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Immune Checkpoint Inhibitor–Associated Cardiovascular Toxic Effects
International Cardio-Oncology Society Position Statement

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IMPORTANCE The introduction of immune checkpoint inhibitor (ICI) therapy has improved cancer outcomes but at the cost of adverse events, mainly related to the immune system. Cardiovascular (CV) toxic effects, and especially myocarditis, are of particular concern and are the subject of this position statement by the International Cardio-Oncology Society with representation of experts from oncology, hematology, and cardiology.

OBSERVATIONS CV toxic effects of ICI therapies include inflammation-associated diseases, such as myocarditis, pericarditis, and vasculitis, as well as the aggravation of chronic inflammatory conditions, such as atherosclerosis with acute ischemic complications (myocardial infarction and stroke). Patients taking ICI therapies can also develop cardiac dysfunction, stress-induced cardiomyopathy (Takotsubo or apical ballooning syndrome), and heart failure without inflammatory cell infiltration of the myocardium. Atrial and ventricular arrhythmias can emerge in the setting of a systemic inflammatory milieu, myocarditis, or ischemia. Of all potential CV adverse effects, myocarditis remains of highest concern, although fatality rates have declined over time with a broadening spectrum of presentations ranging from troponin elevation of uncertain significance to smoldering, nonsevere, and severe or fulminant myocarditis.

CONCLUSIONS AND RELEVANCE Concerns for myocarditis continue to dominate the spectrum of CV toxic effects in patients receiving ICI therapy. Recommendations for management vary according to severity. Multidisciplinary collaborations remain key for managing acute toxic effects and future cancer treatment decisions, including ICI rechallenge. Ischemic heart disease constitutes the main differential diagnosis in these patients, while pericarditis can be concomitantly present, and atrial and ventricular arrhythmias can also complicate the clinical picture. Several gaps in knowledge are identified and require further research.

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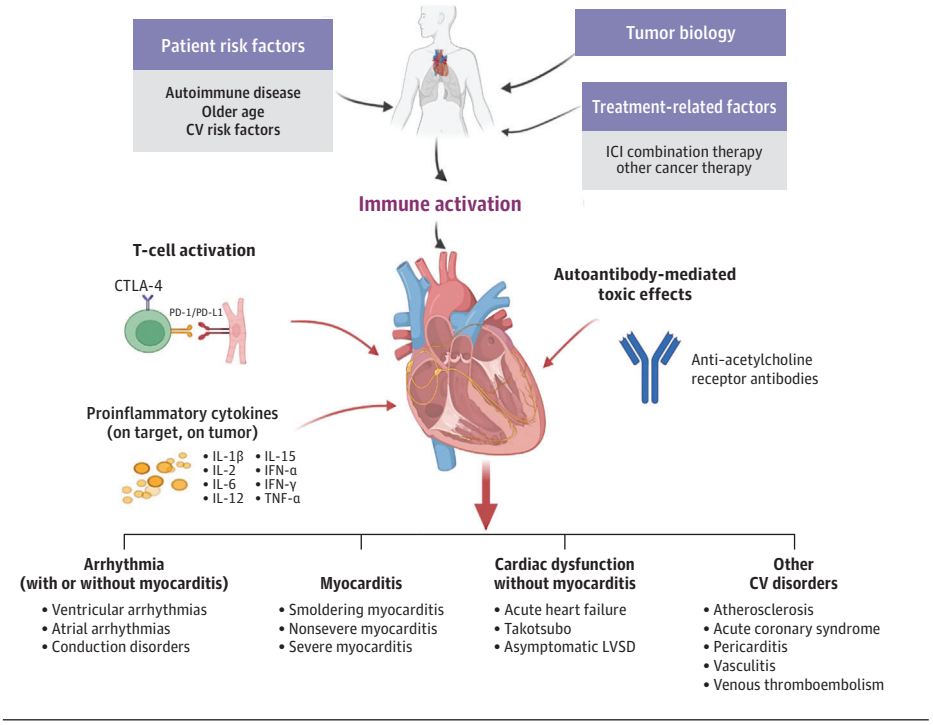
Cancer care has rapidly evolved over the last decade with transformative contributions stemming from the widespread application of immune checkpoint inhibitors (ICIs) (eFigure 1 in the Supplement).[1,2] These benefits come at the risk of immune-related adverse events (irAEs), which can affect any organ system and can lead to life-threatening consequences. Overall, irAE-related mortality has declined from 14% before 2016 to 7.3% in 2021 and 2022.[3] The downward trend extends to the mortality of ICI myocarditis, which decreased from 45.5% to 23% over the same time period but remains the most fatal and hence one of the most important irAEs.[3]

