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Cardio-oncology (MG Fradley, Section Editor)

What the Cardiologist Needs to Know About Cancer Immunotherapies and Complications

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Opinion statement

Immunotherapies have transformed the current landscape for cancer treatment and demonstrated unparalleled improvements in survival rates. Now, a third of cancer patients are eligible for treatment with the most widely used class of immunotherapy, immune checkpoint inhibitors (ICIs). As more patients are treated with these novel agents, it is critical for both oncologists and subspecialists to establish a better understanding of the adverse events which can occur. The incidence of myocarditis associated with ICI therapy has been reported to be between 0.27 and 1.14%, 5 times that of myocarditis from other cancer therapies, and, of those patients, 20–50% develop a fulminant form. However, because of unclear risk factors, a broad clinical spectrum, and lack of specific noninvasive studies for diagnosis, the care of patients with ICI-associated cardiotoxicity can be challenging. Here,

we have provided a brief overview of the current immunotherapy agents with a focus on the emerging evidence regarding diagnosis and management of cardiac adverse events.

Background

Cancer is the second leading cause of death, following only heart disease, and the number of cases is rising [1]. It is estimated that 1.8 million patients will be diagnosed with cancer and 606,520 will die, in 2020 alone [2]. Therapeutic options for patients with localized disease are often very effective, but patients with widespread metastatic disease have historically been more difficult to treat, with modest response rates that have limited duration. In recent years, however, treatment with immunotherapy is making dramatic improvements to survival rates in some cancers. One such success story is metastatic melanoma. Prior to immunotherapy, the palliative chemotherapy agent approved for advanced melanoma, dacarbazine, had only a 10.2% response rate with a median survival of 7 months [3]. Today, the long-term survival rates are much improved with immune-modulating agents such as ipilimumab (26% alive at 5 years), nivolumab (44%), or nivolumab plus ipilimumab (52%) [4•].

These and other immuno-oncology agents have revolutionized the care of a variety of cancer types. The most widely used agents, immune checkpoint inhibitors (ICIs), target specific molecular "off switches," including the molecules cytotoxic T lymphocyte-associated protein (CTLA-4), programmed cell death protein-1 (PD-1), and its ligand (PD-L1). Ipilimumab, a CTLA-4 inhibitor, was the first approved ICI in 2011. Since that time, due to their unparalleled and robust response rates, six additional checkpoint inhibitor drugs have been approved by the US Food and Drug Administration (FDA) for over 50 indications in more than 15 cancer types, with response rates ranging from 10.9 to 69% [5, 6]. Remarkably, it is estimated that 36% [6, 7] of all cancer patients in the USA are eligible for treatment with ICIs. The regulatory approvals and promising results have supported a robust pipeline of investigational ICIs and other immuno-oncology agents. For inhibitors of PD-1 and PD-L1 alone, there have been 3362 clinical trials initiated [8], with a ~600% increase from 2015 to 2017.

All currently approved ICIs are monoclonal antibodies that block signals which normally act to inhibit immune responses and, more specifically, the function of T cells. The inhibition of these signals therefore removes one of the mechanisms of peripheral tolerance to self by T cells, leading to T cell activation. Predictably then, these agents can also spur an assault on healthy organs provoking autoimmune side effects (e.g., myocarditis, colitis, pneumonitis, hepatitis, dermatitis, nephritis, endocrinopathies), termed immune-related adverse events (irAEs) which can be severe or even fatal [9•]. The risk of any ICI toxicity is as high as 86% with a single agent or 96% when the patient is receiving a combination of agents [4•]. Most are mild, but between 13% (single agent) and 42% (combination) of patients experience a high-grade irAE requiring discontinuation of therapy [4•].

As the current field continues to be dominated by immuno-oncology development, it is critical for the general cardiologist to understand the potential cardiac effects of these novel therapeutics. This review gives an overview of the types of immunotherapies, addresses potential cardiac complications, and offers guidance for appropriate diagnostics and management of these conditions.

Types of immunotherapies

Chimeric antigen receptor (CAR) T cell therapy

CAR T-cell therapy is a rapidly emerging class of agents in which a patient's own cells are collected, engineered to target antigens expressed on malignant cells [10], and re infused (Fig. 1). Currently, approved CAR T-cell therapy is limited to CARs that target the antigen CD19, present on B-cell-derived blood tumors

