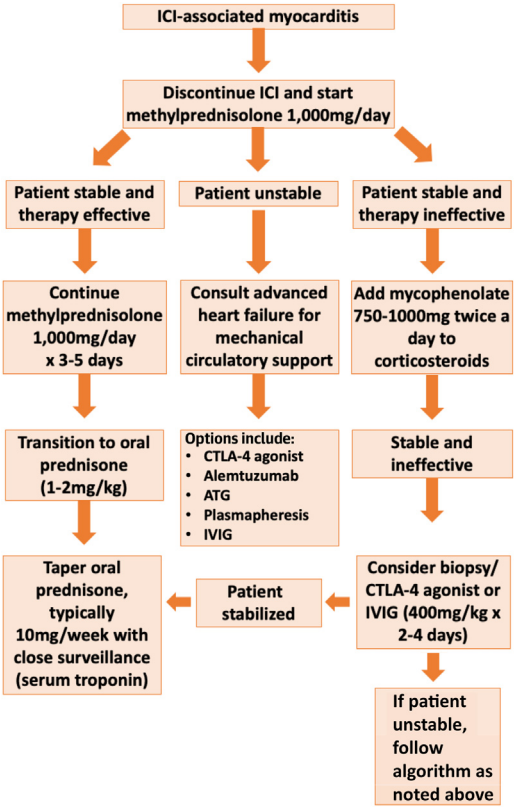
elevated T2-weighted STIR signal (41). Thirty-one patients had pathological fibrosis, among whom 11 patients (35.5%) had LGE (41). Immunohistochemistry for cell-specific markers such as T lymphocytes (CD3), macrophages (CD68), or human leukocyte antigens may be additive and improve the sensitivity of the test and the understanding of the disease (69). Most reports of immunohistochemical staining predominantly show a CD8+ T cell infiltration intermixed with subsets of CD4+ T cells and CD68+ monocyte/macrophage lineages. In addition, EMB have shown PD-L1-positive immunohistochemical stains in both patients treated with CTLA-4 inhibitors and PD-1 inhibitors (42,70). EMB is also useful for the detection of other etiologies of myocarditis. Recently, a case of giant cell myocarditis due to enterovirus during treatment with ICI therapy was reported. Enterovirus RNA genomes were detected in EMB samples with mean virus load of 6,000 genome copies/μg (71).

Proposed diagnostic algorithm. We propose a diagnostic algorithm based on our experience using different diagnostic tests (**Figure 2**). Among patients presenting new cardiac signs or symptoms early after starting ICIs (especially within 3 months) or patients with recent ICI use, myocarditis should be considered the principle diagnosis and excluded. We recommend checking an ECG, troponin, BNP, and echocardiogram including GLS as the initial tests because they are widely available and sensitive to myocardial injury.

As acute coronary syndrome is the most common cause of myocardial injury or cardiac dysfunction, coronary ischemia should be considered. However, unlike general paradigms where myocarditis remains a later diagnosis to be considered, it is important that myocarditis remain the primary suspected diagnosis among all patients with a new cardiovascular presentation who are on or who have been recently treated with an ICI, especially those early after initiation of ICI treatment. Similarly, the presence of stable coronary artery disease should not exclude the possibility of ICI-associated myocarditis. If the severity of coronary artery disease is not in proportion to the degree of myocardial injury, especially with the history of active or recent ICI use, myocarditis should still be considered. Importantly, PD-1 and PD-L1 receptors may remain occupied for more than 1 year after the last infusion of the ICI, suggesting that the biological effect may remain long after the infusions of ICI have stopped (72). This may explain, in part, the wide range in median onset of myocarditis (>1 year in some series) and supports the need for clinical suspicion in patients who may present late after starting treatment or who are no longer being actively treated with an ICI.

For stable patients, the next line in testing is CMR imaging which should include standard tissue characterization and parametric mapping (61). Published data suggest that the normal noninvasive test may not exclude all myocarditis cases, and in cases of persistent uncertainty, additional invasive testing such as an EMB should be considered, given the reported sensitivity of a RV biopsy for myocarditis of approximately 70% (67). This modest sensitivity is principally related to sampling error and quality with higher sensitivities noted with additional samples and analysis that extends beyond routine histology.

FIGURE 3 Proposed Treatment Algorithm for Immune Checkpoint Inhibitor-Associated Myocarditis



We propose the following treatment algorithm based on our experience. The arrows represent steps forward in the treatment. Immune checkpoint inhibitors (ICI) should be discontinued and high-dose corticosteroids (i.e., methylprednisolone 1,000 mg/day) should be initiated in patients with ICI-associated myocarditis. Based on patients' clinical presentations and responsiveness to the initial therapy, different therapeutic approaches can be considered. There are no high-level data supporting the proposed treatment approach. ATG = antithymocyte globulin; IVIG = intravenous immunoglobulin; other abbreviations as in Figures 1 and 2.

