Received: 17 October 2019 | Accepted: 28 January 2020 | Published on: 4 March 2020

DOI: 10.1111/ajco.13326

REVIEW

WILEY

Cardiovascular immune-related adverse events: Evaluation, diagnosis and management

Yingxian Liu | Wei Wu

Department of Cardiology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Science, Beijing, China

Correspondence
Wei Wu, Department of Cardiology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Science, Beijing 100730, China.
Email: camsww@hotmail.com

Abstract

Cardiotoxicities are associated with immune checkpoint inhibitor (ICI) therapy. Recent case series and retrospective studies have shown that cardiac immune-related adverse events (irAEs) are rare but potentially fatal complications of immunotherapy, with various underlying risk factors such as combinations of different ICIs. High mortality rates and overreactive inflammation have been observed with ICI-associated cardiotoxicities, highlighting the necessity of baseline and serial evaluations and the identification and management of cardiac irAEs as early as possible. The clinical presentations of irAEs range from asymptomatic cardiac biomarker elevation, myocarditis and pericardial diseases to heart failure and mild to fatal arrhythmia. Troponin measurement and electrocardiogram are sensitive initial tests, whereas cardiac magnetic resonance imaging and endomyocardial biopsy are both gold standard components of the diagnostic criteria. Close monitoring and timely consultation with a cardiologist are important for the diagnosis of ICI-related cardiotoxicities, with decisions of stopping or rechallenging ICIs and strategies to manage heart injuries. Treatment principles are made according to risk stratifications. The first-line medication is glucocorticoids of various doses, and the second-line immunosuppression includes intravenous immunoglobin, antithymocyte globulin and other immunosuppressants, which are recommended in life-threatening cases or in cases of resistance/no response to steroids.

KEYWORDS
cardiotoxicity, immune checkpoint inhibitor, myocarditis

1 | INTRODUCTION

Immune checkpoint inhibitors (ICIs) are effective medications that block inhibitory receptors expressed on T lymphocytes, such as cytotoxic T-lymphocyte–associated protein-4 (CTLA-4) and programmed cell death protein-1 (PD-1),[1-4] as well as on tumor cells, for example, programmed cell death 1 ligand-1 (PD-L1).[5,6] When these inhibitory receptors are blocked, T cells are activated to recognize and target cancer cells in the host and display antitumor activity. ICIs have shown remarkable effects in treating a variety of cancers, and more than 1200 registered trials are currently evaluating ICIs worldwide.[7]

However, magnifying the immune response against cancer is accompanied by the potential for autoimmune inflammation of off-target tissues.[8-10] The adverse events associated with ICIs, which are termed immune-related adverse events (irAEs), have been noted in several organs, including the skin, gastrointestinal tract, liver and endocrine system. Cardiac toxicities are among the relatively rare but most severe complications.[11] In recent years, a number of case reports, case series and cohorts have raised awareness of unexpected cardiac immune responses for patients undergoing ICI treatment.[12-15] Clinical presentations vary from subclinical manifestations (from mild cardiac troponin elevation to fulminant myocarditis) to cardiac shock and even sudden death. The aims of this review are to present the latest data on the cardiovascular toxicities of ICI treatment, focusing on epidemiology, clinical syndromes, related mechanisms, patients' findings, clinical management and outcomes.

2 | EPIDEMIOLOGY AND RISK FACTORS

Although the initial clinical trials of ICIs did not routinely evaluate cardiac functions and myocardial injuries, growing evidence of cardiac irAEs has been reported.[12-16] After two cases with ICI-associated fatal myocarditis on the combination therapy of anti-PD-1 and anti-CTLA4 were presented, Johnson *et al.* searched the database from the manufacturer of ipilimumab and nivolumab and found 18 cases of myocarditis in 20 594 patients (0.09%) from the Bristol-Myers Squibb safety database.[13] The combination of nivolumab and ipilimumab significantly increased the incidence of ICI-related severe myocarditis (0.27%) compared with nivolumab monotherapy (0.06%).[13] Recently, in another study including 964 patients receiving ICIs, 35 patients (1.14%) developed myocarditis.[17] The incidence of myocarditis was 0.5% in patients with anti-PD-1 alone, 2.4% with anti-PD-L1 alone, 3.3% with anti-CTLA-4 alone, 2.4% with a combination of anti-PD-1 and anti-CTLA-4 and 1% with a combination of anti-PD-L1 and anti-CTLA-4. Regarding the incidence of myocarditis among different single ICI therapies, pembrolizumab accounted for 1.3% and nivolumab accounted for 0.6%, which represented nearly all the myocarditis cases related to anti-PD-1. Data on other ICI-related irAEs are limited. The different distributions of prevalence in ICIs was partially due to patient selection, prespecified adjudication, the well-recognized difficulty with the diagnosis of myocarditis, and reporting bias by investigators not suspecting this as a potential toxicity.[17] It is suspected that most of the published reports might underestimate cardiac irAEs.[18-22]

Combination immunotherapy with CTLA-4 and PD-1/PD-L1 monoclonal antibodies is an important risk factor for cardiovascular irAEs. Compared with controls (treated with ICIs without cardiovascular complications, $N = 105$), myocarditis cases were more likely to receive combination ICI therapy (9.5% *vs* 34.3%, $P < 0.001$).[17] In analyzing the different combination strategies of anti-CTLA-4 and anti-PD1, especially the combination of ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1), these combinations were more frequent in cases with myocarditis than in controls (26% *vs* 8.6%, $P = 0.02$).

Male sex might be another factor in the cases of cardiac irAEs. In a retrospective analysis including 30 cases of ICI-related cardiotoxicity, 23 cases (77%) were male with a median age of 72 years (range from 23 to 88 years).[23] In addition, 71% (23/35) of ICI-associated myocarditis cases were male in a previous registered multicenter study.[17] It seemed that males underwent more ICI-associated cardiotoxicity than females; however, considering males were the majority at baseline in clinical practices and trials, the predisposition of males was less meaningful.[24]

