



Cardiotoxicity of Immune Checkpoint Inhibitors

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Abstract

Purpose of review Immunotherapies, particularly immune checkpoint inhibitors (ICI), are revolutionary cancer therapies being increasingly applied to a broader range of cancers. Our understanding of the mechanism, epidemiology, diagnosis, and treatment of cardiotoxicity related to immunotherapies remains limited. We aim to synthesize the limited current literature on cardiotoxicity of ICIs and to share our opinions on the diagnosis and treatment of this condition.

Recent findings The incidence of ICI-associated myocarditis ranges from 0.1 to 1%. Patients with ICI-associated myocarditis often have a fulminant course with a case fatality rate of 25–50%. The diagnosis of this condition poses many challenges because independently a normal electrocardiogram, biomarkers, or a preserved left ventricular function do not rule out ICI-associated myocarditis. Endomyocardial biopsy should be pursued when clinical suspicion remains despite normal non-invasive tests. Data on optimal screening and surveillance tools are lacking. Cessation of ICIs, combined with high dose corticosteroids and other immunosuppressant approaches are the cornerstones of the treatment of ICI-associated myocarditis. This condition may recur when patients are re-challenged with these agents and the decision to resume ICIs should be made through a multidisciplinary discussion.

Summary Immunotherapies have changed the landscape of cancer treatment. Recognizing and managing cardiotoxicity related to ICIs is of critical importance. Our understanding of ICI-cardiotoxicity has improved, but large information gaps remain for further research. Due to the high case fatality rate, any type of cardiac symptoms or signs in a patient who has recently started an ICI should prompt consideration of ICI-cardiotoxicity.

Introduction

Harnessing the power of the immune system has been recognized as a potential treatment of malignancies for decades. There are multiple approaches available but for this review, we will focus on immune checkpoint inhibitors (ICI). Cytotoxic T lymphocyte-associated molecule-4 (CTLA-4), programmed cell death receptor-1 (PD-1), and programmed cell death ligand-1 (PD-L1) are the most widely studied and recognized immune checkpoint pathways. Drugs blocking these pathways leverage the immune system to target cancer cells. They are the first in recent decades of immunotherapy research to demonstrate significant clinical benefit with tolerable toxicities and are currently approved for a multitude of solid tumor indications [1–4]. The first of these agents was ipilimumab [1], a CTLA-4 inhibitor, which was approved in 2011. Trials investigating pembrolizumab (PD-1) [5] and nivolumab

(PD-L1) [4, 6] followed shortly after. The use of ICIs is rapidly expanding and moving towards the first-line metastatic and adjuvant settings with multiple ongoing studies testing them and in combination with standard cytotoxic chemotherapies and targeted therapies. For context, as of September 2017, there were 2004 immuno-modulatory agents against 303 targets, from 864 companies in 3042 active clinical trials [7].

Immune-related adverse events (irAEs) are complications that arise presumably from misguided targeting of normal (non-malignant) tissue by the immune system and can involve any organ system. Cardiotoxicity is an uncommon irAE, but it often has a fulminant course. The absence of highly sensitive and specific diagnostic tests and lack of experience and evidence pose some of the many challenges related to this condition.

An ICI-associated myocarditis case

A 69-year-old man with hypertension and diabetes was diagnosed with metastatic renal cell carcinoma. He was treated with nephrectomy. Two years later, the cancer recurred and he was started on bevacizumab and atezolizumab. After receiving two doses of atezolizumab, he presented to

the emergency department with fatigue and shortness of breath. His heart rate was 110 and his blood pressure was 100/60. Electrocardiogram (ECG) (Fig. 1a) demonstrated sinus tachycardia and non-specific ST/T wave changes. Conventional troponin T was 1.25 ng/ml and remained stably elevated thereafter. The patient underwent a cardiovascular magnetic resonance (CMR) imaging (Fig. 1b) which showed a markedly decreased left ventricular ejection fraction (LVEF) of 20%. The patient rapidly declined and needed inotropic support due to development of cardiogenic shock. He underwent a coronary angiogram which did not reveal significant obstructive coronary disease and subsequently