The incidence of ICI myocarditis is approximately 0.75% for single-agent ICI therapy and ranges between 1% and 2% for combined ICI therapy.[3-6] Other cardiovascular (CV) complications may occur more commonly, including pericarditis at a prevalence of 0.55% (95% CI, 0.21-1.41), CV death at a prevalence of 0.67% (95% CI, 0.21-2.09), conduction disorders at a prevalence of 0.85% (95% CI, 0.14-5.05), acute coronary syndromes (ACS) at a prevalence of 1.73% (95% CI, 0.81-3.70), stroke at a prevalence of 2.17% (95% CI, 1.35-3.47), tachyarrhythmias at a prevalence of 3.15% (95% CI, 1.60-6.22), heart failure (HF) at a prevalence of 3.40% (95% CI, 1.52-7.61), and pericardial effusions at a prevalence of 3.98% (95% CI, 0.54-29.60).[6] Vasculitis and thromboembolism have also been reported in patients treated with ICIs, but estimates of risk are not well defined.[7,8]

Led by the International Cardio-Oncology Society (IC-OS), this cross-disciplinary international position statement summarizes the current understanding of CV toxic effects associated with ICI therapy (**Figure 1**), including recommended strategies for diagnosis, treatment, and potential rechallenge and an outline of relevant knowledge gaps.

Figure 1. Overview and Proposed Mechanisms of Cardiovascular (CV) Toxic Effects With Immune Checkpoint Inhibitor (ICI) Therapies



CTLA-4 indicates cytotoxic T-lymphocyte antigen 4; IFN, interferon; LVSD, left ventricular systolic dysfunction; PD-1, programmed cell death 1 protein; PD-L1, programmed cell death 1 ligand 1; TNF, tumor necrosis factor.

Risk Factors and Pathophysiology

Dual ICI therapy has most consistently been associated with an increased risk for ICI myocarditis, with some data also demonstrating a higher risk when ICIs are combined with a tyrosine kinase inhibitor.[9,10] Patients with melanoma are at higher risk relative to other cancer types, while patients with thymic epithelial tumors, especially those with high radio-pathological thymus grade, are at the highest risk of developing ICI myocarditis (10-fold to 30-fold higher than with other cancers) and adverse outcomes.[11] The presence of anti–acetylcholine receptor autoantibodies increases the risk of ICI myocarditis more than 5-fold and doubles the risk of severe heart and respiratory muscle failure, highlighting the role of thymic-associated autoimmunity. Other risk factors include a history of myasthenia gravis, autoimmune disease, and older age (age 75 years and older).[10,12,13] Preexisting CV disease and CV risk factors, including evidence of coronary and aortic calcifications, have been associated with CV events in patients taking ICI therapy, including myocarditis.[10,14] An overview of experimental studies on the pathophysiology of ICI cardiotoxic effect (myocarditis and cardiomyopathy) is provided in the eText in the Supplement.