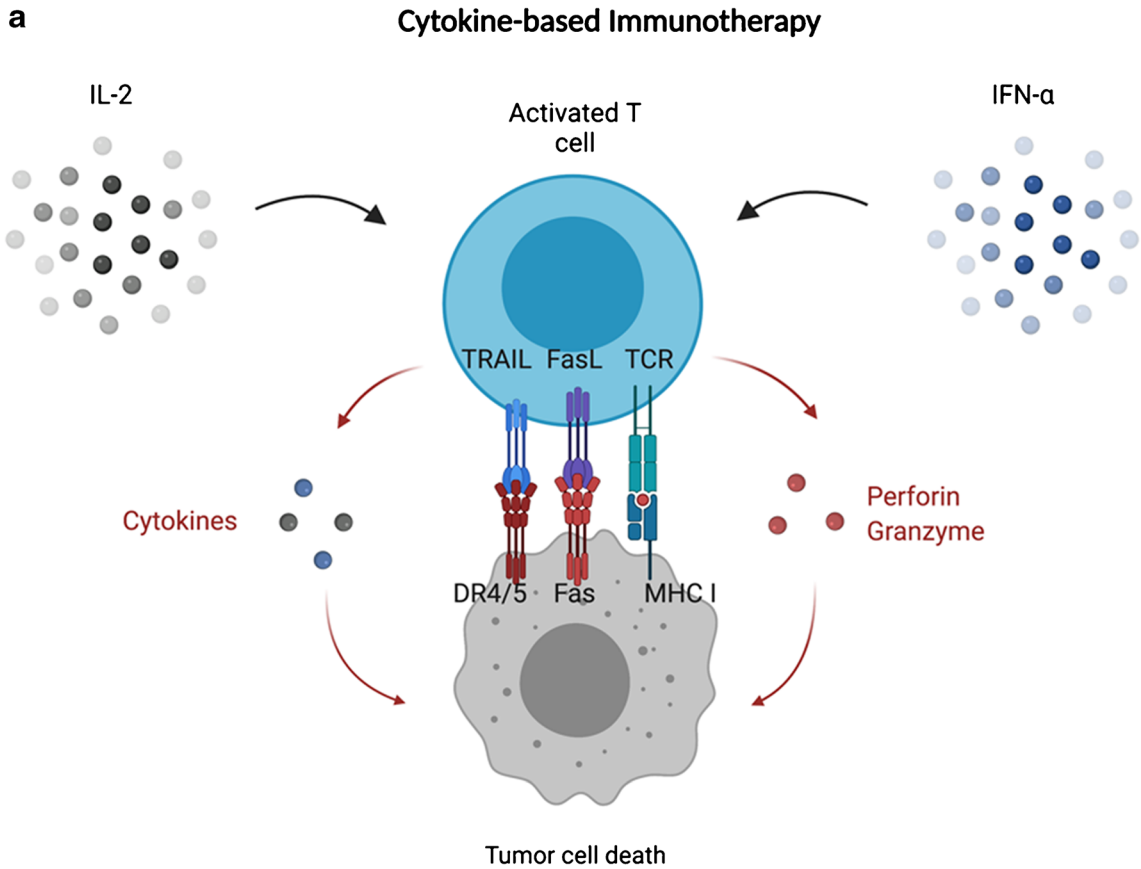
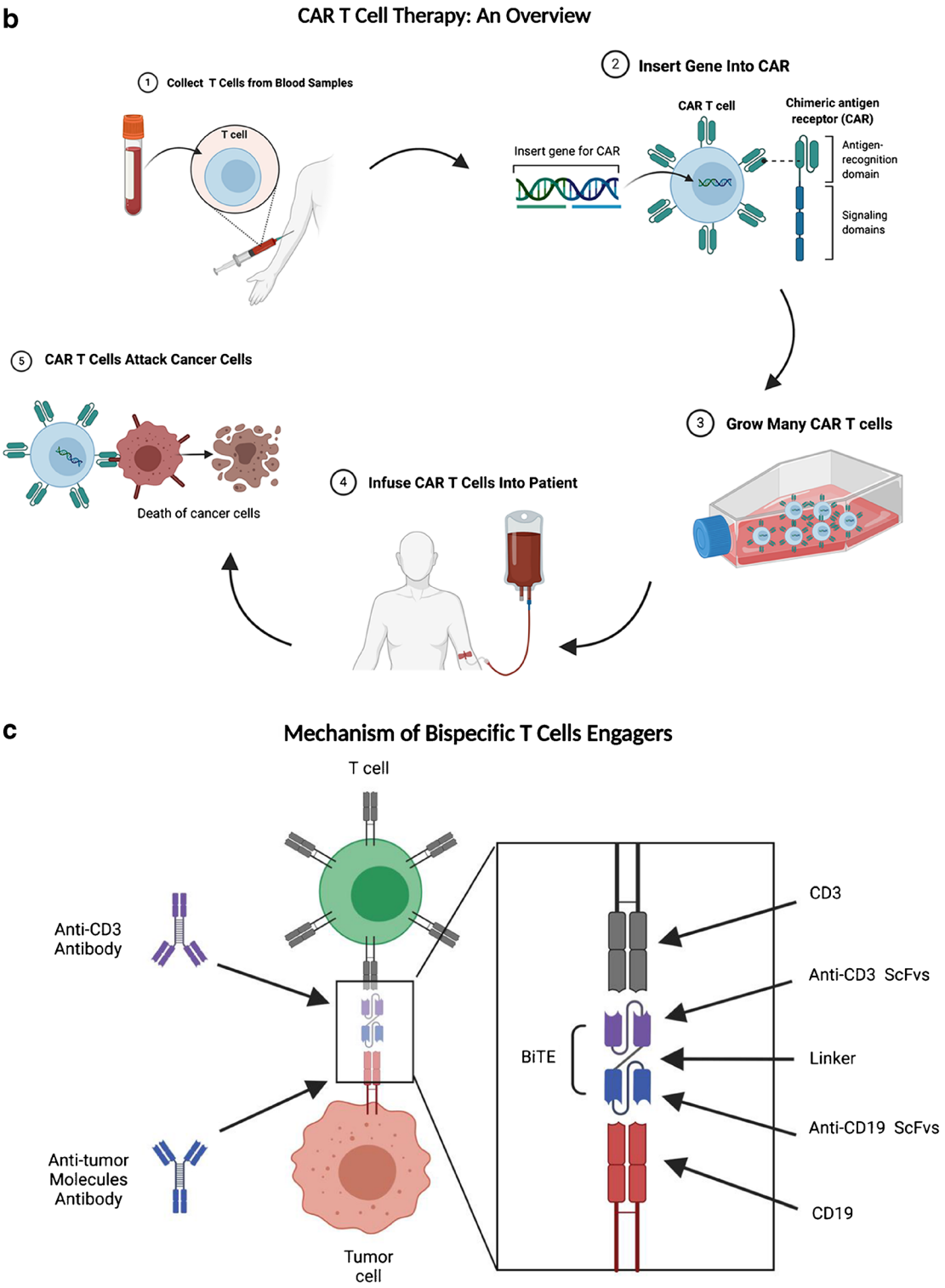


Fig. 1. Immunotherapy – Mechanisms. **a** Cytokine-based Immunotherapy. This treatment takes advantage of the role of proinflammatory cytokines, which can amplify the number of effector immune cells in the tumor microenvironment, enhance antigen priming, and improve effector immune cell cytolytic activity. Created with. **b** Mechanism of CAR T-cells; native T cells are harvested from patients. The T cells will be genetically engineered to express a specfici CAR, which target tumor antigen present on the tumor surface. Then, the resulting CAR T-cells will be infused into patients to attack their tumors. Created with. **c** Mechanism of bispecific T cells engagers (BiTEs). BiTEs are fusion proteins consisting of two single-chain variable fragments (scFvs) of different antibodies. One of the scFvs binds to T cells via the CD3 receptor, and the other to a tumor cell via tumor specific molecule. Created with. **d** Immune checkpoint blockade antibodies block the activity of PD-1 and/or CTLA-4, which increases T cell proliferation and cytokine production, thereby leading to anti-tumor activity. Created with. **e** Diversity of immune checkpoints beyond those targeted by currently approved therapies (CTLA-4, PD-1, and PD-L1). Newer agents targeting other molecules such as LAG-3, T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), T cell immunoglobulin and ITIM domain (TIGIT), VISTA, and B7-H3 are under investigation. Created with BioRender.com

such as acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL) [11, 12]. However, CAR T-cells targeting many other blood cancer antigens, including CD33, CD123, and FLT3 in acute myeloid leukemia (AML), CD30 in refractory Hodgkin's lymphoma, and BCMA in multiple myeloma [13], are now in development. Given the demonstrated role of this type of cellular therapy in liquid malignancies, clinical trials are underway to test their utility against solid tumors.