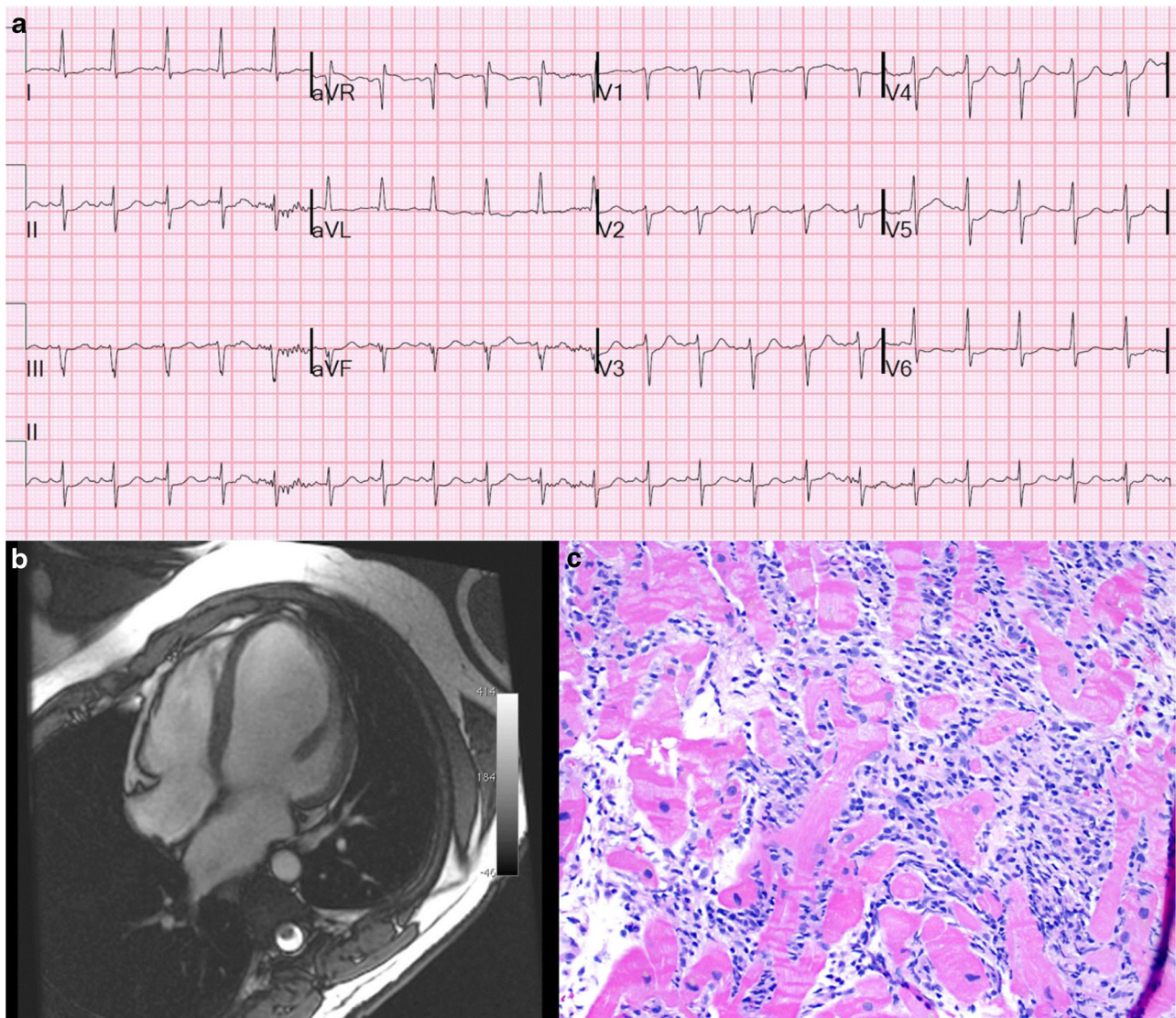


Fig. 1. Electrocardiogram (ECG), cardiac magnetic resonance, and endomyocardial biopsy (EMB) findings in a patient with immune checkpoint inhibitor-associated myocarditis. ECG demonstrated sinus tachycardia and non-specific ST/T wave changes (a). CMR showed a markedly decreased left ventricular ejection fraction of 20% (b). EMB revealed a lymphocytic myocarditis (c).

had an EMB which revealed lymphocytic myocarditis (Fig. 1c). He was treated with antithymocyte globulin and subsequently improved. Several weeks later, he had an echocardiogram which showed recovery of LVEF to 59%.

Immunotherapies and cancer

Since the time of William Coley in the late nineteenth century, harnessing the immune system has been recognized as a potential approach for the treatment of malignancies [8]. Only in the last decade has this strategy become a mainstream clinical reality. Immunotherapies utilize various approaches to activate immune system, generally through one of two mechanisms: (1) stimulating effector mechanisms by vaccination with tumor antigens, augmentation of antigen presentation, adoptive cellular therapy, administration of oncolytic viruses, or the use of antibodies targeting the tumor necrosis factor receptor superfamily; and (2) counteracting immune-inhibitory mechanisms by the use of antibodies to suppress regulatory T cells or antibodies against immune checkpoint molecules. T cells are capable of identifying and destroying malignant cells; however, this mechanism fails in many malignancies. This adaptive immune resistance is a hallmark of malignancies, characterized by downregulation of major histocompatibility complex (MHC) antigen expression, secretion of cytokines that downregulate the immune response, and expression of so-called “checkpoint” molecules [9]. PD-1 and CTLA-4 are proteins on the surface of regulatory T cells with a role in regulating the immune system by downregulating the immune response. In some malignant cells, programmed death-ligand 1 (PD-L1) proteins are overexpressed to inhibit the function of anti-tumor T cells by combining with PD-1. Checkpoint inhibition refers to the mechanism by which drugs block the function of these checkpoint molecules, thereby leading to the activation of cytotoxic T cells and their targeting of malignant cells. The most clinically notable checkpoint inhibitors block PD-1, the receptor for PD-L1, and CTLA-4.