Clinical Features

Clinical Presentation

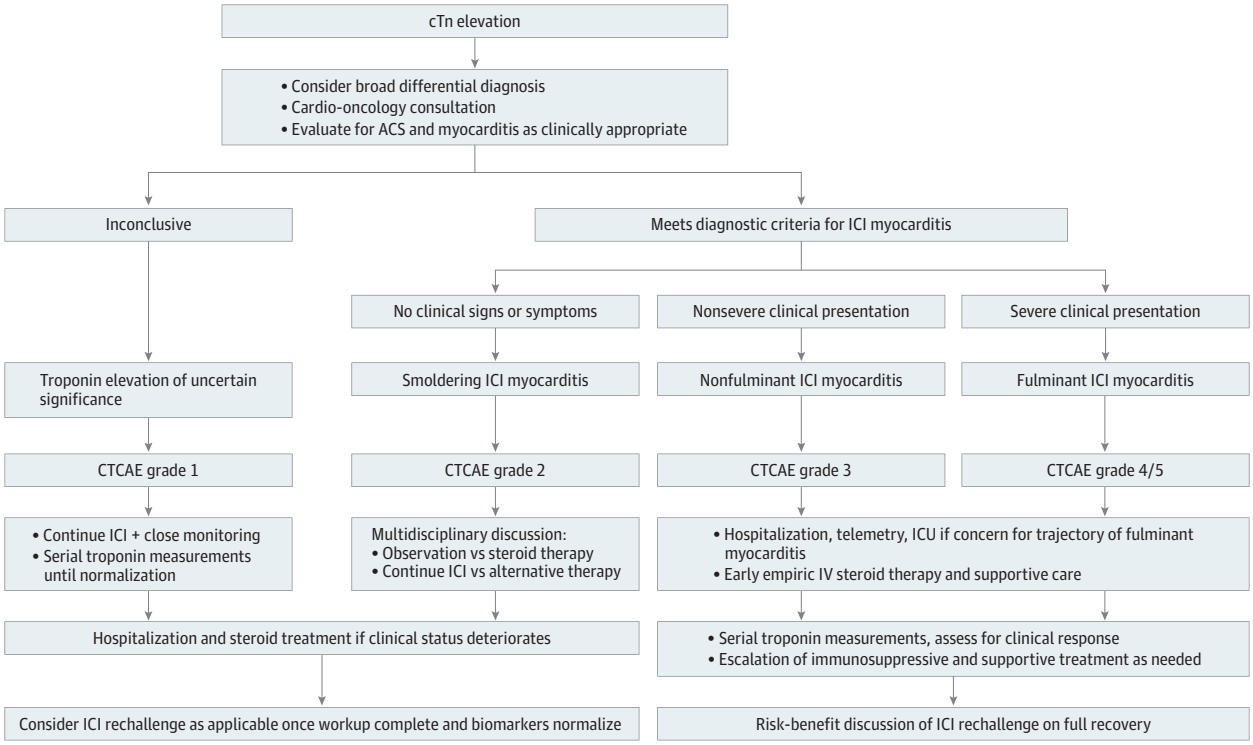
Myocarditis severity can range from smoldering to fulminant forms. Most patients present with mild symptoms, such as chest pain, fatigue, dyspnea, and palpitations, often with preserved left ventricular ejection fraction, despite significant myocardial inflammation detected on endomyocardial biopsy (EMB) or cardiac magnetic resonance imaging (CMR). In these cases, cardiac biomarkers and electrocardiography (ECG) are more sensitive and provide better prognostic value than echocardiography.[15] Identifying overlapping syndromes, such as hepatitis, myositis, or myasthenia gravis–like syndromes is critical. In reverse, among any patient presenting with symptoms such as muscle weakness, myalgia, ptosis, diplopia, or blurred vision, it is essential to perform an ECG, assess cardiac biomarkers, and promptly initiate further diagnostic evaluation for myocarditis if any abnormalities are detected.[16]

Patients with or without myocarditis may present with new conduction abnormalities (atrioventricular block or bundle branch block) or arrhythmias (atrial fibrillation/flutter, ventricular ectopy, nonsustained and sustained ventricular tachycardia, and even ventricular fibrillation). In cases with severe conduction disease or arrhythmias, myocarditis should be considered.[17]

Noninflammatory HF generally occurs later in the course of treatment, especially in patients with preexisting CV conditions.[18] The diagnostic and management strategies are similar to those for classic HF, although myocarditis and Takotsubo syndrome should be ruled out.[19,20]

Vascular toxic effects, related to accelerated atherosclerosis from systemic and vascular inflammation induced by ICIs, can lead to complications, such as ACS or stroke.[21] Patients treated with ICIs also have an increased risk of developing immune-mediated pericarditis, with or without concurrent myocarditis. Pericarditis is more common as a late CV event and rarely leads to cardiac tamponade.[22,23]

Figure 2. Spectrum of Immune Checkpoint Inhibitor (ICI)–Related Myocarditis/Myocarditislike Scenarios Encountered in Clinical Practice



In patients presenting with a troponin elevation, a broad differential diagnosis should be considered, including acute coronary syndrome (ACS), myocarditis, and troponin elevations in the setting of sepsis, respiratory failure, or pulmonary embolism. If the initial evaluation does not identify a clear etiology (ie, is inconclusive), then patients are diagnosed with a troponin elevation of uncertain significance. These patients can generally be continued on ICI therapy but should still be closely monitored as this may represent early, subclinical myocarditis. CTCAE indicates Common Terminology Criteria for Adverse Events; cTn, cardiac troponin; ICU, intensive care unit; IV, intravenous.