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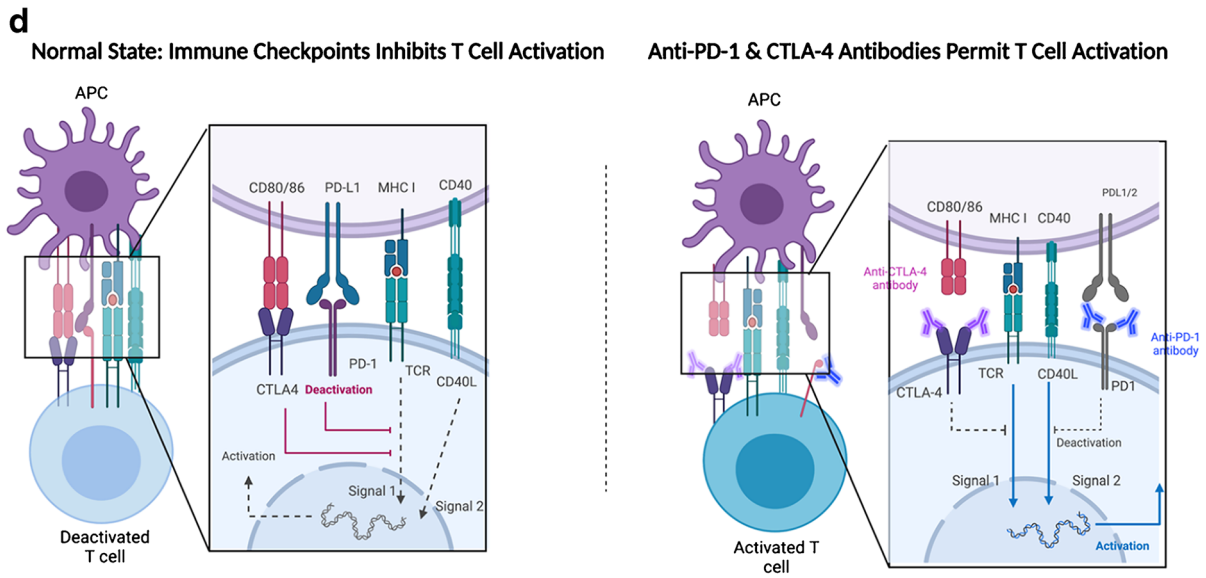


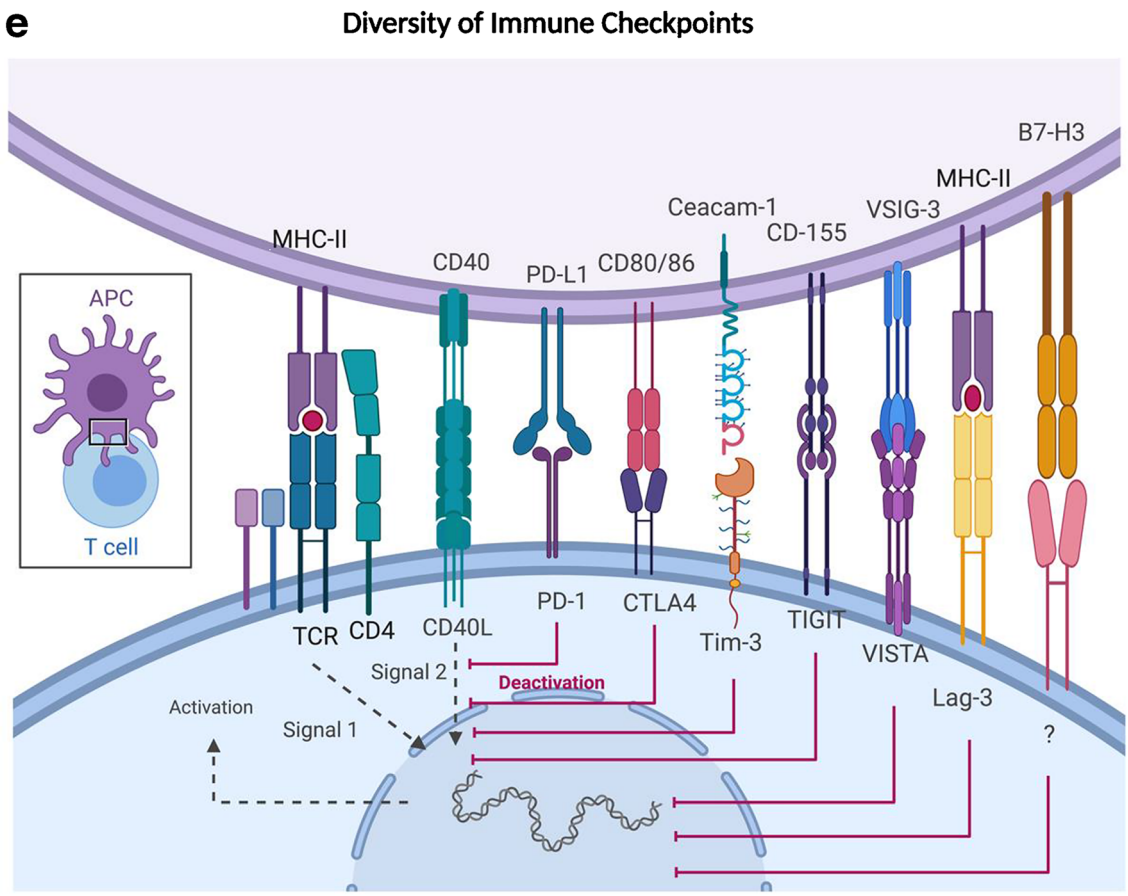


Fig. 1. (continued)

Presentation of cardiovascular side effects from CAR-T treatment

CAR-T therapies stimulate and direct the T cell response, which can cause a rapid and massive release of cytokines into the bloodstream. Clinically, this can lead to high fevers and a precipitous drop in blood pressure [14, 15]. In patients treated with CAR-T, this side effect is called cytokine release syndrome (CRS). Notably, the symptoms of CRS include adverse cardiovascular events, such as tachycardia, capillary leakage, cardiac arrest, ischemia, cardiac arrhythmias, and cardiac failure [16, 17]. Importantly, cardiac injury and adverse cardiovascular events are common post-CAR-T therapy [18]. In 137 patients treated with CAR-T, CRS was observed in 59%. Among patients with more severe presentations of CRS, an elevated troponin was associated with subsequent adverse cardiovascular (CV) events in 55% of patients. These events included CV death, decompensated heart failure, and arrhythmia. Arrhythmias were reported in 7 of 55 patients (13%) and this included supraventricular tachycardia and atrial fibrillation/flutter with RVR. Eight of 55 patients (15%) developed new onset heart failure, and in the 29 patients that had pre- and post-CAR-T echocardiographic data, 8 (28%) had a new reduction in LVEF. The reduction in ejection fraction post-CAR-T was present in patients with an increase in troponin and a higher-grade (grade 2 or higher CRS) post-CAR-T [19•].

Diagnosis and grading

Initially, several methods of grading CRS were available, but the American Society for Transplantation and Cellular Therapy recently formulated a guidance statement with consensus grading:

Consensus grading for CRS [20, 21]:

- Grade 1 – Temperature ≥ 38 °C and no hypotension and no hypoxia. The patient might present with other constitutional symptoms such as myalgia, malaise, and headache.
- Grade 2 – Temperature ≥ 38 °C plus hypotension that does not require vasopressors and/or hypoxia that requires low-flow nasal cannula (≤ 6 L/min or blow-by oxygenation) and Common Terminology Criteria for Adverse Events (CTCAE) grade 2 organ toxicities.
- Grade 3 – Temperature ≥ 38 °C plus hypotension that requires one vasopressor (with or without vasopressin) and/or hypoxia requiring high-flow nasal cannula (≥ 6 L/min), facemask, non-rebreather mask, or Venturi mask that is not attributable to any other cause and CTCAE grade 3 organ toxicity or grade 4 transaminitis.
- Grade 4 – Temperature ≥ 38 °C plus hypotension that requires multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure and CTCAE grade 4 organ toxicity, excluding transaminitis.