Immune checkpoint inhibitors and heart—basic science

PD-1 signaling axis has a clear role in the protection of the heart from autoimmunity. PD-L1 is expressed on both murine and human heart. Certain mouse strains lacking the PD-1 gene develop a severe dilated cardiomyopathy [10] secondary to the development of autoantibodies to cardiac troponin I [11, 12]. As a result, it was hypothesized that PD-1 plays an important role in autoimmune cardiac pathologies. Indeed, a fatal and diffuse lymphocytic myocarditis developed in the PD-L1 null (−/−) MRL mice [13]. Notably, the loss of the PD-1 gene led to the development of antibodies specific for cardiac myosin [14]. In a mouse model of T cell-mediated myocarditis, PD-1 protected against T cell-mediated myocarditis [15] through the upregulation of cardiac endothelial PD-L1 [16]. More recently, studies have suggested that PD-1/PD-L1 interactions are important in modulating immune response and subsequent immune-mediated cardiac damage following myocardial infarction and ischemia-reperfusion injury [17].

CTLA-4 is known to play a distinct, though less specific, role in cardiovascular biology. CTLA-4 acts as a key negative regulator of T cell activation, with knockout models demonstrating diffuse, lethal T cell-mediated toxicity across organ systems. These models have also been demonstrated to spontaneously produce lymphoproliferation and lymphocytic infiltrates in multiple organs, including the heart where they cause severe myocarditis [18]. Further demonstrating the cardioprotective role of CTLA-4, inoculation of T cells deficient in CTLA-4 and augmented with IL-12 led to significant intracardiac infiltration of lymphocytes, prominent lymphoproliferation within intracardiac nodes, and development of a near-fatal myocarditis [19].

Immunotherapies and immune-related adverse events

Toxicities associated with immunotherapies are novel, in comparison to toxicities associated with traditional therapies [20]. As regulatory elements of immune response is inhibited, the potential for immune related adverse events (irAEs) occurs. It has been estimated that irAEs (of any severity) occur in up to 70% of ICI recipients, with grade 3–4 events reported in 10–15% [21, 22]. When anti-CTLA4 and anti-PD-1/PD-L1 agents are used in combination, irAEs appear to be more frequent and more severe [3]. Presentation of these toxicities is variable. Though irAEs mostly occur during the first 3–6 months of treatment [23, 24], delayed immune effects have been reported, in some cases up to 2 years after treatment [25]. The most commonly affected tissues have been the gastrointestinal tract, skin, endocrine organs, liver, and lung. Such a pattern may fit with the immunological characteristics of these tissues, as they each have high exposure to foreign antigens [26].

Incidence of cardiotoxicity

While there has been increased reporting of ICI-associated myocarditis [27], the true incidence is likely underestimated due to challenges in diagnosis, lack of awareness, and the limitations of current systems of reporting adverse events in clinical trials. Myocarditis from ICIs was first noted in case reports and phase II and III clinical trials of ICIs, and later in case series [3, 28–34]. Johnson and colleagues analyzed the Bristol-Myers Squibb corporate safety database to report the incidence of myocarditis in patients being treated with nivolumab, ipilimumab, or both. Among 20,594 patients, myocarditis was reported in 0.06% of patients who received nivolumab alone, and 0.27% of patients who received combination therapy [31]. We previously reported that among 964 patients who received ICIs at the Massachusetts General Hospital, either as monotherapy or combination therapy, ~1% developed myocarditis [33]. This range may be explained, in part, by the wide potential presentations as it is important to note that there are other potential ICI-cardiotoxicity beyond myocarditis, including cardiomyopathy, conduction defects (heart block), atrial and ventricular tachyarrhythmias, and acute coronary syndromes [35–37]. For example, pericarditis is also underrecognized, underreported, and undertreated, and is associated with a relatively high case fatality rate (around 13%) [38]. A recent meta-analysis of 22 clinical trials involving single-agent PD-1 or PD-L1 inhibitors in non-small cell lung cancer suggested incidence rates of 2.0% for

heart failure, 1.0% for myocardial infarction, 1.0% for cardiac arrest, 0.7% for cardiac tamponade, and 0.5% for myocarditis. This report suggested a 5.2% overall rate of significant cardiac events during a brief follow-up period [37].