Definitions of Events

The definition of CV events follows currently accepted guideline statements and practice patterns for ACS, HF, and thromboembolism.[24,25] Based on the IC-OS consensus criteria (incorporated into the European Society of Cardiology cardio-oncology guidelines),[24,25] the diagnosis of ICI myocarditis is made either by pathology or by clinical presentation (new or significant increase from baseline in cardiac troponin [cTn] and [1] CMR findings diagnostic for myocarditis or [2] at least 2 minor clinical, ECG, or imaging criteria). ICI myocarditis can be further graded as smoldering, nonsevere, or severe (fulminant) (eTable 1 in the Supplement; **Figure 2**). It cannot be overemphasized that the key differential diagnosis of ACS should be addressed expeditiously and conclusively with the understanding that myocarditis and ACS can occur concurrently. As myocarditis can be life-threatening, the IC-OS consensus definition sought to balance sensitivity with specificity and includes some less specific clinical symptoms, such as fatigue and muscle weakness, in the minor criteria. Integrating time of onset within 3 months after starting ICI and requiring 3 instead of 2 minor criteria has been shown to increase the diagnostic specificity from 70% to 83% while maintaining a sensitivity of 93%.[26] Given the clinical implications of diagnosis and the impact on cancer therapy, the diagnosis of ICI myocarditis should be confirmed, when possible, with CMR or biopsy in centers with appropriate expertise.

In addition to established criteria for CV events, patients may present with a troponin elevation of uncertain significance (approximately 10% to 15% of patients treated with an ICI) (Figure 2). The challenge with this presentation is determining the onset, etiology and clinical significance of the cTn elevation. While a clear etiology may not always be identified, a thorough investigation for other etiologies of cTn elevation, such as ACS, Takotsubo syndrome, HF, pulmonary embolism, kidney dysfunction, gastrointestinal tract bleeding, respiratory disease, thyroid disease, sepsis, neurologic event, and even ICI myositis without myocarditis and cardiac metastases, should be considered.[27-30]

Diagnostic Evaluation

Identifying CV disease related to ICI therapy requires clinical suspicion and careful clinical assessment, often with multimodality testing (**Table**). When interpreting cTn elevations, in addition to the clinical presentation, it is important to consider dynamic changes over baseline values (eText and eFigure 2 in the Supplement).[29] As with echocardiography, abnormalities of CMR strain are not specific to myocarditis but tend to correlate with late gadolinium enhancement, may precede changes in left ventricular ejection fraction, and have prognostic significance.[31-37]

Table. Diagnostic Testing

Diagnostic test	Availability[a]	Utility	Notable findings and implications	Additional comments

Cardiac biomarkers (cTn, BNP, and NT-proBNP)	++++	• Routinely assessed
		• Invaluable in diagnosis of myocarditis, myocardial infarction, and cardiomyopathy/HF
			• Myocarditis:
			  • cTn elevation usually has an evolving plateau
			  • Peak cTn level correlates with prognosis
			  • cTn levels can be only mildly elevated and rarely may be normal
			  • cTn may rapidly improve with steroids in steroid-responsive patients
			• Myocardial infarction:
			  • Typically sharp pattern of rising and falling cTn
			  • Area under the curve correlates with extent of infarction
				• cTnI more specific for the heart, while cTnT can also reflect myositis
				• cTnT appears to have greater prognostic utility in ICI myocarditis
				• cTn elevation can be elevated prior to immunotherapy in patients with CV risk factor burden or disease
				• cTn can also be elevated due to myocardial injury in the setting of, eg, sepsis or respiratory failure

Electrocardiography	++++	• Routinely assessed
		• Can detect myocardial inflammation and injury, essential for evaluation of STEMI, NSTE-ACS, and complications of myocarditis
			• Myocarditis complications (nonspecific, can also be seen in ischemia/infarction):
			  • Atrial and ventricular ectopy
			  • SVTs, including AF
			  • VT, sustained and nonsustained
			  • Conduction abnormalities, including prolonged QRS and typically bundle block
			  • AV block
			  • QT prolongation
			• Myocardial infarction:
			  • ST-segment depression
			  • ST-segment elevation (coronary distribution)
			  • T-wave inversion
			• Pericarditis:
			  • Diffuse ST-segment elevation (noncoronary distribution)
				NA