Management

All grades of CRS require close monitoring and vigilant supportive care, with grade 2 or above preferably admitted to an acute care setting where hemodynamics and organ function can be closely monitored for signs of deterioration, with rapid intervention when necessary to prevent potentially irreversible organ dysfunction [22].

Mild CRS, including grade 1 and grade 2, is treated symptomatically with antihistamines, antipyretics, and fluids [22]. The balance of benefit versus toxicity with symptomatic treatment is more favorable than using high-dose steroids and tocilizumab or interrupting the infusion [21].

However, in cases of grade 2 CRS in older patients or those with significant comorbidities, or CRS grade 3 and 4 patients, tocilizumab should be dosed 8 mg/kg (maximum 800 mg/dose) for adults and 12 mg/kg for patients with a weight of <30 kg infused over an hour [21]. If clinical improvement does not occur within 24 h or rapid clinical deterioration occurs, repeat doses of tocilizumab are recommended, and a second-line agent, such as corticosteroids, should be administered simultaneously [23]. Specific protocols vary by institution.

Cytokines

Cytokine-based immunotherapy was the first to be approved in 1988. This treatment takes advantage of the role of proinflammatory cytokines, which can amplify the number of effector immune cells in the tumor microenvironment, enhance antigen priming, and improve effector immune cell cytolytic activity (Fig. 1**).** Two cytokine-based treatments, IL-2 and IFN-α, have demonstrated clinical benefit. IL-2 is approved for the treatment of metastatic melanoma and advanced renal cell carcinoma (RCC) [24]. IFN-α is approved for the treatment of melanoma, AIDS-related Kaposi's sarcoma, hairy cell leukemia, and follicular non-Hodgkin lymphoma [25]. Other cytokines, such as IL-15, IL-21, IL-10, IL-12, and GM-CSF, are under investigation for their potential use in cancer treatment [25] either as a single agent or in combination with additional therapies. These agents are used less frequently, and there is limited data regarding management. Each has unique side-effect profiles and a capillary leak syndrome can be seen when using IL-2 with the development of hypotension, renal failure/oliguria, and confusion [26]. Treatment of this capillary leak syndrome centers around supportive care, intravenous fluids, and vasopressors [26].

Bispecific T cell engager (BiTE)

BiTEs are a class of artificial bispecific monoclonal antibodies (Fig. 1). A BiTE fusion protein binds both a receptor on the T cell and a tumor-specific molecule simultaneously, in order to induce activation and release of cytokines and cytotoxic activity by a T cell [27]. Currently, the only FDA-approved BiTE is blinatumomab, which is approved for the treatment of released and/or refractory B cell precursor acute lymphoblastic leukemia (B-ALL) [28]. In general, these agents cause fatigue, count abnormalities such as leukopenia and neutropenia, and nausea/vomiting/abdominal pain. However, a common side effect, similar to CAR-T therapies, is cytokine release-related syndrome [29].

Immune checkpoint inhibitors (ICI)

Immune checkpoint inhibitors (ICI) are the most commonly used agents in immunotherapy treatment. To understand the mechanism of immune checkpoint inhibition, a review of the dual signaling pathways in T cell activation is needed. In this tightly regulated system, naive CD4 or CD8 T cells must receive two signals to be fully activated [14]. Engagement of the T cell receptor (TCR) with the antigen-HLA complex on antigen-presenting cells (APCs) provides signal 1, and the binding of B7 on APCs to CD28 molecules on T cells provides

the costimulatory signal 2; together, these two signals induce activation and expansion of T cells (Fig. 1). Upon activation, inhibitory immune checkpoint receptors such as CTLA-4 and PD-1 are upregulated on the T cell surface. Inhibitory signals are sent to T cells upon engagement of B7 and PD-L1 on APCs with CTLA-4 and PD-1 on T cells, respectively. In this manner, immune checkpoint molecules prevent the induction of autoimmunity by attenuating local T cell responses and minimizing tissue damage [15]. Notably, cancers can exploit this system through upregulation of these inhibitory molecules, which in turn act to suppress the T cell response to the malignant cells.

Therapeutic ICIs are monoclonal antibodies which target and block specific checkpoint molecules, preventing tumor-reactive T cells from receiving inhibitory signals and thus allowing and sustaining an enhanced antitumor response [15] (Fig. 1). The currently approved ICIs target CTLA-4, PD-1, and PD-L1, though newer agents targeting other molecules such as LAG-3, T cell immunoglobulin, and mucin domain-containing protein 3 (TIM-3), T cell immunoglobulin and ITIM domain (TIGIT), VISTA, and B7-H3 are under investigation [16].

Cardiovascular side effects from immune checkpoint inhibitors

Due to the frequency with which immune checkpoint inhibitors (ICI) are used for cancer treatment, cardiologists can expect to encounter a growing number of irAEs in patients who are receiving these agents.

Case presentations of cardiovascular irAEs

The clinical presentation of cardiovascular irAEs varies from asymptomatic to life-threatening. To date, myocarditis, pericarditis, vasculitis, cardiomyopathy, cardiac fibrosis, and cardiac arrest have all been reported as irAEs secondary to immune checkpoint inhibitors [17].

Pericardial disease

The clinical presentation of ICI-associated pericardial disease can include chest pain, shortness of breath, and rapid progression to respiratory failure. ECG changes might include T wave inversion and low QRS voltage. In more severe cases, pericardial effusion and clinical tamponade signs can also be observed [18].

Per the WHO's VigiBase database, ICI-associated pericardial disease, including pericarditis, pericardial effusions, and cardiac tamponade, is the second most commonly reported cardiac irAE [30] with a median time to onset of ICI-associated pericardial disease at 30 days (IQR 8.5–90). Literature on pericardial disease secondary to ICIs are scarce, and only case reports have been published [31]. Pericarditis can occur in less than 1% of patients treated with ipilimumab [32], and pericardial effusions secondary to anti-PD1 drugs specifically are even more rare, with a reported incidence of <1% [31]. Pericardial disease symptoms are typically nonspecific, such as chest pain and shortness of breath, thereby making diagnosis challenging. Common findings include diffuse ST elevations and PR depression on ECG, a pericardial effusion on echocardiogram, and active pericardial inflammation on cardiac MRI or cardiac CT/PET [33].

Colchicine and nonsteroidal anti-inflammatory drugs (NASIDs) are the cornerstone of therapy for idiopathic pericarditis, and steroids are usually avoided due to concerns about promoting recurrent inflammation as steroids are weaned [33, 34]. However, in a data-limited zone, most experts recommend

steroids as first-line therapy for ICI-related pericarditis [35–37] [38]. Termination of ICI administration is recommended when ICI-associated pericardial disease is suspected. Decisions to rechallenge with ICI can be made on a case-by-case basis. Importantly, the fatality rate of ICI-associated pericardial disease is reported as 21% [30], which is far greater than non-ICI-associated pericarditis [39]. Histopathology on three postmortem tissues of ICI-related pericarditis patients demonstrated moderate to severe lymphocytic inflation and fibrinous exudate [40].