Several other challenges may also lead to underestimation of incidence of cardiotoxicity. First, the current non-invasive tests are lacking in sensitivity. In our experience, a relatively normal ECG, lack of major symptoms, or a normal LVEF are not sufficient to rule out ICI-associated myocarditis [33]. Second, subclinical myocarditis can be challenging as demonstrated 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 [39]. Lastly, an EMB should be strongly considered when clinical suspicion remains despite normal results from non-invasive testing. However, EMB is often underutilized due to its invasive nature.

Presentation

Consistent data suggest that most cases of ICI-associated myocarditis occur early after starting treatment [27, 32, 33]. For example, Escudier and colleagues reported that the median time to presentation of cardiotoxic effects was 65 days from the start of treatment (equivalent to three ICI cycles), but with a wide variation of 2 to 454 days [32]. Moslehi and colleagues reviewed 101 cases of ICI-associated myocarditis from the World Health Organization's Vigibase and found that 64% of myocarditis occurred after the first or second ICI dose, and 76% occurred within the first 6 weeks of treatment [40]. Mahmood et al. 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 [33]. However, 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 after starting ICI therapies [32, 41]. It is unclear whether these late-onset cases represent the late diagnosis of myocarditis that had begun much earlier or a truly delayed development of myocarditis after ICI administration.

The risk factors for ICI-associated myocarditis are generally poorly understood. Patients with underlying autoimmune disease, pre-existing cardiovascular disease, and diabetes mellitus may be at increased risk [20, 33, 42, 43]. Consistent data showed that patients receiving combination ICI therapies are at more than the double risk [31, 33]. Screening with cardiovascular testing is often considered in the presence of a cardiotoxicity; however, limited early data suggests that there is no difference in ECG or echocardiogram findings between cases and controls prior to starting an ICI [33]. Patients with ICI-associated myocarditis can have pre-existing or concomitant non-cardiac irAEs [27, 32, 33]. Concomitant myositis may be found in 25% of patients [27, 32]. Moslehi and colleagues reported that myasthenia gravis occurred in 11 of 101 patients with myocarditis [27]. In another report describing ten patients with immune-related myositis, four patients also had evidence of myocarditis [34]. These data suggest that patients with ICI-related myositis should undergo evaluation to exclude cardiac involvement.

Presentation of ICI-associated myocarditis may range from nonspecific to fulminant. Patients can present with fatigue, dyspnea, orthopnea, myalgia,

palpitation, chest pain, lower extremity edema, lightheadedness, syncope, or change in mental status [33, 44]. Severe cases can present with cardiogenic shock or cardiac arrest. Contributing to the diagnostic challenges is that symptomatic patients may present to oncology, cardiology, or general medicine providers in an outpatient setting, or to acute or emergency care in a hospital setting. Any relevant alerting symptoms should trigger immediate testing and referral to cardiology/cardio-oncology specialists if necessary [33].

Diagnosis—ECG, echocardiogram, biomarkers, CMR, EMB

Due to its potentially fulminant course, a prompt and accurate diagnosis is critical so that ICIs are immediately discontinued and effective treatment can be initiated [33]. Commonly used diagnostic tests of ICI-associated myocarditis are summarized in the Table 1.

An ECG is an inexpensive and widely available test and should be performed immediately upon presentation. On ECG, findings range from a normal ECG to a range of conduction abnormalities and atrial or ventricular arrhythmias [32, 45]. In our cohort of 35 ICI-associated myocarditis patients, the ECG was abnormal in 89% of patients [33]. Although ECG abnormalities, such as tachycardia, conduction abnormalities, ST segment/T-wave abnormalities, QT prolongation, presence of Q wave, or atrial or ventricular arrhythmias are nonspecific, their identification can be instrumental, especially if new, towards triggering further investigation. Importantly, a normal ECG does not rule out myocarditis. As patients with ICI-associated myocarditis frequently develop tachy- and brady-arrhythmias, clinically suspected patients should be closely monitored with a cardiac telemetry or an ambulatory ECG monitor.