Combined with other anticancer therapies, such as vascular endothelial growth factor (VEGF) inhibitors, anthracycline chemotherapy and radiotherapy may increase the risk of ICI-associated cardiac irAEs. In the real world, before the initiation of ICIs, many patients with metastatic cancer have received chemoradiotherapy or targeted therapy. These treatments might induce the exposure of cardiac antigens and the development of cardiac-specific immune responses. Cardiovascular damage is initially subclinical and can then be amplified after multiple doses of ICI therapy. In a trial involving 55 cases treated with avelumab and axitinib, the latter of which was a VEGF inhibitor, one patient (2%) developed fatal myocarditis.[5] Some ongoing clinical trials further provided increasing evidence of the cardiotoxic side effects of combining ICIs with VEGF inhibitors.[25,26] VEGF inhibitors might increase cardiovascular risk by blocking the VEGF receptor and the platelet-derived growth factor receptor and altering resting blood flow to the myocardium or the coronary flow reserve.[27] Hu *et al.* summarize the common principles of ICIs and other anticancer therapy as follows: one therapy causes myocardial injury, and the subsequent use of another molecular cancer therapy amplifies the damage, such as ICIs followed by Raf and MEK inhibitors and anthracyclines followed by trastuzumab, which might be caused by targeting certain pathways expressed in both cancer cells and cardiomyocytes.[28]

Other potential risk factors include concomitant cardiovascular disease (prior myocardial infarction, heart failure, myocarditis or advanced bradycardia) or a previous history of chemoradiotherapy-associated left ventricular dysfunction (Figure 2).[22]

3 | CLINICAL MANIFESTATIONS

The interval from the initiation of ICI therapy to the presentation of cardiac toxicity ranges widely. Onset usually occurs within 1 to 2 months after initiating ICIs, while the time until cardiac abnormalities develop can be delayed by several months. In the aforementioned study, the median onset time from starting ICI treatment to clinical myocarditis was 34 days (interquartile range 21–75 days), which was earlier than other immune therapy-mediated side effects, including renal, hepatic, endocrine, pulmonary and gastrointestinal injuries (3.75, 2.62, 2.16, 1.93 and 1.63 months, respectively).[17] According to the World Health Organization's (WHO) Vigibase, which stored case safety information for medications, 64% of 59 cases (with available dosing information) within the initial two ICI doses and 76% of 33 cases (with available data for the onset time) soon after the first 6 weeks of treatment were reported to have ICI-triggered myocarditis.[29] If a combination of PD-1/PD-L1 and CTLA-4 antibodies were conducted, myocarditis might occur even earlier, with a median of 17 days after the first combined treatment (range from 13 to 64 days).[13] In another report, the time from starting treatment to the onset of cardiotoxic effects varied from 2 to 454 days (or one to 33 ICI infusions), with a median interval of 65 days (equivalent to three ICI cycles).[23] Although a higher incidence of cardiotoxicity was usually observed early after the exposure to an ICI, cardiotoxicity could occur at any time during the treatment.

If dyspnea, palpitation and edema happened after ICI therapy, special attention should be paid to cardiac function or heart rhythm (Figure 1).

ICI-related myocarditis was the most common cardiac irAE (45%).[30] Chief complaints could be dyspnea due to acute heart failure and pulmonary edema, syncope or decreasing blood pressure due to cardiogenic shock and severe arrhythmias (e.g., heart block and both atrial and ventricular arrhythmias), and even sudden death.[31]

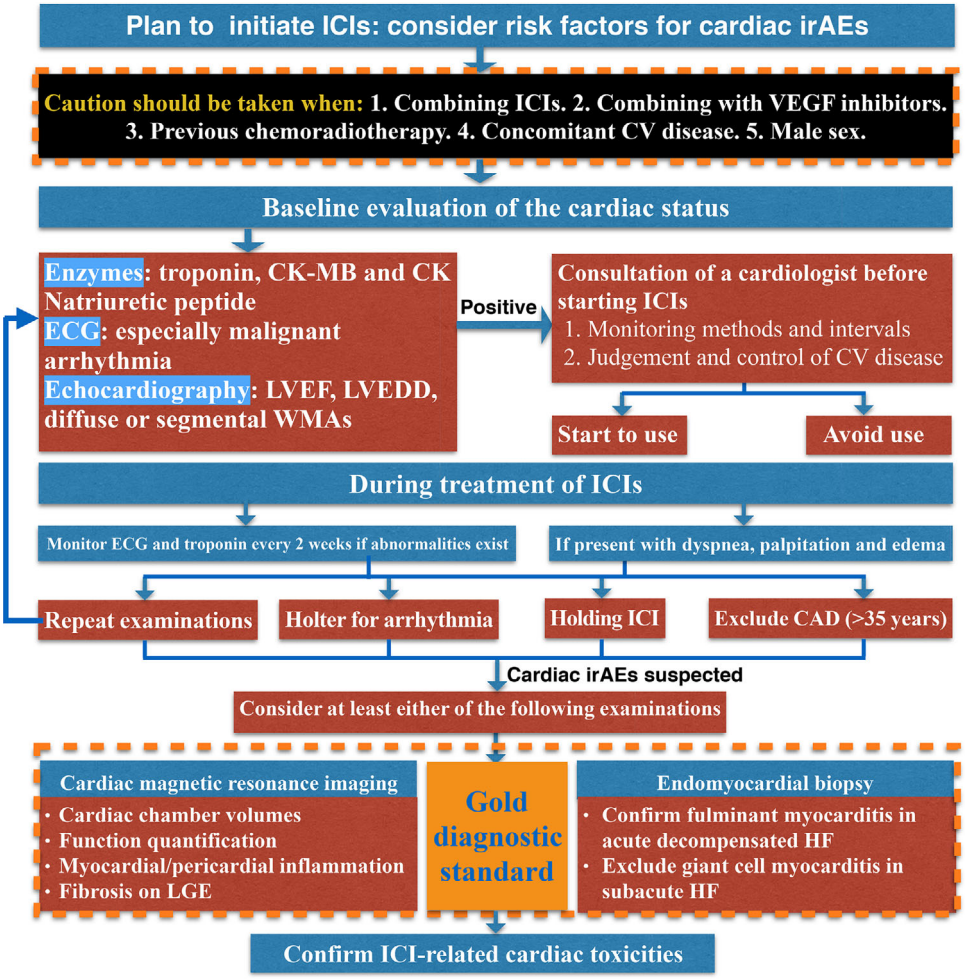

FIGURE 1 Evaluation of irAEs before and during the treatment of ICIs. Baseline testing, e.g., troponin, ECG and echocardiography, are recommended for patients who are preparing to receive ICIs. If a patient has cardiac symptoms or dynamic ECG and/or troponin changes during ICI treatment, cardiac rhythm, new-onset WMAs and exclusion of coronary artery disease (CAD) should be evaluated. CMR and/or EMB are suggested to confirm the diagnosis [Colour figure can be viewed at wileyonlinelibrary.com]