Echocardiography	+++(+)	• Routinely assessed • Assesses cardiac function and RWMAs	• Myocarditis: depending on the extent, may be normal or exhibit strain abnormalities, new RWMAs and multi-RWMAs, and/or global hypokinesis and new reduction in LVEF • Myocardial infarction: depending on the extent, new RWMAs may be present and new reduction in LVEF	NA
CMR	++	• Recommended in patients with any concern for myocarditis or patients with poor acoustic windows on echocardiography • High yield for the diagnosis of myocarditis and myocardial infarction if positive but may remain nondiagnostic in cases with small degrees of injury	Myocarditis: modified 2018 Lake Louise criteria: 1. Presence of nonischemic myocardial injury (measured using T1-based imaging and including abnormal T1 mapping, abnormal extracellular volume or late gadolinium enhancement) 2. Presence of myocardial edema (elevated T2 values based on T2 map or abnormal signal on qualitative T2 imaging)	• Requiring both positive T1 and positive T2 criteria increases the specificity for myocarditis but can miss the diagnosis in about 50% of patients • Requiring only 1 abnormal T1 or T2 marker (ie, suggestive of myocarditis) significantly increases sensitivity (100% of patients with ICI myocarditis) but reduces specificity • Timing of the CMR may also play a role: edema (T2 abnormality) may resolve early, particularly after initiation of steroids, while late gadolinium enhancement may be a delayed finding
Coronary angiography/ cardiac CT	+++	• Should be considered in patients with signs/symptoms of ACS • High yield to rule out culprit lesions for ACS	NA	• CT coronary angiography may be preferred to invasive angiography to rule out CAD in patients at lower risk for ACS • Obstructive CAD can coexist with myocarditis
Endomyocardial biopsy	++	Recommended when diagnosis is unclear, especially if confirmation of myocarditis will help with cancer management	Myocarditis: high yield if positive but can be falsely negative due to the patchy nature of the disease (sampling error)	• Interpretation requires appropriate expertise; biopsy specimens should be reviewed by pathologists with experience in myocarditis or heart transplant rejection • Unclear how long after starting corticosteroid treatment myocardial necrosis and an immune infiltrate will remain visible on biopsy (in general, biopsies have shown positive results 7 d after initial presentation) • Voltage map guidance may potentially increase the diagnostic yield

(continued)

Table. Diagnostic Testing (continued)

Diagnostic test	Availability[a]	Utility	Notable findings and implications	Additional comments
FDG-PET	+	• Not recommended for routine use • High yield for inflammatory disease entities, such as cardiac sarcoidosis, but not fully defined for ICI myocarditis	NA	NA

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CMR, cardiac magnetic resonance imaging; CT, computed tomography; cTn, cardiac troponin; cTnI, cardiac troponin I; cTnT, cardiac troponin T; CV, cardiovascular; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; HF, heart failure; ICI, immune checkpoint inhibitor; LVEF, left ventricular ejection fraction; NA, not applicable; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; NT-proBNP, N-terminal pro–B-type natriuretic peptide; RWMA, regional wall motion abnormality; STEMI, ST-elevation myocardial infarction; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

[a] Grading scale defined as rarely available (+), usually available (++), very available (+++), and highly available (++++).

Timing of the CMR may play a role in the sensitivity and specificity for myocarditis (eg, positive for late gadolinium enhancement in 22% and 72% of cases when performed within or after 4 days of admission, respectively).[38] It is crucial to recognize that no single clinical or imaging finding is specific to ICI myocarditis, as abnormalities can also be seen with several other CV conditions, and any diagnosis requires the correct clinical scenario. An EMB can be helpful if a clinical diagnosis is to be established quickly or remains unclear after noninvasive assessment. It can also be helpful if tissue confirmation of the diagnosis or grading of the pathologic severity of myocarditis is needed for future cancer treatment considerations, especially since CMR findings may be nonspecific (eText in the Supplement).[39-46]