Vasculitis

Vasculitis is composed of a diverse group of disorders that cause tissue necrosis by inflammation and damage to blood vessel walls [41]. The clinical presentation can vary from constitutional symptoms, such as myalgias, fever, arthralgias, malaise, rash, weight loss, to serious organ-specific manifestations, such as renal failure and massive hemoptysis [42]. The incidence of ICI-associated vasculitis is currently unknown. However, among reported cases, the median time to vasculitis onset is 55 days (IQR:21–98) after ICI initiation. Per a systematic review of case reports, the most common ICI-associated vasculitis is temporal (giant cell) arteritis [43]. The clinical presentation of temporal arteritis can range from jaw claudication, amaurosis fugax (transient monocular visual loss), diplopia, headache (cephalgia), to other more nonspecific systemic symptoms. Inflammatory markers, such as C-reactive protein and erythrocyte sedimentation rate, are typically elevated [44]. Ultrasound is a noninvasive imaging tool that can be used when temporal arteritis is suspected but the lack of experience with this test in routine practice makes the temporal artery biopsy an essential diagnostic measure. The pathology typically reveals granulomas formed by macrophages and CD4+ T cells [45]. Given the complications from untreated temporal arteritis, which include blindness, aortic aneurysm, and aortic dissection, urgent immunosuppressive treatment is critical. Per consensus guidelines, patients without risk of blindness should be administered oral prednisone at 40–60 mg daily. Patients at risk of visual loss should be treated with intravenous methylprednisolone 500–1000 mg daily for three consecutive days, followed by a tapering course of oral corticosteroids. Termination of ICI therapy is recommended when temporal arteritis is suspected. The incidence of death related to ICI-associated vasculitis is 6% [46].

Takotsubo syndrome

Takotsubo syndrome (TTS), also known as stress cardiomyopathy, is defined as an acute, reversible, noninflammatory, left ventricular systolic dysfunction and is often provoked by intense emotional or physical stressors. TTS is typically associated with transient regional wall motion abnormalities involving the apical and mid-LV myocardium in the absence of culprit atherosclerotic coronary artery disease [18]. Classically, TTS will present with chest pain, dyspnea, and palpitations. ECG abnormalities are typically new from baseline and reversible. ST changes, such as ST segment elevation or non-ST segment elevation, deep T wave inversion, and QT prolongation, can be present. Diagnostic laboratory values may reveal a significantly elevated BNP or NT-proBNP, positive cardiac troponin, and increase in C-reactive protein [47].

Among the oncologic population, the development of TTS has been associated with various types of targeted therapy as well as cytotoxic chemotherapy [48]. TTS has also been reported following ICI therapy [49]. Although the underlying mechanism of TTS is unknown, it has been hypothesized that TTS is the indirect result of adrenergic stress during early ICI therapy rather than direct ICI-related effect due to the noninflammatory nature of TTS [50]. When ICI-related TTS is present, termination of ICI therapy is recommended. Although there are no guidelines on immunosuppression for TTS, high-dose corticosteroid therapy (1 g methylprednisolone daily) was effective in two case studies [48]. Due to the frequency of QTc prolongation in TTS, medications that extend this interval should be avoided, including certain antiarrhythmics such as amiodarone. Currently, there is no consensus on the practicality of ICI rechallenge following TTS.

Atherosclerotic plaque

Atherosclerosis is a chronic inflammatory pathologic process involving the coronary, cerebral, and peripheral arteries and the aorta. Growing evidence supports the essential role of T cells as drivers and modifiers of the atherosclerotic plaques build up. CD4+ T helper 1 (TH1) cells have pro-atherogenic properties, which drive immune responses to peptide epitopes related to atherosclerosis [51]. A recent retrospective study revealed that ICIs are also associated with a 3-fold higher risk for atherosclerotic cardiovascular events including ischemic strokes, coronary revascularization, and myocardial infarction. In addition, ICIs are associated with a >3-fold higher rate of aortic plaque progression. The increase in aortic atherosclerotic plaque was attenuated by concomitant statin and corticosteroid use, which had an approximate 50% reduction in plaque progression [52]. In a recent animal model, after ICI administration, there was an increase in the adaptive immune response in the arterial wall of hyperlipidemic mice. The plaques progressed toward a lymphoid-based inflammatory phenotype, characterized by a 2.7-fold increase of CD8+ T cells and a 3.9-fold increase in necrotic core size. This result suggests that short-term ICI therapy in mice induces T cell–mediated plaque inflammation and drives plaque progression [53]. Further study is essential to understand the impact of ICI on chronic conditions.

Myocarditis

Myocarditis is the most common cardiovascular side effect from ICI therapy. Presentations of myocarditis can range from asymptomatic to fulminant cardiogenic shock and death [54•]. In the mild cases, the presentation can be as benign as asymptomatic elevation in cardiac biomarkers alone. In the moderate cases, the clinical presentation can consist of new-onset heart failure [55], chronic heart failure [56], and acute coronary syndrome [57]. Symptoms may include chest pain, shortness of breath, paroxysmal nocturnal dyspnea, orthopnea, fatigue, and palpitations [58]. Severe cases may manifest as cardiogenic shock, ventricular tachycardia, atrioventricular block, or other arrhythmias [38, 55]. Abnormal lab findings include elevated troponin and NT-proBNP levels and increased inflammatory markers [59]. The diagnosis of ICI myocarditis is often challenging due to the lack of noninvasive diagnostic studies with high specificity for the condition. Potential biological mechanisms, epidemiology,

risk factors, grading, diagnostics, typical biopsy findings, and management of myocarditis are discussed in the following sections.

Potential driving mechanisms in ICI-associated myocarditis

In animal models, expression of the immune checkpoint PD-L1 on cardiac endothelial cells is upregulated by interferon-gamma (IFN-γ). This has been hypothesized to reflect a protective mechanism against activated T cells [60]. A protective role for PD-1 in the heart was demonstrated through the generation of PD-1-deficient mice, which develop a dilated cardiomyopathy [61]. The mechanism of cardiac pathology is thought to be from autoantibodies against troponin I, and therefore these mice may not represent an optimal model system for understanding clinical ICI myocarditis [62].

The underlying molecular and cellular mediators underlying ICI-related myocarditis are unknown. Based on the preclinical data mentioned above, hypotheses include (1) T cells targeting a shared antigen that is present on the tumor and heart, (2) T cell receptors targeting similar though not identical antigens between the two tissues, (3) viral infection or other toxic medication triggering the condition, or (4) autoantibodies specific to cardiac proteins [63, 64].

To date, there has been very little study of human ICI myocarditis samples. A case report revealed specific clones present in myocardium and tumor using next generation TCR sequencing from myocardial T cells and tumor T cells of ICI-related myocarditis patients [63], but larger studies are needed to investigate the underlying mechanisms of this condition.