Cardiovascular irAEs are usually serious in most myocarditis cases (102/122, 84%).[32] Ninety-four percent of patients with ICI-related myocarditis presented elevated troponin, 66% reported elevated natriuretic peptides, 89% had abnormal electrocardiogram (ECG) and 51% retained normal left ventricular ejection fraction (LVEF).[17] In another case series, acute congestive heart failure was the most frequent clinical manifestation, and left ventricular systolic dysfunction was reported in 79% of patients.[24] The median LVEF was 35% with a range from 15% to 73%, whereas severe systolic dysfunction (LVEF less than 35%) was seen in half of the heart failure patients.[24] ICI-related myocarditis was also characterized by new left ventricular segmental or diffuse motion abnormalities on cardiac magnetic resonance imaging (CMR) and active myocardial inflammatory changes on cardiac 18F-fluorodeoxyglucose (18F-FDG) PET/CT or histopathological exam.[13,33]

To diagnose and stratify patients with different clinical profiles for further treatment strategy assessment, ICI-associated myocarditis has been defined as "definite myocarditis, probable myocarditis, and possible myocarditis," according to different results of modalities.[28] Specifically, the definite diagnosis of myocarditis should reach at least one criterion as follows: (1) sufficient histopathological evidence on endomyocardial biopsy (EMB); (2) typical features in CMR and clinical syndromes by a combination of cardiac biomarkers or ECG; or (3) meeting "new-onset wall motion abnormality (WMAs) on echocardiography, clinical syndromes, elevated cardiac biomarkers, abnormal ECG and negative coronary angiography" at the same time. CMR is more important for discovering myocardial edema and fibrosis than echocardiography. The necessity of CMR is emphasized especially when EMB is unavailable. Myocarditis could not be diagnosed by occasional elevated troponins or abnormal wall motions without any clinical symptoms.[28,34] According to the severity and disease course, ICI-associated myocarditis can be categorized as fulminant, clinically significant and subclinical. Presentation with concomitant hemodynamic and/or electrophysiological instability fulfills "fulminant myocarditis," whereas the recognition of clinical performance with a relatively stable status is "clinically significant," and myocarditis with no evidence of clinical significance is considered "subclinical."[34,35]

Pericarditis is the second most common cardiac complication of ICIs. The typical manifestations include isolated pericardial effusion,[15,36,37] cardiac tamponade[36,38,39] and perimyocarditis.[32] Pericardial diseases were most seen in patients with lung cancer (49/87, 56%), and the majority of cases suffered from severe cardiovascular irAEs (77/95, 81%).[32] Ninety-five cases of ICI-associated pericardial disease from the WHO database presented a median time of 30 days from ICI initiation to the onset of toxicity (interquartile range 8.5–90 days). Pericardial toxicities were reported more often in males than females (60.0% male) without an age predisposition.[32] Elevated cardiac troponin could be found in cases with perimyocarditis. The ECG changes of pericarditis featured low voltage on limb leads, widespread saddle-shaped ST elevation and tachycardia. Echocardiography was a sensitive examination to prove new pericardial effusion, evaluate the volume of effusion and judge the presence of cardiac tamponade. CMR and cardiac 18F-FDG PET/CT were both helpful in detecting the evidence of active pericardial inflammation.[22,40] The pathophysiology of ICI-induced pericarditis remains undefined because no specific studies have investigated the mechanism and because of the lack of available animal models for pericardial disease. However, in limited human histologic data from autopsies, epicardial lymphocyte infiltration could be found, suggesting that inflammation via a T-cell–mediated immune response might play a key role in the progression of pericardial effusion.[40] There is no consensus recommended for the diagnosis of ICI-associated pericardial disease. Referring to non-ICI settings, pericarditis could be diagnosed by meeting at least two of the following criteria: sharp pleuritic chest pain, pericardial friction rubs on auscultation, widespread ST segment elevation on ECG and the presence of pericardial effusion on echocardiography.[41]

Various forms of arrhythmia are also important clinical characteristics in patients with ICI-related cardiotoxicities. Atrial fibrillation ($N = 9$, 30%), ventricular arrhythmia ($N = 8$, 27%) and conduction disorders ($N = 5$, 17%) are reported most commonly.[23] However, because atrial arrhythmias usually occur in patients with cancer while the status is nonsustained or weak, atrial fibrillation might not indicate direct cardiotoxicity. Patients with supraventricular arrhythmias in the ICI population ($N = 222$) are commonly concomitant with other irAEs, and it is reasonable that these arrhythmias are secondary to concurrent irAEs such as myocarditis rather than due to the ICI treatment itself. In addition, ventricular tachycardia and ventricular fibrillation can be isolated or associated with coexisting myocarditis, which can lead to sudden cardiac death.[42,43]

ICI-mediated conduction disease could be one of the most serious and fatal cardiac complications.[44] One of the reasonable mechanisms might include inflammatory T cells infiltrating the conduction system.[13] Once ECG shows interval prolongation of P wave to R wave, bundle branch block or second-degree heart block, the threshold for introducing pacing should be low since rapid progression to advanced heart block is common in acute myocarditis. Furthermore, conduction disorders could be an isolated potential cause of sudden death in cases using ICIs without any evidence of myocarditis. To avoid fatal adverse events, all patients receiving ICIs should undergo ECG screening regularly (baseline and every 1–2 weeks for 6 weeks).[45] After heart block or bradycardia is noticed, detailed investigations, such as Holter monitoring and echocardiography, are necessary. CMR could provide more details about myocardial injuries and subclinical inflammation. To evaluate the cessation of ICIs or the introduction of a temporary/permanent pacemaker, an urgent referral of a cardiologist should be arranged.[28]

Other noninflammatory ICI-related cardiovascular toxicities have also been reported occasionally, such as hypertension, symptomatic sinus tachycardia, angina pectoris, myocardial infarction and coronary vasospasm.[46-49] However, whether these events are directly caused by ICI therapy or are coincident is still unclear. It is more probable that ICIs increase the risk of these cardiovascular events. Acute heart failure featured as Takotsubo syndrome has also been related to ICI-related cardiac toxicities.[12,50–52] Significant coronary arterial stenosis and active viral myocarditis should be excluded according to cardiac imaging before making the diagnosis of ICI-related Takotsubo syndrome.