There are limited data on the use of an EMB in ICI-associated myocarditis. A single study suggested that the sensitivity of RV EMB was likely higher due to the diffuse myocardial inflammation in patients with ICI-associated myocarditis (41).

Unstable patients (e.g., patients presenting with cardiogenic shock, cardiac arrest, or unstable arrhythmias) should undergo cardiac catheterization without delay to rule out acute coronary syndrome, with a hemodynamic assessment and an EMB. Mechanical circulatory support can be placed during cardiac catheterization for patients needing additional support other than inotropes. There is a balance between the accuracy of making the diagnosis and the rapid institution of treatment. This is challenging as making the definitive diagnosis is important because it affects critical cancer treatment decisions and the use of high-dose corticosteroids with a potentially prolonged taper.

SCREENING AND SURVEILLANCE. Data on optimal screening and surveillance approaches are lacking. Screening and surveillance are important when patients are at risk of cardiotoxicity from cancer therapies (e.g., measurement of LVEF in patients receiving anthracycline). However, measurement of LVEF before ICI therapy may not be helpful because most patients who developed myocarditis on ICI therapy had a normal pre-ICI LVEF (38). An abnormal ECG and troponin elevation are common at the presentation of ICI-associated myocarditis (38,51). Additionally, given the increasing awareness, the measurement of a modestly detectable troponin during therapy has the potential to create a diagnostic dilemma. Therefore, we believe the measurement of an ECG and troponin at baseline is of value and should be performed. Whether surveillance is useful is unclear and should be only routinely performed within the structure of a research study where test characteristics and utility can be defined.

MANAGEMENT. There are no prospective studies or randomized trials evaluating treatment options for ICI-associated myocarditis. Current recommendations leverage the treatment of other irAEs and cardiac allograft rejection. Early initiation of immunosuppression is one of the cornerstones of the treatment (73). We propose a management algorithm (**Figure 3**) that summarizes our approach. With suspected myocarditis, patients should be admitted to an oncology unit/medicine unit with telemetry or cardiac care unit depending on the severity of their presentation. For unstable patients, we recommend discontinuing ICI and prompt initiation of immunosuppression without any delay for confirmatory tests. A cardiology or cardio-oncology consultation should be obtained, and in relevant cases, an advanced heart failure consultation (25). Guideline-directed medical therapy and appropriate supportive therapy for patients with heart failure should be initiated (74).

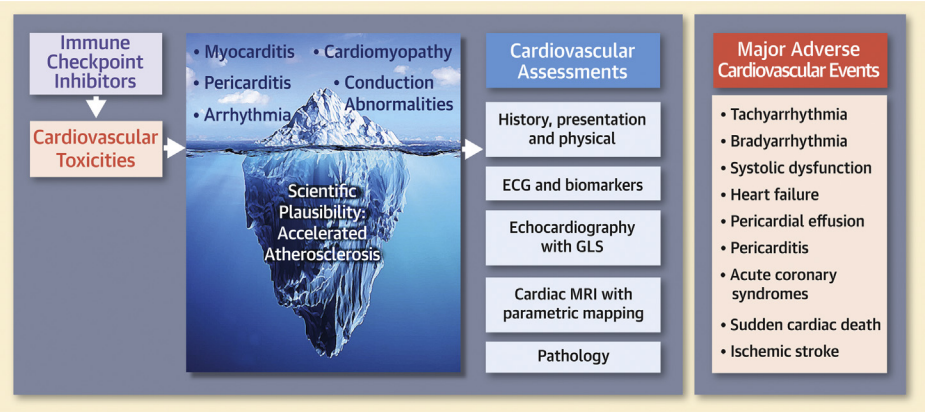
Corticosteroids are the first-line immunosuppressant for the treatment of ICI-associated myocarditis (25,75,76). We typically start methylprednisolone at 1,000 mg/day. There are very limited systematic data on the use of corticosteroids in treating ICI-associated