Epidemiology in ICI-associated myocarditis

The incidence of ICI-associated myocarditis is estimated to be between 0.27 and 1.14% [54, 63], which is 5-fold higher than myocarditis from other cancer therapies [65]. Recent evidence suggests that cardiac toxicities are likely underreported because of a lack of effective noninvasive diagnostic tools and subtle patient presentations [66•]. Patients generally present after 1–2 doses of ICI with a median time of 30–34 days [46, 63]. While higher incidence rates of cardiotoxicity in the first and third months of treatment have also been reported, it is important to consider that these cardiovascular manifestations can develop at any time during or after treatment [49]. Presentations can range from asymptomatic troponin elevation to fulminant cardiogenic shock with unstable hemodynamics and the need for intensive care [67].

The likelihood of developing ICI-associated myocarditis is increased when patients develop other irAEs (pneumonitis, colitis, hepatitis, etc.) [68]. All patients experiencing an irAE should be considered for cardiac evaluation. Furthermore, ICI-induced myocarditis can develop concurrently with other muscle-related irAEs such as myositis and myasthenia gravis [69].

Risk factors

Very few risk factors for ICI-associated myocarditis have been identified. Age appears to confer no predisposition [35]. A male predominance (66.7%) has been reported, but male sex could not be established as a risk factor because males were overrepresented in clinical trial enrollment and at baseline in ICI use. Other risk factors reported to date include the use of combination checkpoint inhibition [54, 63], diabetes [54], HF, and ACS [70]. Future studies are

needed, however, to identify additional risk factors which could help to risk stratify ICI recipients. This, in turn, could inform efforts to surveil those patients at the highest risk.

Grading

Recent guidelines for the management of ICI-related toxicities have classified myocarditis into 4 grades, based on the severity of clinical presentation and degree of abnormality in laboratory testing and imaging studies [71] (Table 1). Despite these distinct categories, cardiac toxicities have significant variability in clinical presentation and evolution.

Diagnostics

The broad and nonspecific spectrum of clinical manifestations of cardiotoxicity makes diagnosis, and choice of appropriate management, challenging. When ICI myocarditis is suspected, the recommended workup includes cardiac biomarkers, electrocardiogram (ECG), echocardiogram, and cardiac MRI [72] (Table 2). The use of cardiac computed tomography (CT) or coronary angiography during the evaluation of suspected ICI-related myocarditis is used on a case-by-case basis to exclude the possible diagnosis of coronary artery disease.

Cardiac biomarkers

Cardiac biomarkers are the primary laboratory tests recommended when evaluating for ICI-related cardiotoxicity. Troponin I (TnI) and Troponin T (TnT) have been most closely linked to the diagnosis of myocarditis [73] with 94% of patients having an abnormal troponin at diagnosis [54]. A relationship has been described between troponin level and prognosis with regard to the occurrence of major adverse cardiac events (MACE; includes cardiac death, complete heart block, cardiogenic shock, and cardiac arrest) [54]. A discharge TnT value of ≥1.5 ng/mL is associated with a 4-fold increased risk of MACE [54] .

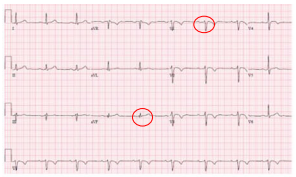
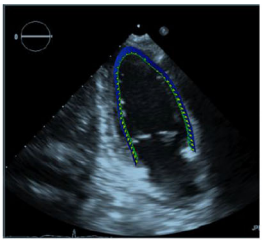
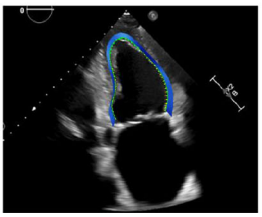
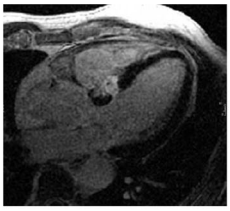
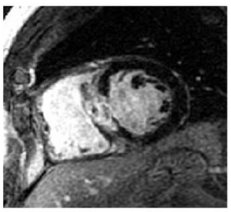
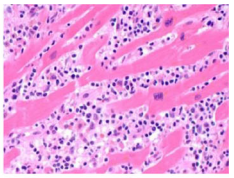
Serial checks of troponin may not provide sufficient diagnostic certainty. Recently, a combined diagnostic approach of TnI and global longitudinal strain (GLS) on echocardiography increased sensitivity for detection of cardiotoxicity from 48 and 74, respectively, for each in isolation, to 87% combined [73, 74], but further validation is needed to determine the usefulness of combined diagnostics.

Despite the potential promise, the use of troponin as a screening tool for ICI-associated myocarditis had not shown benefit to date. A recent study evaluated the effectiveness of screening TnI and ECG in 76 asymptomatic advanced

Table 1. Grading of CAR-T toxicity

Grade	Definition
1	≥ 38°C without hypotension or hypoxia
2	≥ 38°C with hypotension not requiring vasopressors or hypoxia needing Only low-flow nasal cannula
3	≥ 38°C with hypotension requiring 1 vasopressor or hypoxia requiring high flow/facemask or non-rebreather
4	≥ 38°C with hypotension requiring multiple pressors or hypoxia requiring non-invasive or invasive ventilation

Table 2. Myocarditis: diagnostics, grading, management, rechallenge considerations

Diagnostics	**ECG**  • Increases in QRS duration • Variable increase QTc interval • No change in PR interval • Abnormalities vary	**Echocardiogram** (speckle tracking: normal strain)  **Echocardiogram** (speckle tracking: abnormal strain) 	**CMR** (long axis)  **CMR** (short axis)  • LGE present • Reduced EF	**Biopsy**  • Multifocal myocarditis • CD8+ T-cell and macrophage lymphohistiocytic infiltrate • PD-L1 in areas of injury • No granulomas or giant cells

	G1	G2	G3 (severe)	G4 (life-threatening)
Grading	• Asymptomatic • Mildly abnormal screening tests (cardiac biomarker, ECG)	• Mild symptoms • Abnormal screening tests	• Moderate or severe symptoms with arrhythmia • Significantly echocardiographic findings (without hypotension) • Elevated cardiac biomarkers	• Moderate to severe decompensation • Hemodynamic instability • Cardiac biomarker greater than three times the upper limit of normal • Cardiogenic shock and arrhythmias (advanced atrio-ventricular block or ventricular tachycardia)
Management	• Hold ICI therapy • Baseline ECG and biomarker assessment to establish notable changes • Mild abnormalities should be observed closely during therapy	• Hold ICI therapy • Control cardiac diseases (heart failure, atrial fibrillation) optimally • Control cardiac disease risk factors proactively	• Permanently discontinue ICI therapy • Methylprednisolone pulse dosing 1 g/day for 3–5 days • Treat until cardiac function returns to baseline, taper over 4–6 weeks • Inpatient care	• Permanently discontinue ICI therapy • Methylprednisolone 1 g/day for 3–5 days • Treat until cardiac function returns to baseline, switch to oral corticosteroids taper over 4–6 weeks • Severe refractory cases: If no improvement within 24 hours on steroids, consider adding additional immunosuppressive agents (Mycophenolate mofetil, anti-thymocyte globulin - ATG, or infliximab) • Give additional inpatient supportive treatments, including appropriate treatment of heart failure/ multisystem organ failure such as vasopressor support (inotropic agents), ICU-level monitoring and transient/permanent pacemaker in patients with arrhythmia
Rechallenge	• Consider resuming upon resolution of symptoms	• Permanent discontinuation of immunotherapy is warranted in the setting of grade 2–4 myocarditis (See figure 2)		

Table Information Modified from NCCN, ASCO, SITC, ESMO guidelines

melanoma patients, who underwent combination ICI therapy with ipilimumab and nivolumab. In the 76 patients, thirteen had minimally detectable non-diagnostic TnI levels (≥0.01ng/mL and <0.06ng/mL). When TnI was detected, none of the thirteen patients had any acute cardiac and/or systemic pathology. At follow-up, eleven patients had undetectable TnI, and two had stable levels. Furthermore, twelve of the patients received further ICIs without cardiac complication, and one discontinued ICI therapy because of disease progression [75].

Brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT pro-BNP) are indicators of increased ventricular wall stress which occurs in the setting of volume overload [73] and are frequently elevated in ICI-associated myocarditis [72]. To date, BNP levels have not been predictive of MACE [54]. A larger meta-analysis recently showed that neither BNP nor NT-proBNP was able to consistently predict systolic dysfunction [76]; therefore, recent guidelines removed the previous recommendation for assessing BNP and NT-proBNP in suspected ICI-related myocarditis cases [66•].

American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines for the management of ICI-related toxicities recommend that total creatine kinase (CK) and creatine kinase muscle/brain (CK- MB), as well as other inflammatory biomarkers, be used to aid in the diagnostic workup. However, these biomarkers, like troponins and natriuretic peptides, are nonspecific [58].

Electrocardiography

In one of the largest clinical case series of ICI myocarditis to date, 89% of patients with cardiac toxicity had abnormal ECGs as compared to baseline [54]. In addition, the results presented from a multicenter registry with 110 ICI myocarditis cases and 178 controls revealed 47% of cases had a prolonged QRS duration >110 ms[77]. Importantly, QRS duration >110 ms conferred a 2.6-fold risk of major adverse cardiac events (MACE). Similarly, patients with QTc > 450 ms also had a 2.6-fold risk of MACE [77]. While a variety of arrhythmias have been reported in association with ICI myocarditis, including atrial fibrillation, ventricular arrhythmias, and conduction abnormalities [49], whether ECG parameters can aid in the diagnosis is an area of active study. The presence of arrhythmias is a criterion for the definition of grade 3 and 4 cardiotoxicity [72].

Echocardiography

Echocardiography is a first-line imaging modality used to evaluate cardiac function in patients who are symptomatic or are suspected to have ICI-related myocarditis. A significant reduction in left ventricular ejection fraction (LVEF) has been widely reported in patients presenting with cardiovascular toxicity, particularly those with grade 4 or fulminant myocarditis [54•]. Yet, up to half of the patients can have a normal LVEF, and even of those who develop MACE, 38% have a normal LVEF [54•]. GLS has been shown to be significantly reduced in cases of ICI-related myocarditis independent of the ejection fraction. GLS proved to be a strong predictor of MACE among myocarditis cases, despite EF measures, and may have value in risk assessment [73, 78].

Cardiac magnetic resonance imaging

Cardiac magnetic resonance (CMR) imaging is a fundamental imaging modality for the diagnosis of myocarditis [79], as described in the Lake Louise criteria. CMR allows for a noninvasive means of tissue characterization with the use of late gadolinium enhancement (LGE), T2-weighted imaging, extracellular volume fraction as well as other advanced techniques [58, 72]. These tools can be used to better evaluate the degree of myocardial inflammation and injury [58]. However, CMR lacks both sensitivity and specificity for the diagnosis of ICI-associated myocarditis. In a retrospective study of 103 patients with ICI-related myocarditis, the analysis of CMR scans indicated that LGE was present in 48% of all patients (55% of those with reduced EF and 43% of those with preserved EF) [79]. Cardiac MRI can provide structural and functional information, but these results demonstrate that a CMR negative for features consistent with myocarditis does not rule out the diagnosis of ICI myocarditis. If the clinical suspicion for myocarditis remains high, an endomyocardial biopsy should be performed.

Cardiac biopsy

Endomyocardial biopsy (EMB) is considered the gold standard approach for the diagnosis of myocarditis. Using a bioptome via jugular vein access, this procedure involves the collection of multiple small fragments of tissue from the right ventricular side of the interventricular septum. The risks of the procedure include access site bleeding, arrhythmia, and right bundle branch block, but the most severe complication is right ventricular free wall perforation leading to hemorrhagic tamponade. ASCO management guidelines make note of the risks of this procedure and state that EMB should be reserved for patients who are unstable and failed to respond to initial therapy or for whom the diagnosis is in doubt [36]. When deemed worth the procedural risk, cardiac biopsy allows for a definitive diagnosis of ICI-related myocarditis. The biopsy can be assessed by the Dallas criteria for myocarditis which requires (1) inflammatory infiltrate and (2) myocardial necrosis [58] be present. Biopsy findings can be similar to cardiac allograft rejection [80], though an analogous grading scheme has not yet been described. Typically, ICI-associated myocarditis is multifocal/diffuse. In addition, immunohistochemical staining often reveals a lymphohistiocytic infiltration with CD8+ T cells and PD-L1 expression in areas of injury [63, 80, 81]. Granulomas and giant cells have not been observed [54•, 80]. A recent report has suggested a correlation between histologic grade and outcome [80], but further work to predict poor clinical outcomes is essential to guide management recommendations.

Multi-organ involvement

Immune-related adverse events can affect multiple organ systems in an individual patient. With the combination ipilimumab and nivolumab, toxicities affecting more than one organ system occur 25% of the time, and 7% of patients have three or more organs involved [82]. Myocarditis has been associated with a wide range of toxicities including autoimmune thyroiditis, uveitis, colitis,

hepatitis, hypophysitis, and myasthenia gravis [17, 83]. Thus, it is important to have a broad differential for other possible autoimmune-like conditions in a patient presenting with symptoms or a diagnosis related to irAE.

Management

There has been limited evidence to help guide the management of ICI-related cardiotoxicity. Many of the current recommendations for best practices are based on individual case reports and expert opinions (Table 2). At Massachusetts General Hospital, we have an algorithm for therapeutic management of myocarditis based off the clinical stability of the patient (Fig. 2).

The guidelines recommend an immediate cardiac consultation for any suspected case of myocarditis/cardiac toxicity when the patient is receiving ICI treatment. For moderate to severe (grade 3), or life-threatening (grade 4) cases, methylprednisolone 1 g per day should be administered for 3–5 days. The dose of steroids and the timing is critical. A recent study demonstrated that high-dose steroids had a 73% lower risk of MACE than those treated with low-dose steroids; furthermore, those treated within 24 h of presentation had a lower rate of MACE (7%) versus those for whom steroids were started 24–72 h (34%) and > 72 h after the presentation (85%) [84].