4 | DIAGNOSTIC METHOD

To diagnose and evaluate cardiovascular involvement in ICI-related toxicities, several modalities should be considered, such as changes in ECG, cardiac biomarkers (troponin and natriuretic peptide), echocardiography and CMR. If any significant myocardial injury is noticed, EMB is recommended to obtain tissue pathology results and establish a definite diagnosis of myocarditis.

ECG is a fast, inexpensive and convenient exam for detecting ICI-related cardiovascular toxicities. More than 90% of cardiac irAE patients have dynamic ECG changes, such as ST segments or T wave changes, atrioventricular block or bundle branch block, and atrial or ventricular arrhythmia. ECG has high sensitivity and low specificity in detecting cardiac irAEs. Some ECG changes or arrhythmia, such as atrial fibrillation and premature atrial or ventricular complex, can be found in cancer populations with or without concomitant cardiovascular disease. However, significant multiple leads ST elevation mimicking myocardial infarction often indicates diffuse myocardial injuries and fulminant myocarditis (Figure 2). It is recommended to perform ECG each time before ICI dosage and whenever the patients have cardiac symptoms. Cardiologist consultation is reasonable when dynamic ECG changes are observed.

The serum troponin test is an inexpensive, widely available and sensitive testing tool with an elevation that can be seen in over 90% of cases with ICI-associated myocarditis and can reflect cardiomyocytic injuries during ICI therapy. Because fulminant myocarditis often occurs within a month after the initiation of ICI, serum troponin should be monitored closely in patients at increased risk of cardiac irAEs, such as prior to ICI initiation and every 2 weeks of ICI infusions.[32] The serum levels of troponin are also useful in determining adverse cardiac outcomes.[17] Positive troponin warrants immediate evaluations of further imaging examinations and referral to cardiologists.

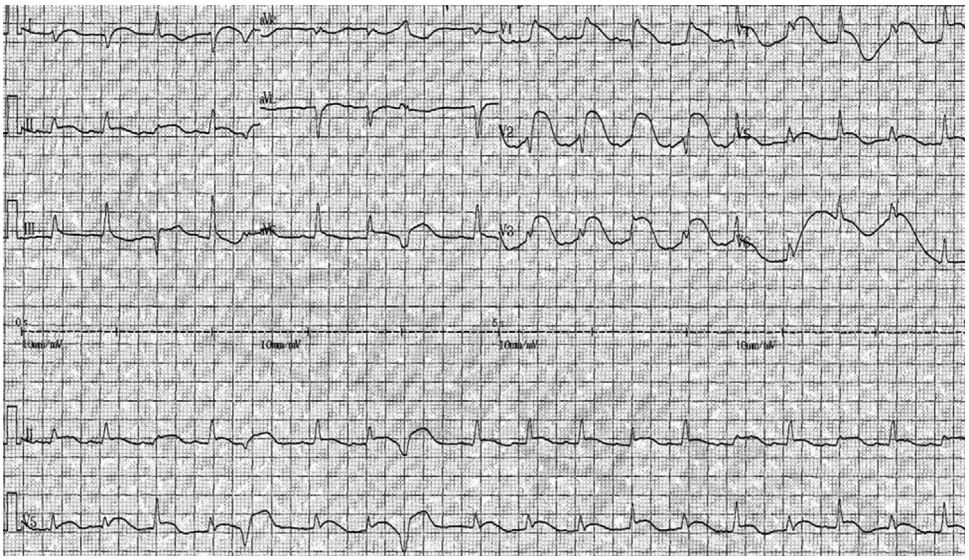

FIGURE 2 Electrocardiogram of a patient with ICI-related myocarditis. Significant multiple leads ST elevation mimics acute myocardial infarction

After evidence of elevated biomarkers and/or arrhythmia is detected, echocardiography is followed to detect the existence of new-onset diffuse or segmental WMAs, as well as left ventricular systolic and diastolic function, geometric changes in the cardiac chambers and pericardial effusion. WMA is the most important parameter in echocardiography and provides diagnostic value for ICI-related myocarditis. Definite myocarditis is confirmed if new WMA cannot be explained by another diagnosis based on typical clinical syndromes, elevated biomarkers, positive ECG findings and nonobstructive coronary arteries.[28] The LVEF is insensitive and delayed in finding myocardial injuries when compared with troponin and ECG. In the cohort study according to WHO's Vigibase, all immune-related myocarditis cases had normal LVEFs in their baseline measurements. At the onset time of symptoms, 51% of cases still maintained normal LVEFs.[17] If the baseline cardiac dimensions and function are normal, heart failure with preserved cardiac dimensions may suggest an acute process, whereas remodeling and dilatation suggest a relative chronic process after ICI therapy. Notably, one cohort observed that heart failure recovered completely in half of the surviving patients after therapy, indicating that the rescue and reversal of decreasing left ventricular systolic function were possible.[23]

CMR offers more benefit not only for cardiac chamber volumes and function quantification but also for accurate myocardial tissue characterization.[53-55] The value of CMR for diagnosis and prognosis in myocarditis and nonischemic cardiomyopathies has been well established.[56] The features of myocarditis include edema, necrosis, and scar formation, detailed according to the Lake Louise criteria.[57] In a previous study of ICI-associated myocarditis,[17] CMR was able to detect myocardial edema in 33% of cases (5/15) and fibrosis in 23% of cases (3/13). CMR could provide useful information for cases suspected of ICI-associated cardiac toxicity. It provides confirmative information for the noninvasive diagnosis of ICI-related myocarditis with the presence of edema on T2-weighted images and late gadolinium enhancement (LGE) on postcontrast images. Reports have demonstrated a direct correlation between areas of LGE and T-lymphocytic infiltration histologically.[40] T1 mapping may be another important supplement to detect the location, extent and patterns of acute myocarditis.[58-60] CMR is also useful to supply prognostic information for patients with acute myocarditis, which could help cardio-oncologists modify the therapeutic strategy and subsequent clinical decisions.[61]

EMB is the gold standard to verify ICI-related myocarditis. However, considering the safety, convenience and expense of invasive procedures, especially in critically ill patients, it is not indicated for routine myocarditis diagnosis in daily clinical practice. On autopsy of a case with perimyocarditis, the myocardial lesions was composed almost exclusively of T cells, with an admixture of CD4+ and CD8+ T cells. Furthermore, moderate fibrosis was shown in the areas of LGE, and PD-L1 staining was positive on the membrane of cardiomyocytes in the areas of LGE.[62] In the previous registry involving 35 cases with ICI-related myocarditis, 11 patients had a cardiac biopsy or autopsy. The histology feature was consistent with patchy to diffuse lymphocytic infiltration within the myocardium. Inflammatory cells were predominantly T cells, whereas no granulomas or giant cells could be found.[17] The pathological findings were similar to those observed in acute allograft rejection after cardiac transplantation.[13]