myocarditis; this has resulted in variability in currently recommended treatment strategies from professional societies and consensus guidelines (25). In a multicenter study, higher initial dose and earlier initiation of corticosteroids were associated with improved outcomes (38). Specifically, in a cohort of 126 patients with ICI-associated myocarditis treated with corticosteroids, higher initial corticosteroids dose (methylprednisolone equivalent dose >500 mg daily) and earlier initiation (within 24 h after admission) were associated with improved cardiovascular outcomes (47). However, it is unclear whether higher-dose corticosteroids compromise anticancer efficacy of ICIs (77–80). In animal models, early but not late corticosteroids inhibited memory CD8+ T cells, which have been associated with lasting antitumor response in a mouse melanoma model treated with anti-CTLA-4 or anti-PD-L1 at different time points (8). Clinical reports have presented conflicting findings. Previous investigations suggested that systemic corticosteroids treatment for irAEs did not affect overall survival or objective response rate (77,78,81). However, more recent studies have provided conflicting results (79,80). For example, Arbour et al. (79) identified 90 of 640 patients treated with an ICI for lung cancer who received ≥10 mg of prednisone equivalent daily. Baseline corticosteroids use was independently associated with decreased progression-free survival and overall survival after adjusting for smoking history, performance status, and history of brain metastases (79). Similarly, Faje et al. (80) reported that among 98 patients with melanoma complicated with hypophysitis, high-dose (>7.5 mg prednisone or equivalent during the initial 2 months) was associated with lower survival and a shorter time to treatment failure. For reference, the corticosteroids dose used in ICI-associated myocarditis is significantly higher than 7.5 mg per day. Future research is needed to study whether initiating moderate dose corticosteroids at early stage or in combination with other immunosuppressants can result in similar outcomes as high-dose corticosteroids. Intravenous corticosteroids are followed by oral prednisone (1 to 2 mg/kg) and a careful tapering plan when the patient is stable or biomarkers (especially troponin) have started to decline (25,27,58). The optimal length of these therapies or the speed of taper in unknown, but it is reasonable to continue the treatment until resolution of symptoms and normalization of troponin, LVEF, and conduction abnormalities, which is usually more than 6 to 12 weeks. The use of high-dose corticosteroids may be associated with complications, such as opportunistic infections, hyperglycemia, increased blood pressure, fluid retention, gastrointestinal bleeding, and osteoporosis. Therefore, prophylactic strategies such as pneumocystis pneumonia prophylaxis and proton-pump inhibitors should be considered while patients are on high-dose corticosteroids therapy.

In unstable patients or patients who do not respond to high-dose corticosteroids, other options should be considered, each with limited supporting data. These options include abatacept (blocks CD86/CD80-CD28 interaction), belatacept (a second-generation form of abatacept with increase the binding affinity to CD86/CD80), alemtuzumab (CD52 monoclonal antibody), antithymocyte globulin (deplete T lymphocytes) or intravenous immunoglobulin (multiple activities) (82–84). There are several reports on the use of infliximab (tumor necrosis factor-α inhibitor) as a second-line therapy (36,38); however, it should be used with caution in patients with heart failure (85). In a systemic review including 73 studies and 88 cases with cardiotoxicity related to ICI, infliximab, mycophenolate, intravenous immunoglobulin, antithymocyte globulin, and/or plasmapheresis were used in 12 patients; 9 of them survived (75%) (86). Immunosuppressants should be administered together with inotropic agents and/or temporary mechanical circulatory support in patients with cardiogenic shock. The latter should be done in consultation with an advanced heart failure specialist (87–89). Close monitoring of the side effects of these immunosuppressants is crucial for the recovery of these patients. There are no high-level data supporting the proposed treatment approach. We recognize that the specific therapeutic approach can be variable between institutions based on local experience and expertise. Future research on the comparison of efficacy and safety of these therapeutic options is warranted.

It is recommended to definitively discontinue ICIs in cases of severe (grade 3) or life-threatening (grade 4) toxicities (25). Previous research on other irAEs revealed that in 38 patients retreated with anti-PD-1/L1 agents, 18 (48%) patients had no subsequent irAEs, 10 (26%) had recurrence of the initial irAE, 10 (26%) had a new irAE, and most of the irAEs were mild and manageable (90). More broadly, retrospective studies have indicated that after severe irAEs related to anti-CTLA-4 monotherapy or combination therapy with CTLA-4 and PD-1 blockade, most patients tolerated rechallenge with an anti-PD-1 agent well (91,92). Specifically, with cardiotoxicity, Escudier et al. (37) reported that an ICI was administered again after the first episode in the 4 out of 30 patients in their cohort without any recurrences. Balanescu et al. (70) described a patient successfully rechallenged with monotherapy (nivolumab) after

CENTRAL ILLUSTRATION **Immune Checkpoint Inhibitors Leading to Cardiotoxicities and Major Adverse Cardiovascular Events**



Zhang, L. et al. J Am Coll Cardiol CardioOnc. 2021;3(1):35–47.