Serum biomarkers are commonly used in the assessment of myocarditis. Troponin levels, indicating the degree of myocardial damage, and

Table 1. Diagnostic tests for cardiotoxicity of immunotherapies

| Diagnostic tests | Potential results |
|----------------------------|--|
| Electrocardiogram | Sinus tachycardia, atrioventricular block, ST segment/T-wave abnormalities, QRS increased, QT increase and prolongation, presence of Q wave, atrial or ventricular arrhythmia or normal |
| Troponin | Normal or elevated |
| B-type natriuretic peptide | Normal or elevated |
| Echocardiogram | Reduced left ventricular ejection fraction, increased left ventricular end diastolic volume, global or focal wall motion abnormalities, diastolic dysfunction, right ventricular dysfunction, pericardial effusion or normal |
| Cardiac magnetic resonance | Presence of late gadolinium enhancement, increased qualitative T2 signal, left or right ventricular dysfunction, or normal |
| Endomyocardial biopsy | T cell- predominant lymphocytic infiltration with or without presence of pathological fibrosis, may also be normal |

B-type natriuretic peptide (BNP), a marker suggesting wall stress, are instrumental in the diagnosis and prognosis of myocarditis. Our data revealed that 94% of patients with ICI-associated myocarditis had an elevated troponin, and 66% had an elevated N-terminal (NT)-pro BNP [33]. However, Escudier and colleagues reported that 46% of patients with various types of ICI-cardiotoxicity had elevated troponin and 100% had an abnormal BNP [32]. Variation in these results could be due to differences in patient cohorts and timing of the tests/presentation with the time to presentation being significantly longer in the Escudier's study. Similar to ECG, a normal biomarker is not sufficient to rule out myocarditis. It is also prudent to rule out coronary ischemia with either coronary angiography, coronary computed tomography angiography, or stress testing if clinically indicated; however, among patients presenting early after starting ICI, myocarditis should be considered the principle diagnosis and excluded.

Echocardiogram is the first-line non-invasive imaging test in the assessment of ICI-associated myocarditis. Unlike myocarditis due to other etiologies, more than half of ICI-associated myocarditis patients (51%) have a preserved LVEF [33], and severe LV dysfunction (LVEF \leq 35%) was not commonly seen [32]. Wall motion abnormalities, indices of diastolic function, and valvular function in ICI-associated myocarditis have not been investigated and represent important topics of future research. Pericardial effusions are found in 7–17% of patients with ICI-associated myocarditis [32, 33], in some representing an occurrence of perimyocarditis, typically with the presentation of pericardial pain. Myocardial strain assessment using speckle tracking echocardiography has been applied in the monitoring of traditional chemotherapy-associated cardiotoxicity [46]. Early unpublished experience from our group suggests that global longitudinal strain may have utility in the diagnosis and prognosis of patients with ICI-associated myocarditis.

CMR is the gold-standard noninvasive test for the diagnosis and risk prediction of myocarditis [47, 48]. The use of advanced tissue characterization in CMR such as late gadolinium enhancement (LGE) and the presence of myocardial edema provides a unique opportunity for differentiating myocarditis from other myocardial diseases [47]. Beyond research letters and case reports, there are no data on the use of CMR in the diagnosis of ICI-associated myocarditis [32]. Escudier and colleagues reported that LGE was presented in 23% of 13 patients in their cohort [32]. In comparison, LGE is present in about 80% of cases of non-ICI myocarditis [49, 50]. The limited availability, high cost, and difficulty of obtaining in critically ill patients may limit the use of CMR in some clinical scenarios.

EMB remains the gold-standard test for the diagnosis of myocarditis. There are established criteria using a right ventricular biopsy to diagnose myocarditis [51], and when five or more samples are available, the accuracy is increased but cases may still be missed [52, 53]. EMB should be performed by experienced interventionists in specialist centers under echocardiography/fluoroscopic 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 6%), EMB is rarely pursued as the first-line test [54]. There are limited

data on EMB in ICI-associated myocarditis. Escudier and colleagues reported that 89% (8/9) of patients had lymphocytic infiltration [32]. Based on unpublished experience from our group, all suspected ICI-associated myocarditis patients who underwent EMB had histopathology, demonstrating a lymphocytic infiltration, and 56% had myocardial fibrosis. 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 [55].