Screening and Surveillance

The 2022 European Society of Cardiology guideline on cardio-oncology gives a class I (must do) recommendation (level of evidence B) for baseline (ie, pre-ICI therapy) ECG, measurement of cTn and natriuretic peptides in all patients, and echocardiography in all high-risk patients (ie, those taking dual ICI therapy or combination ICI cardiotoxic therapy, and those with ICI-related non-CV events or history of CV disease).[25] The cost-effectiveness of routine cardiac surveillance during ICI treatment remains undefined, however, even though the prospect of early detection of myocardial inflammation is appealing.[47] Additionally, there is a tangible risk of misinterpretation and mismanagement associated with routine cTn screening. In the general population, an elevated troponin is 7-fold more likely to reflect myocardial infarction than myocarditis and traditional major adverse events are also more common than myocarditis in patients taking ICI.[47,48] Further, cTn elevation may reflect expression of cTn by the malignant cell clone or release of cTn due to malignant infiltration of the myocardium.[27,30,49-51]

Management and Outcomes

Troponin Elevation of Uncertain Significance

Troponin elevation alone should not prompt discontinuation of ICI therapy or initiation of immunosuppression. The decision on continuation vs discontinuation of ICI therapy should be made with input from multiple teams. As this scenario may still represent early, subclinical ICI myocarditis, serial monitoring of cardiac biomarkers, ECGs, and signs and symptoms of CV disease are warranted with or without ongoing ICI treatment.

Smoldering Myocarditis

Individuals who meet the diagnostic criteria for ICI myocarditis but remain asymptomatic with minimal abnormalities on testing are classified as having smoldering or subclinical myocarditis. In this unique group of patients, ICI therapy should initially be held but may be restarted after multidisciplinary review if it remains the best option for cancer treatment. At present, there are insufficient data to inform the frequency of progression to more clinically significant or severe disease with continuation of ICI therapy, and patients should be closely monitored. While no strict criteria exist, patients with a decrease in left ventricular ejection fraction, new conduction abnormalities or ventricular arrythmias, or significant elevations in troponin, even if asymptomatic, should generally be managed as clinical myocarditis as opposed to smoldering or subclinical myocarditis. The extent of cTn elevation may provide another risk estimate and is a key element in the International ICI-Myocarditis Registry prediction score for severe or life-threatening cardiomyotoxic events.[52,53] In the prospective validation cohort for this risk score, all 7 patients with a score of 0 remained without any such severe event, even without immunosuppressive therapy (only ICI therapy cessation). Likewise, in 28 consecutive patients who underwent EMB for suspected ICI myocarditis, 5 patients with no evidence of myocytolysis and mainly low-level inflammatory infiltrate on biopsy (cTn levels similar to those with negative EMB findings in 4 patients) never received corticosteroids or any other immune modulators, 4 of whom continued ICI therapy, and all remained asymptomatic and without CV complications.[43]

Nonsevere Myocarditis

For symptomatic patients meeting diagnostic criteria for ICI myocarditis but without hemodynamic or electrical instability, ICI therapy should be discontinued and the patient should be admitted for telemetry monitoring and multidisciplinary evaluation. Intravenous methylprednisolone, 500 to 1000 mg per day, should be initiated as soon as possible after diagnosis is confirmed and transitioned to oral prednisone, 1 to 2 mg/kg per day (most centers generally use less than 100 mg per day) once cTn levels trend down and continue to decline.[15,54] Prednisone can then be tapered by approximately 10 mg per week, guided by cTn levels and clinical status, with a slower taper once the dose reaches 10 mg per day. Faster tapers have been used successfully with milder forms of disease. When tracking cTn

levels, it is important to consider that both cTnI and cTnT peak early (median time, day 3 vs day 7, respectively), and cTnI levels normalize faster than cTnT (median time, day 17 vs day 133, respectively).[52]

These dynamics pose challenges for defining response to therapy and steroid resistance.[55] For steroid-refractory cases, defined herein as worsening clinical presentation and/or continued cTn increase despite high-dose methylprednisolone, the addition of second-line immunosuppressive agents should be considered (eText in the Supplement). Abatacept, a cytotoxic T-lymphocyte antigen 4 immunoglobulin fusion protein that downregulates T-cell activation by binding CD80/CD86 on antigen-presenting cells, has emerged as a preferred agent for reversing ICI-activated pathways based on small sample sizes and nonrandomized data.[56] Ruxolitinib, a Janus kinase 1 (JAK1)/JAK2 inhibitor that rapidly inhibits T-cell activation, has been used to enhance efficacy and bridge time lapses of pharmacokinetic efficacy as abatacept has a slower onset of (peak) effect. Trials are ongoing to evaluate the efficacy of abatacept in mild to moderate ICI myocarditis (NCT05335928) and severe ICI myocarditis (NCT05195645).