According to a recently published systematic review and our experience, if an ICI-treated patient complains of symptoms (such as chest pain, dyspnea, palpitations, presyncope or syncope) or has abnormal troponin, natriuretic peptide and ECG are needed before referral to a cardiologist. Moreover, testing serum creatine kinase-MB and creatine kinase are necessary to provide evidence of concomitant myositis. Echocardiography is an initial imaging examination to assess WMA and global LVEF, while CMR is an imaging gold standard to evaluate myocardial inflammation, edema and fibrosis. EMB is considered when the cause of heart failure is unclear to exclude persistent viral

infection and giant cell myocarditis. Baseline and regular surveillance of ECG and troponin every 2 weeks or in cases of symptom onset and echocardiography if necessary are strongly recommended in those patients from ICI initiation.

5 | MANAGEMENT

According to the recommendations of the Society for Immunotherapy of Cancer (SITC),[45] 4 grades of cardiovascular irAEs have been defined. Grade 1 is defined as abnormal cardiac biomarkers or abnormal ECG findings, which demand close monitoring during therapy as the patient is asymptomatic. Grade 2 irAEs are defined as abnormal screening tests with mild symptoms, which are managed by holding ICIs and controlling coexisting cardiac diseases and related risk factors such as hypertension or hyperlipidemia. Grade 3 irAEs are defined as moderately abnormal testing or at least mild active symptoms, which are recommended to stop ICIs and to initiate high-dose corticosteroids (1–2 mg/kg of prednisone) rapidly. Grade 4 irAEs include moderate to severe decompensated cardiac impairment and life-threatening conditions. Intravenous medication or intervention are required. For patients who do not respond to steroids, pulse therapy (methylprednisolone 1 g every day) and the addition of either intravenous immunoglobulins (IVIg), mycophenolate, infliximab or antithymocyte globulin (ATG) should be considered.[45,63] The evaluation and treatment strategies of cardiovascular irAEs are detailed in Figure 3.

The initial dose of glucocorticoid depends on the subtype and severity of the cardiovascular irAEs. In milder cases, less-intense immunosuppression and close monitoring might be appropriate. Once the diagnosis of myocarditis is identified, 1–2 mg/kg methylprednisolone intravenous is recommended, and the tapering period may last for 4–5 weeks. If there is no improvement in 24 hours or if the patient is hemodynamically unstable (decreased blood pressure, malignant arrhythmia, sudden decrease in LVEF, etc.), intravenous methylprednisolone 500–1000 mg daily should be given immediately.[28] Pulse therapy of intravenous methylprednisolone is also recommended in cases of pericarditis complicated by cardiac tamponade, advanced atrioventricular block or sinus arrest. For other relatively nonurgent cardiac complications, such as acute pericarditis or pericardial effusion without tamponade, oral prednisolone 1 mg/kg once daily might be adequate to control the disease. However, the appropriate initial dosage is still unclear due to a lack of experience and evidence in other ICI-related cardiac complications, such as atrial fibrillation, Takotsubo syndrome, first degree heart block and asymptomatic abnormalities in troponins and natriuretic peptide.[22]

In patients who underwent treatment with intravenous methylprednisolone, when the clinical situation turns to stable, which is usually after 3–5 days, the doses of glucocorticoid can taper to oral prednisolone 1 mg/kg once daily, followed by weaning at 1–2 week intervals in decrements. Full control of myocardial inflammation usually occurs after 1 month or later.[22] The median initial dose of methylprednisolone is 120 mg equivalently.[22] To obtain a better outcome and avoid major adverse cardiac events (MACEs), a higher dose of glucocorticoids might be more appropriate. MACE subgroup patients received an average initial steroid dose of 0.84 mg/kg ($N = 16$), whereas a dose of 2.06 mg/kg was initiated in the subgroup without MACE ($N = 19$, $P = 0.041$).[17]

If first-line immunosuppression with intravenous methylprednisolone is unsuccessful or the condition is refractory, the diagnosis should be reviewed, and other second-line immune suppressors would be appropriate.[17,28,47] On the other hand, immune suppressors, such as ATG, mycophenolate mofetil, tacrolimus and infliximab, are needed to help taper glucocorticoids during the chronic disease course.[28,64-67] ATG is a polyclonal antibody against human thymocytes and thoracic duct lymphoid cells and is primarily applied in allograft rejection and severe aplastic anemia. ATG might induce a rapid reduction in T cell overexpression and a decrease in lymphocytic infiltration, which suggests potential efficiency in ICI-related myocarditis.[68] Some authors have reported the direct use of ATG, which resulted in favorable outcomes for ICI-related cardiac toxicity.[17,62,68] Infliximab is a monoclonal antibody blocking tumor necrosis factor-alpha, a proinflammatory cytokine, that has been used in recurrent episodes of steroid-refractory myocarditis secondary to checkpoint inhibitors.[62] Several case reports have documented the use of infliximab in the setting of severe steroid refractory myocarditis.[13,64,68] However, infliximab might be contraindicated at high doses in cases presenting with moderate-severe heart failure.[63] Abatacept is a fusion protein of the extracellular domain of CTLA-4, which is designed as a CTLA-4 analogue and demonstrates efficacy in the treatment of temporal arteritis. In a case of severe ICI-related myocarditis, it induced a decrease in serum troponin T and ameliorated ventricular arrhythmia and heart failure.[69] Additionally, plasmapheresis was used in limited patients who presented with myocarditis. Clinical improvement and survival were noticed in some of these patients.[64,70]

Furthermore, cardiology management strategies also include the close monitoring of the cardiac status and proper treatment.[22] Standard anti-heart failure and anti-myocardial remodeling therapy are essential to all patients with ICI-associated myocarditis. If tolerable, β-blockers and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) should be prescribed and titrated to the goal dosage. To date, no evidence has shown that cardiac medications such as ACEIs/ARBs or β-blockers can prevent ICI-mediated cardiotoxic effects; however, in the context of new LVEF reduction, these medications are indicated and might be effective against noninflammatory left ventricular systolic dysfunction. Other appropriate treatment interventions include temporary or permanent pacemaker implantation for sinus arrest or advanced atrioventricular block, antiarrhythmic agents and pericardiocentesis for cardiac tamponade.