Treatments

There are no prospective studies or randomized trials evaluating treatment options for ICI-associated myocarditis. Based on early experience-based studies, prompt discontinuation of ICI therapies, and initiation of corticosteroids, and other immunosuppression are the cornerstones of the treatment (Fig. 2). 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. Cardiology or cardio-oncology consultation should be obtained, and in relevant cases, an advanced heart failure consultation [56]. Guideline-directed medical therapy for patients with heart failure should be initiated [57]. ICIs should be discontinued, and high-dose corticosteroids, as the first-line therapy, should be initiated promptly in unstable patients without any delay for confirmatory tests (1000 mg methylprednisolone/day). In unstable patients who do not respond to high-dose steroids, antithymocyte globulin or intravenous immunoglobulin should be considered 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 who are experienced in the use of immunosuppression [58–60]. In stable patients, it may be reasonable to wait for confirmatory testing by CMR or EMB. Stable patients should also be treated with 1000 mg of methylprednisolone once the diagnosis is confirmed. A taper of steroids should be performed when the patient is stable or biomarkers (especially troponin) have started to decline. When stable patients do not respond to corticosteroids, second-line interventions including infliximab, mycophenolate mofetil, and plasma exchange could be considered [61, 62]. There are several reports on the use of infliximab as a second-line therapy [31, 33]; however, it has to be used with caution in patients with heart failure, and in our experience, the success rate is modest [63]. Intravenous steroids are followed by oral prednisone (1–2 mg/kg) and a careful tapering plan (depending on clinical response) [43, 44, 56]. The optimal duration of these therapies is unknown, but it is reasonable to continue the treatment until resolution of symptoms and normalization of troponin, LVEF, and conduction abnormalities, which is usually over 4–6 weeks. Prophylactic strategies, such as pneumocystis pneumonia prophylaxis, proton-pump inhibitor, and nystatin for oral candidiasis are recommended while patients are on high-dose corticosteroids therapy. In our registry, steroids

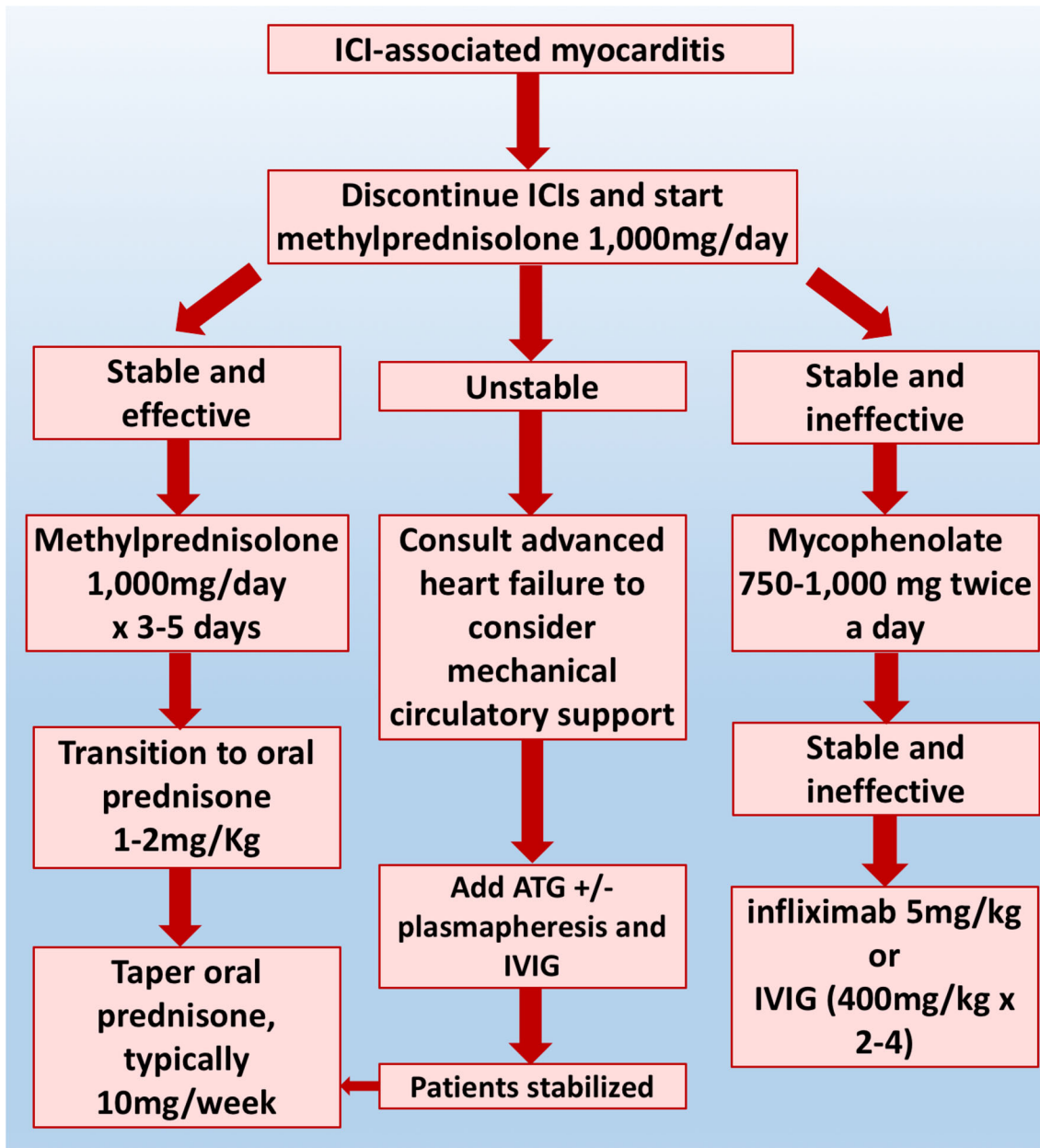


Fig. 2. Treatment algorithm for ICI-associated myocarditis. ATG, antithymocyte globulin; ICI, immune checkpoint inhibitor; IVIG, intravenous immunoglobulin.