Other immunosuppressive agents adapted for the treatment of ICI myocarditis are listed in eTable 2 in the Supplement. Infliximab has been associated with higher rates of CV death and should be avoided, especially in patients with HF.[57] Mycophenolate can serve as a steroid-sparing agent for patients experiencing significant adverse effects from prolonged steroid use, patients unable to taper their steroid regimen, or those at high risk of opportunistic infections due to additional immunocompromise, such as hematological malignant neoplasms. Prophylactic antibiotics (eg, trimethoprim and sulfamethoxazole) and antifungals (eg, nystatin) as well as prophylactic proton pump inhibitors are standard of care in patients taking long-term steroids (dose of prednisone, 20 mg, per day or greater for 4 or more weeks).[58] Screening for and prompt management of infections are critical with immunosuppressive therapies. Significant metabolic implications, such as hyperglycemia, have to be considered as well. Lastly, high-dose immunosuppressive therapy may antagonize any primary therapeutic effect of ICI therapy, especially if started early (within the first 2 months) of treatment, although some controversy exists.[59-62]

Severe Myocarditis

Patients with evolving signs of electrical or hemodynamic instability in the setting of ICI-associated myocarditis should be admitted to the intensive care unit with oncology and cardiology involvement. ICI therapy should be discontinued, and high-dose steroid therapy (intravenous methylprednisolone, 500 to 1000 mg per day) should be initiated immediately, in parallel with further diagnostic steps and clinical stabilization. Temporary pacing may be required for patients with advanced heart block or cardioversion/defibrillation for those with unstable arrhythmias. Cardiogenic shock should be treated with vasopressors and inotropes as necessary with temporary mechanical circulatory support in select cases as a bridge to treatment or bridge to recovery.[63,64] For patients presenting with severe or fulminant myocarditis or triple M syndrome (myositis, myocarditis, and myasthenia gravis), it is recommended to default to an upfront combination of high-dose steroids with another immunosuppressant, such as abatacept, either alone or in combination with a JAK inhibitor, antithymocyte globulin, and/or intravenous immunoglobulin and plasma exchange.[25,56] Intravenous immunoglobulin and/or plasma exchange are especially indicated for myasthenia gravis–like presentations. Care for patients with severe ICI myocarditis or triple M syndrome often requires multidisciplinary input, and strong consideration should be given to transfer these patients to a facility capable of managing the potential complications.

ICI Pericarditis and Other Complications

Patients with ICI pericarditis should be monitored for pericardial effusion and tamponade.[65] In severe cases of pericarditis with myocardial involvement or moderate to severe pericardial effusion, ICI therapy should be discontinued and treatment with corticosteroids, with or without colchicine, should be initiated for 3 to 5 days. With clinical improvement, steroids should be tapered slowly based on symptoms and C-reactive protein levels. The rationale for up-front steroids, unlike in other forms of pericarditis, is due to the putative mechanism of ICI pericarditis being driven by activated T lymphocytes.[23] For refractory cases, IL-1 antagonists, such as anakinra or rilonacept, can be considered. For uncomplicated ICI pericarditis, ICI therapy may be continued with high-dose nonsteroidal anti-inflammatory agents (aspirin, 750 to 1000 mg, every 8 hours or ibuprofen, 600 mg, every 8 hours for 1 to 2 weeks) and colchicine, 0.6 mg, twice daily for 3 months. In uncomplicated cases, rechallenge with ICI therapy can be considered on the background of colchicine.

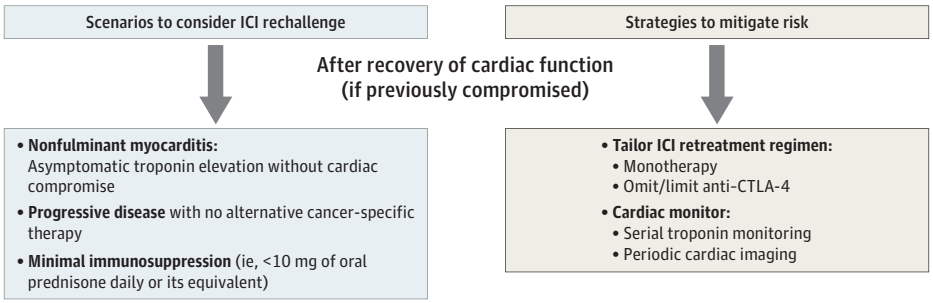
Other cardiac complications, such as ACS and cardiomyopathy, should be treated as per standard cardiology guidelines but with multidisciplinary input.[25] In case of Takotsubo syndrome, patients may do well resuming ICI therapy on resolution of the cardiomyopathy, as also observed for these patients with other cancer therapies.[66,67]