Because no standard management exists, the decision of restarting ICIs should be considered carefully and individually in each case, not only according to the cardiac function and the severity of toxicity but also depending on the cancer status.[23] The decision of continuing or stopping ICIs should be discussed between the oncologists and the cardiologists. Considering the potential for the fatal recurrence of cardiotoxicities, it was not advised to rechallenge ICIs in cases who

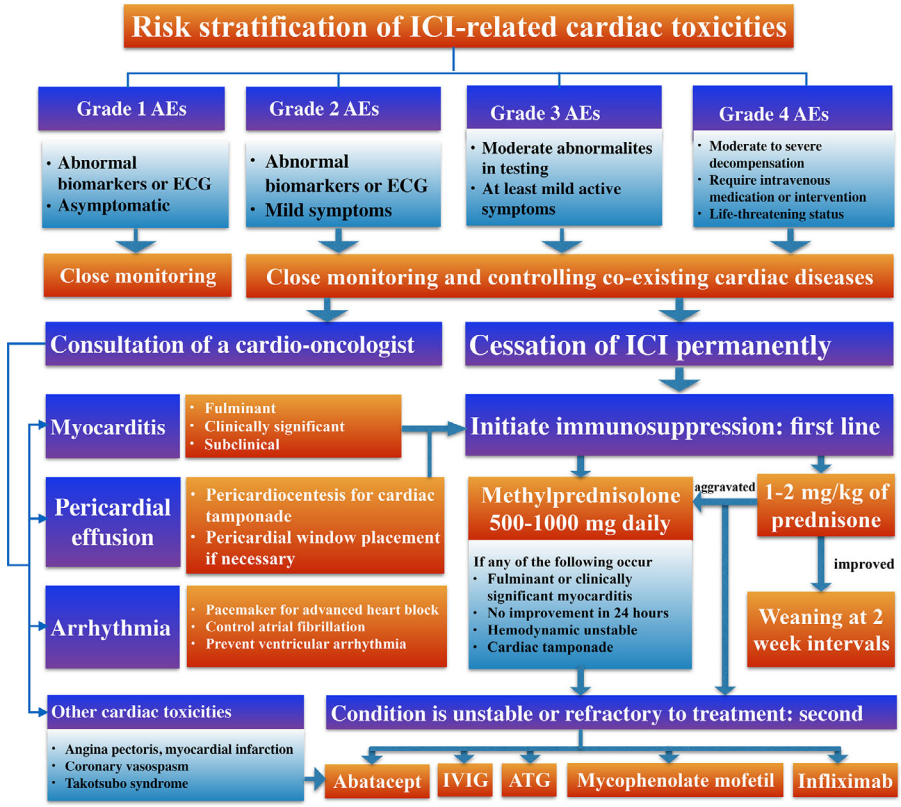

FIGURE 3 Risk stratification and treatment principles of cardiovascular irAEs. AEs of grade 1–4 depend on the results of biomarkers, ECG, symptoms and cardiac complications. Holding ICIs is essential when the irAEs are grade 2–4. A cardiologist will help define the cardiac diseases and subtypes of ICI-related cardiotoxicities, as well as the following management. Prompt glucocorticoid and immunosuppressor therapy are necessary in treating cardiovascular irAEs [Colour figure can be viewed at wileyonlinelibrary.com]

once suffered from severe ICI-mediated myocarditis and advanced conduction disease (second-degree or third-degree heart block).[71] However, resuming ICI therapy is possible if isolated troponinemia returns to normal within two weeks.[28] In fact, there were patients with the readministration of ICIs after the first episode of cardiotoxicity who had no recurrences.[23]

6 | CLINICAL OUTCOME

There are limited data regarding the survival rate and mortality of patients with cardiac irAEs, especially the long-term prognosis. ICI-related myocarditis is particularly life-threatening because of its early onset, fulminant progression and high fatality rate.

In a French series focusing on ICI-associated toxicities, 8 out of 12 patients with decreased LVEF were treated with high-dose steroids and eventually recovered. Complete recovery of left ventricular dysfunction was achieved in 50% of the 18 surviving patients.[23] A systematic review enrolled 73 studies and a total of 99 cases with ICI-related cardiotoxicities. The overall fatality rate was 35%.[64] The incidence of MACE was approximately 50% in ICI-related myocarditis,[23,32] which was significantly higher than that in the broad populations with myocarditis.[72,73] Cardiovascular mortality was associated with a high troponin level, reduced LVEF, conduction abnormalities and combination therapy. In the aforementioned study, after a median follow-up of 102 days, nearly one-half of the cases experienced MACE (16/35), including six cases of cardiovascular death, three cases of cardiogenic shock and three cases of cardiac arrest or complete heart block. It is worth noting that six of the 16 MACEs occurred in patients with a normal LVEF.

7 | CONCLUSION

ICI-related cardiotoxicities are relatively rare but critical adverse complications for patients receiving immunotherapies. Myocarditis, pericardial diseases and arrhythmia are the most frequent cardiac manifestations. ECG and serum troponin levels are sensitive in detecting cardiac irAEs and should be monitored routinely. Echocardiography and CMR should be considered once ICI-related cardiovascular toxicities have been suspected according to ECG and troponin abnormalities or patients' symptoms. The diagnosis of ICI-related myocarditis could be made by sufficient histopathological evidence on EMB or typical features in CMR and clinical syndromes and abnormal biomarkers or ECG. Considering the possibility of rapid deterioration and a higher rate of mortality, even if there are only nonspecific symptoms and subclinical damages, consultation with a cardiologist cannot be overstated for suitable management, such as the judgment of cardiac

events, monitoring methods and intervals, strategies for heart injuries and the decision of holding or rechallenging ICIs. Prompt glucocorticoid and immunosuppressors, if necessary, are important in treating cardiovascular irAEs when they are more serious than grade 2. Finally, all aspects of judgment and decision making should be made on a case-by-case basis.