were administered in 89% of 35 patients. The mean time from admission to steroid administration in patients without a major adverse cardiac event (MACE) was 18.3 days, shorter than in patients who developed a MACE (27.2 days). A higher initial dose of steroids was associated with lower rate of MACEs and lower discharge serum troponin levels [33]. The data on additional strategies are more limited. In a systemic review

including 73 studies and 88 cases with cardiotoxicity related to ICIs, infliximab, mycophenolate, intravenous immunoglobulin, antithymocyte globulin, and/or plasmapheresis were used in 12 patients and 9 of them survived (75%) [38].

For patients with cardiovascular risk factors and cardiotoxicity of high grade, a longer follow-up time and routine surveillance of cardiac function is reasonable. In our registry, there have been no recurrence after the initial diagnosis of ICI-associated myocarditis over a median follow-up time of 209 days [33]. Although it is recommended to definitively discontinue ICIs in cases of severe (grade 3) or life-threatening (grade 4) toxicities [56], re-challenging patients with a single agent can be carefully considered when no effective alternative oncologic therapy exists provided the patient fully comprehends the risk of recurrent and potentially fulminant cardiotoxicity. The risk of recurrence of cardiotoxicity when patients are re-challenged with a ICI is unknown, but 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 [64]. If re-initiation of immunotherapies is considered necessary, monotherapy with a different specific agent and close cardiac monitoring may be a reasonable approach. Our experience suggested that monotherapy with an anti-PD-1 agent was related to a lower risk of cardiotoxicity [33]. Escudier reported that immune therapy was administered again after the first episode of cardiotoxicity in the 4 out of 30 patients in their cohort without any recurrences [32]. 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, the majority of patients tolerated re-challenge with an anti-PD-1 agent well [65, 66].

Outcomes

ICI-associated myocarditis can have a fulminant course and is potentially fatal. In our registry, 46% of the 35 myocarditis cases experienced a MACE: cardiovascular death ($n=6$), cardiogenic shock ($n=3$), cardiac arrest ($n=4$), or CHB ($n=3$) [33]. Eight out of the 35 patients (23%) died of cardiovascular causes during the median follow-up time of 102 days. Escudier and colleagues reported a case fatality rate of 27% [32]. According to the World Health Organization pharmacovigilance database, comprising more than 16,000,000 adverse drug reactions, myocarditis had the highest fatality rate of 40% (52 out of 131 reported cases), whereas 2–17% of toxic effects of other organ-system had fatal outcomes [67]. In contrast, among 670 patients admitted with non-ICI myocarditis, MACEs occurred in 15% of patients, and death occurred in 4% of patients during a median follow-up time of 4.7 years [48]. Table 2 summarizes the difference between ICI-associated myocarditis and non-ICI myocarditis.

Predictors of adverse outcomes in ICI-associated myocarditis are not well characterized. Escudier and colleagues reported that cardiovascular mortality

Table 2. Difference between ICI-associated myocarditis and non-ICI myocarditis

| | ICI-associated myocarditis | Non-ICI myocarditis |
|----------------------------|---|--|
| Etiology | Immune-related adverse events due to overreaction of immune system | Mostly viral infections |
| Incidence | 0.1–1% in patients undergoing ICIs usually within 3 months of the first dose, but the true incidence is likely to be underestimated | 22/100,000 or approximately 1.5 million cases in the 2013 world population [68] |
| Clinical presentation | Nonspecific, including fatigue, dyspnea, orthopnea, myalgia, palpitation, chest pain, lower extremity edema, lightheadedness, syncope, or change in mental status. Severe cases can present with cardiogenic shock, or cardiac arrest | Heterogeneous signs and symptoms, ranging from mild symptoms of chest pain and palpitations to life-threatening cardiogenic shock and ventricular arrhythmia |
| Concomitant symptoms | Myositis may be found in 25% of patients with ICI-associated myocarditis. Other immune-related adverse events may also present. | A viral syndrome involving the respiratory or gastrointestinal tract with associated systemic symptoms might precede the onset of cardiac symptoms. |
| Troponin | Most patients have elevated troponin. | Most patients have elevated troponin. |
| Echocardiogram | More than half of patients have preserved LVEF and severe LV dysfunction (LVEF ≤ 35%) is not commonly seen [32, 33]. | LV dysfunction is more often seen (~70%) [69]. |
| Cardiac magnetic resonance | LGE is present in less than half of patients [32]. | LGE is present in > 80% of cases [49, 50]. |
| Treatment | Discontinuation of ICIs, corticosteroid, or other immunosuppression. | Optimal care of arrhythmia and of heart failure are the main therapies. Anti-viral therapies may have a role [55]. |
| Prognosis | Patients tend to have a fulminant course. About half of patients experience major adverse cardiovascular events. The case fatality rate is 30–40%. | The case fatality rate in patients with acute myocarditis not associated with an ICI is 2–7% [48, 50, 70]. |