Outcomes and Prognosis

A contemporary single-center analysis of 160 patients with suspected ICI myocarditis showed a graded response in 1-year CV mortality rates ranging from 27.6% in severe cases (n = 28) to 5% in nonsevere cases (n = 96) and 8% in nonmyocarditis cases (n = 36),[68] while CV-related admissions within 1 year after the index admission were numerically but not statistically higher in nonsevere than severe and nonmyocarditis cases (16% vs 4% and 6%, respectively). Intriguingly, there was no significant difference in overall mortality (64% vs 57% and 53%, respectively).

Patients requiring more than 1 immunosuppressive agent have a higher mortality (50% vs 21%),[57] as do those with concomitant myositis, myocarditis, and myasthenia gravis–like syndromes. Respiratory muscle involvement is a critical prognostic factor, and shortness of breath and the need for supplemental oxygen have been associated with an increased risk of major adverse events.[15] Other parameters of prognostic significance include peak troponin and troponin trajectory, complete heart block, prolonged QRS (greater than 100 ms) or QTc (greater than 450 ms), abnormal myocardial strain measured by echocardiography or CMR, and elevated native T1 values on CMR.[15,31-33,52,69-71] Considering all parameters available in the International ICI-Myocarditis Registry, Power et al[53] identified 5 predictors of major, severe, and life-threatening cardiorespiratory events that allow an estimate of the clinical trajectory on presentation with concerns of ICI myocarditis and may help with triage decisions (eFigure 3 in the Supplement).

Figure 3. Illustration of Rechallenge Strategies



The decision for rechallenge should balance the severity of the initial presentation, the risk of recurrence, and the potential benefit of re-initiating immune checkpoint inhibitor (ICI) therapy. ICI monotherapy is preferred with a different ICI if possible and avoiding cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors. Serial monitoring with cardiac biomarkers (ie, with each ICI cycle or earlier if symptoms develop) and periodic imaging during rechallenge is advisable to detect early stages of cardiotoxic effects and allow for early intervention, such as ICI discontinuation and initiation of immunosuppression.

Rechallenge

Oncological practice guidelines recommend permanent discontinuation of ICIs for any type of severe irAE (Common Terminology Criteria for Adverse Events grade 4) and any case of myocarditis grade 2 or greater.[54] Data on the risk of recurrent irAEs, including myocarditis, with ICI rechallenge are very limited. In a cohort of 452 patients from Vigibase, 25% to 33% of patients with any irAE had recurrence of the same irAE with rechallenge.[72] Of the 16 patients with nonfatal myocarditis cases (N = 1082) that underwent rechallenge, 6 (38%) experienced ICI recurrence.[3] Other published cases of rechallenge after myocarditis, none with recurrence, are found in eTable 3 in the Supplement.

Rechallenge should only be considered when ICI myocarditis has clinically resolved, need for immunosuppression is at a minimum (ideally less than 10 mg per day of oral prednisone equivalent), and there is a compelling reason to continue ICI therapy. In these scenarios, shared decision-making between the patients and clinicians is crucial, with careful discussion of risks and benefits, including the potential effect of a new or recurrent toxic effect on the patient's quality of life. When considering rechallenge, several mitigating strategies should be implemented (**Figure 3**). The use of prophylactic immunosuppression (such as low-dose prednisone) to minimize de novo and recurrent irAEs is being studied.[73]

Gaps and Future Directions

There are several important knowledge gaps in our current understanding of ICI-associated CV toxic effects. These are detailed in the eText and eTable 4 in the Supplement.

Conclusions

With the increase in ICIs available to a growing population of patients with cancer, not only in number but also in diversity and comorbidity, health care professionals across all medical fields are increasingly confronted with the task of the best possible management of adverse CV events in these patients. Patients benefit from a multidisciplinary and nuanced approach to management that accounts for both the severity of the presentation and the importance of balancing toxic effect with the continuation of life-saving cancer treatment.

ARTICLE INFORMATION

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