After the initial pulse, transition to oral prednisone 1–2 mg/kg with 4–6 week taper. Appropriate prophylaxis against pneumocystis infection, vitamin D/calcium supplementation, and gastrointestinal prophylaxis is recommended. For severe or refractory cases, if the patient shows no improvement within several days of steroid treatment, additional immunosuppressive agents can be considered. Mycophenolate mofetil, anti-thymocyte globulin (ATG), infliximab are among those recommended in guidelines (NCCN/ASCO/SITC/ESMO), and case reports also describe the use of abatacept and alemtuzumab [85, 86]. However, it is important to note that infliximab is associated with a significant increase in heart failure deaths, hospitalizations, and morbidity [87]. This agent is contraindicated in patients with moderate to severe congestive heart failure [87].

Currently, clinicaltrials.gov has no open and accruing trials for ICI myocarditis management. However, there is preclinical evidence for agents such as abatacept and anakinra which is hypothesis-generating [86, 88]. At present, there are open trials for the treatment of rheumatoid arthritis-associated myocarditis with abatacept and (ClinicalTrials.gov number, NCT03619876) acute myocarditis with anakinra (ClinicalTrials.gov: NCT03018834) which will provide insight into the efficacy and potential further study with ICI myocarditis [89].

The benefit of using angiotensin-converting enzyme (ACE) inhibitors and beta-blockers for this condition is unclear. Guidelines note that the current recommendations are derived from anecdotal evidence, and cardiac symptoms should be managed per guidelines from cardiology societies [36]. The European Society of Cardiology states that assessment should be individualized based on the patient's baseline cardiovascular risk, but it does not describe any specific recommendations for the management of ICI-induced cardiotoxicity [90]. The recommended approach by the Society for Immunotherapy of Cancer (SITC) emphasizes the importance of "active, ongoing consultation with a cardiologist to discuss the risk/benefit of continuing ICI therapy, starting corticosteroids, or instituting other cardiac treatments."

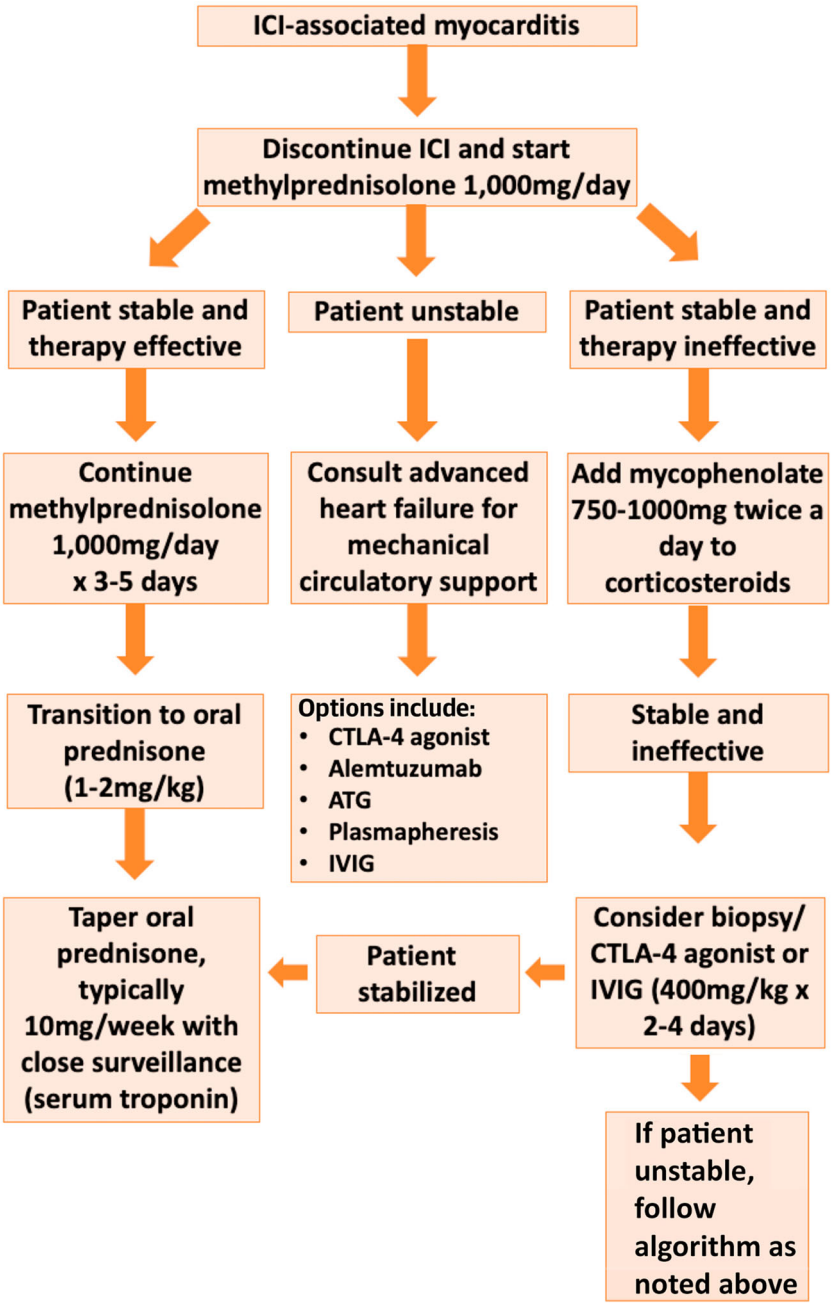


Fig. 2. Therapeutic approach to ICI myocarditis at Massachusetts General Hospital. (Source: *JACC*: CardioOncology. Written permission granted)

To date, there is very little evidence available for guiding the management of cardiotoxicity and even less to guide whether a rechallenge with immunotherapy is safe in cancer patients with progressive disease. Currently, guidelines indicate that the ICI should be discontinued indefinitely; however, there are case reports of patients being rechallenged without recurrence of cardiotoxicity

[49]. The decision to rechallenge should be made on a case-by-case basis in close collaboration between the cardiologist and oncologist and should incorporate the expected clinical benefit of resuming ICI therapy.

Conclusion

Given the rise in the use of ICI therapy for cancer patients, and the potential for improved outcomes for these patients, multidisciplinary teamwork is of critical importance before, during, and after immunotherapy to ensure early detection and appropriate management of cardiac adverse events.

Declarations

Conflict of Interest

Marina Frayberg declares that she has no conflict of interest. Anthony Yung declares that he has no conflict of interest. Leyre Zubiri has received compensation from Merck for service as a consultant. Daniel A. Zlotoff declares that he has no conflict of interest. Kerry L. Reynolds declares that she has no conflict of interest.

Disclosures

Marina Frayberg: No relevant disclosures.
Anthony Yung: No relevant disclosures.
Leyre Zubiri: MERCK consultant.
Daniel A Zlotoff: No relevant disclosures.
Kerry L Reynolds: No relevant disclosures.

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These guidelines represent a valuable resource for clinicians. They are the most up-to-date and describe the main diagnostic and management recommendations for the most common toxicities related to ICI.

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