ECG, electrocardiogram; *LGE*, late gadolinium enhancement; *LV*, left ventricle; *LVEF*, left ventricular ejection fraction; *ICI*, immune checkpoint inhibitor

was significantly associated with conduction abnormalities (80% versus 16%; $p = 0.003$) and ipilimumab-nivolumab combination therapy (57% versus 17%; $p = 0.04$) [32]. We found that a cardiac troponin T of more than 1.5 ng/mL was associated with a fourfold increased risk of MACE, and early administration of corticosteroids could potentially lead to less MACE [33]. We also found that the mean LVEF during the index admission in patients who did not develop a MACE was 49%, higher than in patients who had a MACE in the follow-up period (41%); however, the difference was not statistically significant [33].

Unresolved issues

Our understanding of cardiotoxicity of immunotherapies and ICI-associated myocarditis is rapidly improving, but remains very limited. Screening and surveillance are important to risk stratify and to monitor patients before the

occurrence of these conditions. However, our data suggest that neither a screening ECG nor LVEF assessment by echocardiogram prior to ICIs would be sensitive enough to identify patients at risk of ICI-associated myocarditis [33]. Whether surveillance should be performed in all patients on ICIs, and if so, the optimal approach, are unknown. Based on our experience, most patients have an abnormal ECG or elevated troponin levels on presentation [33], so, a surveillance approach with serial ECGs and troponins should be strongly considered, especially in those at higher risk (for example, combination therapy). As most ICI-associated myocarditis patients present within the first 3 months of starting ICIs, obtaining a baseline ECG and troponin before initiation of ICI and again before each cycle can be considered for at least the first 8–12 weeks [43, 44]. As clinical trials are testing the adjuvant or neoadjuvant use of ICIs, as well as their roles alongside traditional cytotoxic or targeted therapies with cardiotoxicity, surveillance may be especially useful as a part of the clinical trial design and clinical care.

The pathophysiological mechanisms of cardiotoxicity of immunotherapies remain unclear. This information is key towards developing a tailored, effective, and less toxic therapeutic approach, rather than broad immunosuppression that is currently employed. Preventive measures targeting specific pathways should also be identified to help decrease the occurrence of ICI-cardiotoxicity, especially for those at heightened risk. In addition, there is uncertainty around the use of wearable defibrillator or implantable cardioverter defibrillator in these patients who frequently manifest ventricular arrhythmias during the active phase because the long-term risk of sudden cardiac death is unclear. Lastly, whether the use of high-doses immunosuppression for treating cardiotoxicity will affect cancer outcomes is unknown.

Future directions

Immunotherapies, specifically ICIs, have revolutionized cancer treatment, and their clinical use is rapidly expanding, leading to a new and exciting era of oncology care. Managing and reducing cardiotoxicity is critical towards allowing the safe delivery of these effective cancer therapies. Our understanding of the cardiotoxicity of immunotherapies and, in particular, ICI-associated myocarditis, remains limited. The key knowledge gaps that should drive further research include (1) understanding mechanistic pathways of pathogenesis of cardiotoxicity related to immunotherapies; (2) describing genetic, clinical, and immunological risk factors for immunotherapy-related cardiotoxicity; (3) establishing a sensitive and cost-effective approach to monitor cardiotoxicity; (4) identifying diagnostic strategies with superior sensitivity and specificity; and (5) discovering effective and targeted cardiac interventions. Lastly, multidisciplinary efforts between primary care physicians, oncologists, cardiologists, cardio-oncologists, and immunologists will be a key component to advance our understanding in this area [71]. We are hopeful that the ongoing intense efforts of the oncology and cardiology research communities will help to resolve these issues, and thereby allow immunotherapies to achieve their maximum potential impact.

Compliance with Ethical Standards

Conflict of Interest

Lili Zhang, Maeve Jones-O'Connor, Magid Awadalla, and Daniel A. Zlotoff each declare no potential conflicts of interest. Paaladinesh Thavendiranathan reports consulting fees from Takeda, BI, Janssen, and Amgen unrelated to the contents of this manuscript.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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