ORCID

Yingxian Liu https://orcid.org/0000-0003-1155-7130
Wei Wu https://orcid.org/0000-0002-9044-0901

REFERENCES

1. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373:23–34.
2. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2017;377:1345–1356.
3. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med*. 2015;372:311–319.
4. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): A randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2015;16:375–384.
5. Choueiri TK, Larkin J, Oya M, et al. Preliminary results for avelumab plus axitinib as first-line therapy in patients with advanced clear-cell renal-cell carcinoma (JAVELIN Renal 100): An open-label, dose-finding and dose-expansion, phase 1b trial. *Lancet Oncol*. 2018;19:451–460.
6. Gulley JL, Rajan A, Spigel DR, et al. Avelumab for patients with previously treated metastatic or recurrent non-small-cell lung cancer (JAVELIN Solid Tumor): Dose-expansion cohort of a multicentre, open-label, phase 1b trial. *Lancet Oncol*. 2017;18:599–610.
7. Topolian SL. Targeting immune checkpoints in cancer therapy. *JAMA*. 2017;318:1647–1648.
8. Spain L, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. *Cancer Treat Rev*. 2016;44:51–60.
9. Weber JS, Hodi FS, Wolchok JD, et al. Safety profile of nivolumab monotherapy: A pooled analysis of patients with advanced melanoma. *J Clin Oncol*. 2017;35:785–792.
10. Schadendorf D, Wolchok JD, Hodi FS, et al. Efficacy and safety outcomes in patients with advanced melanoma who discontinued treatment with nivolumab and ipilimumab because of adverse events: A pooled analysis of randomized phase II and III trials. *J Clin Oncol*. 2017;35:3807–3814.
11. Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: A review. *JAMA Oncol*. 2016;2:1346–1353.
12. Geisler BP, Raad RA, Esaian D, et al. Apical ballooning and cardiomyopathy in a melanoma patient treated with ipilimumab: A case of takotsubo-like syndrome. *J Immunother Cancer*. 2015;3:4.
13. Johnson DB, Balko JM, Compton ML, et al. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med*. 2016;375:1749–1755.
14. Läubli H, Balmelli C, Bossard M, et al. Acute heart failure due to autoimmune myocarditis under pembrolizumab treatment for metastatic melanoma. *J Immunother Cancer*. 2015;3:11.
15. Yun S, Vincelette ND, Mansour I, et al. Late onset ipilimumab-induced pericarditis and pericardial effusion: A rare but life threatening complication. *Case Rep Oncol Med*. 2015;2015:794842.
16. Voskens CJ, Goldinger SM, Loquai C, et al. The price of tumor control: an analysis of rare side effects of anti-CTLA-4 therapy in metastatic melanoma from the ipilimumab network. *PLoS One*. 2013;8:e53745.
17. Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol*. 2018;71:1755–1764.
18. Boutros C, Tarhini A, Routier E, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. *Nat Rev Clin Oncol*. 2016;13:473–486.
19. Eigentler TK, Hassel JC, Berking C, et al. Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. *Cancer Treat Rev*. 2016;45:7–18.
20. Costa R, Carneiro BA, Agulnik M, et al. Toxicity profile of approved anti-PD-1 monoclonal antibodies in solid tumors: A systematic review and meta-analysis of randomized clinical trials. *Oncotarget*. 2017;8:8910–8920.
21. Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol*. 2015;26:2375–2391.
22. Lyon AR, Yousaf N, Battisti NM, et al. Immune check-point inhibitors and cardiovascular toxicity. *Lancet Oncol*. 2018;19:e447–458.
23. Escudier M, Cautela J, Malissen N, et al. Clinical features, management, and outcomes of immune checkpoint inhibitor-related cardiotoxicity. *Circulation*. 2017;136:2085–2087.
24. Conforti F, Pala L, Bagnardi V, et al. Cancer immunotherapy efficacy and patients' sex: A systematic review and meta-analysis. *Lancet Oncol*. 2018;19:737–746.
25. Atkins MB, Larkin J. Immunotherapy combined or sequenced with targeted therapy in the treatment of solid tumors: Current perspectives. *J Natl Cancer Inst*. 2016;108:djv414.
26. Smyth MJ, Ngiow SF, Ribas A, et al. Combination cancer immunotherapies tailored to the tumour microenvironment. *Nat Rev Clin Oncol*. 2016;13:143–158.
27. Jain D, Ahmad T, Cairo M, et al. Cardiotoxicity of cancer chemotherapy: identification, prevention and treatment. *Ann Transl Med*. 2017;5:348.
28. Hu JR, Florido R, Lipson EJ, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors. *Cardiovasc Res*. 2019;115:854–868.
29. Moslehi JJ, Salem JE, Sosman JA, et al. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. *Lancet*. 2018;391:933.
30. Mir H, Alhussein M, Alrashidi S, et al. Cardiac complications associated with checkpoint inhibition: A systematic review of the literature in an important emerging area. *Can J Cardiol*. 2018;34:1059–1068.
31. Behling J, Kaes J, Munzel T, et al. New-onset third-degree atrioventricular block because of autoimmune-induced myositis under treatment with anti-programmed cell death-1 (nivolumab) for metastatic melanoma. *Melanoma Res*. 2017;27:155–158.
32. Salem JE, Manouchehri A, Moey M, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: An observational, retrospective, pharmacovigilance study. *Lancet Oncol*. 2018;19:1579–1589.
33. Sznol M, Ferrucci PF, Hogg D, et al. Pooled analysis safety profile of nivolumab and ipilimumab combination therapy in patients with advanced melanoma. *J Clin Oncol*. 2017;35:3815–3822.
34. Bonaca MP, Olenchock BA, Salem JE, et al. Myocarditis in the setting of cancer therapeutics: Proposed case definitions for emerging clinical syndromes in cardio-oncology. *Circulation*. 2019;140:80–91.
35. Kindermann I, Barth C, Mahfoud F, et al. Update on myocarditis. *J Am Coll Cardiol*. 2012;59:779–792.
36. Nesfeder J, Elsensohn AN, Thind M, et al. Pericardial effusion with tamponade physiology induced by nivolumab. *Int J Cardiol*. 2016;222:613–614.