Immune checkpoint inhibitors can lead to cardiovascular toxicities, which include myocarditis and pericarditis. Although there are no robust clinical data to support whether immune checkpoint inhibitors (ICIs) accelerate atherosclerosis, there is significant scientific plausibility to support the hypothesis that ICI use increases atherosclerosis. The public health impact of defining the association between ICI and atherosclerosis is significant. Patients with new cardiac signs or symptoms should undergo thorough cardiovascular assessments to evaluate the occurrence of cardiovascular outcomes. ECG = electrocardiogram; GLS = global longitudinal strain.

ICI-associated myocarditis treated with intravenous immunoglobulin, corticosteroids, and statins. However, the risk of recurrence of myocarditis particularly when patients are rechallenged with an ICI is unknown. We believe that ICI rechallenge should be avoided in patients with severe LV dysfunction, advanced conduction disease, or critical ventricular arrhythmias (27).

OTHER ICI CARDIOTOXICITIES

Beyond myocarditis, additional potential cardiotoxicities have been reported (**Central Illustration**). These include cardiomyopathy, conduction defects (heart block), atrial and ventricular arrhythmias, and pericarditis/pericardial effusions (44,93,94). Based on VigiBase reporting, pericardial disease and vasculitis, including temporal arteritis, were overreported after ICI therapy compared to the entire database (45). Pericarditis and pericardial effusions are underrecognized, underreported, and undertreated, and are associated with a high case fatality rate (around 13%) (86). However, Palaskas et al. (95) reported that hemodynamically significant pericardial effusion requiring pericardiocentesis after ICI administration was uncommon (0.38%).

In our view, there is significant scientific plausibility to support the hypothesis that ICIs increase atherosclerosis (**Central Illustration**). Specifically, basic science studies support that the same immune checkpoints being targeted for cancer treatment are established critical negative regulators of atherosclerosis in animal and cellular studies (96–98). More recently, Poels et al. (99) showed that treating Ldlr-/- mice with ICIs for 6 weeks induced an activated T cell profile and subsequent endothelial activation. The short-term antibody-mediated inhibition of CTLA-4 accelerated the progression of atherosclerosis by inducing a predominantly T cell-driven inflammation, and resulted in the formation of plaques with larger necrotic cores and less collagen (99). In 10 melanoma patients treated with ICI therapy for 6 weeks, although plaque size was unaffected, plaques had progressed toward a lymphoid-based inflammatory phenotype and increased endothelial activation was observed (100). However, there are conflicting clinical data on whether ICIs can lead to an increase in atherosclerosis and atherosclerosis-related cardiovascular events (101–104). In a single-center case-control study with 135 subjects, a single cancer type (non-small-cell lung cancer) and a 6-month period of follow-up, there was no increase in nonfatal myocardial infarction with ICIs (HR: 1.18; 95% CI: 0.57 to 2.43; p = 0.66) (104). In contrast, in a study of 92 patients with non-small-cell lung cancer, there was an increase in venous and arterial vascular

events (pulmonary emboli, deep vein thrombosis, cerebrovascular accident, transient ischemic attack, and acute coronary syndrome) as compared to patients being treated with cytotoxic chemotherapy (101). The acute increase in vascular events was primarily observed in patients with a prior history of vascular disease or multiple cardiovascular risk factors. A pooled analysis of 59 oncological trials (n = 21,664) suggested a 35% increased risk for isolated coronary ischemia (95% CI: 0.76 to 2.4) over 6-months of follow-up among patients randomized to an ICI, in comparison to traditional cytotoxic chemotherapies (103). In a recent study by Drobni et al. (106), a 3-fold higher risk for cardiovascular events after starting an ICI was observed in 2,842 patients and 2,842 controls, matched according to age, a history of cardiovascular events, and cancer type. Imaging data are also conflicting. In a single case series of 11 patients, blockade of PD-1 was associated with regression of atherosclerotic plaque in three patients (27%), no change in 7 patients (64%), and an increase in 1 patient (9%) (102). In a study of 40 patients with melanoma treated with ICI, the rate of progression of total aortic plaque volume was >3-fold higher after ICI (from 2.1%/year pre- to 6.7%/year post) (106). The public health impact of defining the association between ICI and atherosclerosis and atherosclerotic-related cardiovascular events is considerable especially as these therapies move into the adjuvant setting.

SUMMARY

Immunotherapies have permanently changed the landscape of cancer therapy and there will be a continued expansion of the indications, the complexity, and the targets leveraged to treat cancers. As physicians who are fortunate to care for cancer patients, we must keep pace with this transformation. Our understanding of cardiotoxicity related to cancer immunotherapies must improve as these novel therapies are being increasingly applied to a broader range of cancers, to cancers in earlier stage, and to community settings.

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