37. Shaheen S, Mirshahidi H, Nagaraj G, et al. Conservative management of nivolumab-induced pericardial effusion: A case report and review of literature. *Exp Hematol Oncol*. 2018;7:11.
38. de Almeida DVP, Gomes JR, Haddad FJ, et al. Immune-mediated pericarditis with pericardial tamponade during nivolumab therapy. *J Immunother*. 2018;41:329–331.
39. Kushnir I, Wolf I. Nivolumab-induced pericardial tamponade: A case report and discussion. *Cardiology*. 2017;136:49–51.
40. Gallegos C, Rottmann D, Nguyen VQ, et al. Myocarditis with checkpoint inhibitor immunotherapy: Case report of late gadolinium enhancement on cardiac magnetic resonance with pathology correlate. *Eur Heart J Case Rep*. 2019;3:yty149.
41. Adler Y, Charron P, Imazio M, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases. The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) Endorsed by: the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2015;36:2921–2964.
42. Tocut M, Brenner R, Zandman-Goddard G. Autoimmune phenomena and disease in cancer patients treated with immune checkpoint inhibitors. *Autoimmun Rev*. 2018;17:610–616.
43. Hid Cadena R, Abdulahad WH, Hospers GAP, et al. Checks and balances in autoimmune vasculitis. *Front Immunol*. 2018;9:315.
44. Gibson R, Delaune J, Szady A, et al. Suspected autoimmune myocarditis and cardiac conduction abnormalities with nivolumab therapy for non-small cell lung cancer. *BMJ Case Rep*. 2016;2016:bcr2016216228.
45. Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer*. 2017;5:95.
46. Zimmer L, Goldinger SM, Hofmann L, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. *Eur J Cancer*. 2016;60:210-225.
47. Yang S, Asnani A. Cardiotoxicities associated with immune checkpoint inhibitors. *Curr Probl Cancer*. 2018;42:422-432.
48. Weinstock C, Khozin S, Suzman D, et al. U.S. food and drug administration approval summary: Atezolizumab for metastatic non–small cell lung cancer. *Clin Cancer Res*. 2017;23:4534-4539.
49. Nykl R, Fischer O, Vykoupil K, et al. A unique reason for coronary spasm causing temporary ST elevation myocardial infarction (inferior STEMI) – Aystemic inflammatory response syndrome after use of pembrolizumab. *Arch Med Sci Atheroscler Dis*. 2017;2:e100–102.
50. Ederhy S, Cautela J, Ancedy Y, et al. Takotsubo-like syndrome in cancer patients treated with immune checkpoint inhibitors. *JACC Cardiovasc Imaging*. 2018;11:1187–1190.
51. Elikowski W, Małek-Elikowska M, Łazowski S, et al. Takotsubo cardiomyopathy in a young male with lung cancer and neoplastic embolization of the coronary microcirculation. *Pol Merkur Lekarski*. 2018;44:54–59.
52. Anderson RD, Brooks M. Apical takotsubo syndrome in a patient with metastatic breast carcinoma on novel immunotherapy. *Int J Cardiol*. 2016;222:760–761.
53. Aquaro GD, Camastra G, Monti L, et al. Reference values of cardiac volumes, dimensions, and new functional parameters by MR: a multicenter, multivendor study. *J Magn Reson Imaging*. 2017;45:1055–1067.
54. Aquaro GD, Todiere G, Strata E, et al. Usefulness of India ink artifact in steady-state free precession pulse sequences for detection and quantification of intramyocardial fat. *J Magn Reson Imaging*. 2014;40:126–132.
55. Ammirati E, Moroni F, Sormani P, et al. Quantitative changes in late gadolinium enhancement at cardiac magnetic resonance in the early phase of acute myocarditis. *Int J Cardiol*. 2017;231:216–216.
56. Friedrich MG, Marcotte F. Cardiac magnetic resonance assessment of myocarditis. *Circ Cardiovasc Imaging*. 2013;6:833–839.
57. Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: a JACC white paper. *J Am Coll Cardio*. 2009;53:1475–1487.
58. Ferreira VM, Piechnik SK, Dall'Armellina E, et al. Native T1-mapping detects the location, extent and patterns of acute myocarditis without the need for gadolinium contrast agents. *J Cardiovasc Magn Reson*. 2014;16:36.
59. Lurz P, Luecke C, Eitel I, et al. Comprehensive cardiac magnetic resonance imaging in patients with suspected myocarditis: The MyoRacer-Trial. *J Am Coll Cardiol*. 2016;67:1800–1811.
60. Messroghli DR, Moon JC, Ferreira VM, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). *J Cardiovasc Magn Reson*. 2017;19:75.
61. Grigoratos C, Di Bella G, Aquaro GD. Diagnostic and prognostic role of cardiac magnetic resonance in acute myocarditis. *Heart Fail Rev*. 2019;24:81–90.
62. Agrawal N, Khunger A, Vachhani P, et al. Cardiac toxicity associated with immune checkpoint inhibitors: Case series and review of literature. *Case Rep Oncol*. 2019;12:260–276.
63. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2018;36:1714–1768.
64. Frigeri M, Meyer P, Banfi C, et al. Immune checkpoint inhibitor-associated myocarditis: A new challenge for cardiologists. *Can J Cardiol*. 2018;34:92.e1–3.
65. Norwood TG, Westbrook BC, Johnson DB, et al. Smoldering myocarditis following immune checkpoint blockade. *J Immunother Cancer*. 2017;5:91.
66. Reddy N, Moudgil R, Lopez-Mattei JC, et al. Progressive and reversible conduction disease with checkpoint inhibitors. *Can J Cardiol*. 2017;33:1335.e13–15.
67. Jain V, Bahia J, Mohebtash M, et al. Cardiovascular complications associated with novel cancer immunotherapies. *Curr Treat Options Cardiovasc Med*. 2017;19:36.
68. Tay RY, Blackley E, McLean C, et al. Successful use of equine antithymocyte globulin (ATGAM) for fulminant myocarditis secondary to nivolumab therapy. *Br J Cancer*. 2017;117:921–924.
69. Salem JE, Allenbach Y, Vozy A, et al. Abatacept for severe immune checkpoint inhibitor-associated myocarditis. *N Engl J Med*. 2019;380:2377–2379.
70. Suzuki S, Ishikawa N, Konoeda F, et al. Nivolumab-related myasthenia gravis with myositis and myocarditis in Japan. *Neurology*. 2017;89:1127–1134.
71. Tajmir-Riahi A, Bergmann T, Schmid M, et al. Life-threatening autoimmune cardiomyopathy reproducibly induced in a patient by checkpoint inhibitor therapy. *J Immunother*. 2018;41:35–38.
72. Ammirati E, Cipriani M, Lilliu M, et al. Survival and left ventricular function changes in fulminant versus nonfulminant acute myocarditis. *Circulation*. 2017;136:529–545.
73. Gräni C, Eichhorn C, Bière L, et al. Prognostic value of cardiac magnetic resonance tissue characterization in risk stratifying patients with suspected myocarditis. *J Am Coll Cardiol*. 2017;70:1964–1976.

How to cite this article: Liu Y, Wu W. Cardiovascular immune-related adverse events: evaluation, diagnosis and management. *Asia-Pac J Clin Oncol*. 2020;16:232–240. https://doi.org/10.1111/ajco.13326