Cardiotoxicities of novel cancer immunotherapies

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ABSTRACT

Immunotherapy revolutionised oncology by harnessing the native immune system to effectively treat a wide variety of malignancies even at advanced stages. Off-target immune activation leads to immune-related adverse events affecting multiple organ systems, including the cardiovascular system. In this review, we discuss the current literature describing the epidemiology, mechanisms and proposed management of cardiotoxicities related to immune checkpoint inhibitors (ICIs), chimeric antigen receptor (CAR) T-cell therapies and bispecific T-cell engagers. ICIs are monoclonal antibody antagonists that block a co-inhibitory pathway used by tumour cells to evade a T cell-mediated immune response. ICI-associated cardiotoxicities include myocarditis, pericarditis, atherosclerosis, arrhythmias and vasculitis. ICI-associated myocarditis is the most recognised and potentially fatal cardiotoxicity with mortality approaching 50%. Recently, ICI-associated dysregulation of the atherosclerotic plaque immune response with prolonged use has been linked to early progression of atherosclerosis and myocardial infarction. Treatment strategies include immunosuppression with corticosteroids and supportive care. In CAR T-cell therapy, autologous T cells are genetically engineered to express receptors targeted to cancer cells. While stimulating an effective tumour response, they also elicit a profound immune reaction called cytokine release syndrome (CRS). High-grade CRS causes significant systemic abnormalities, including cardiovascular effects such as arrhythmias, haemodynamic compromise and cardiomyopathy. Treatment with interleukin-6 inhibitors and corticosteroids is associated with improved outcomes. The evidence shows that, although uncommon, immunotherapy-related cardiovascular toxicities confer significant risk of morbidity and mortality and benefit from rapid immunosuppressive treatment. As new immunotherapies are developed and adopted, it will be imperative to closely monitor for cardiotoxicity.

INTRODUCTION

Immunotherapies, including cytokines, targeted therapies, cell-based therapies and vaccines, harness the immune system to combat tumour cells. Increased understanding of antitumour mechanisms has led to a proliferation of new treatments; in 2017, approximately 940 clinical and 1064 preclinical immunotherapies were under investigation (figure 1).[1] Such treatments target common antitumour mechanisms to allow generalisability to multiple malignancies, maximise efficacy and minimise side effects. However, immune-related adverse events (IRAEs) can affect every major organ system, including the cardiovascular system.[2] With 1.8 million new cancer cases per year and increased indications for immunotherapy, uncommon cardiotoxicities are on the rise.[3] The short-term and long-term cardiovascular effects of these novel treatments require vigilant monitoring. This review describes the current understanding of the mechanisms, epidemiology and management of immunotherapy-related cardiotoxicity, focusing on immune checkpoint inhibitors (ICIs) and chimeric antigen receptor (CAR) T-cell therapies.

IMMUNE CHECKPOINT INHIBITORS

Mechanism

A delicate balance of co-stimulatory and co-inhibitory pathways regulate the adaptive immune system. Antigen-presenting cells express membrane-bound major histocompatibility complex (MHC) together with the second immunological signal required to activate T cells, the co-stimulatory molecules B7-1 (CD80) and B7.2 (CD86). T cells recognise the antigen-MHC complex with the T cell receptor (TCR), and the co-stimulatory molecules with the activating receptor CD28. To prevent excessive immune activation, co-stimulation is antagonised by the dominant expression of the cytotoxic T lymphocyte antigen 4 (CTLA-4), which effectively competes with CD28 and limits the activation step of an immune response (figure 2). Antitumour T cells that pass this first immune checkpoint can be inactivated at the tumour site through the reactive expression of the programmed death ligand 1 (PD-L1). This allows cancer cells to turn off antitumour T cells by triggering the programmed death 1 (PD-1) receptor that leads to T cell exhaustion. This represents a second immune checkpoint at the effector step of an antitumour immune response. ICIs are blocking antibodies to either PD-1 or PD-L1, and to CTLA-4, which block these two immune checkpoints and reactivate the antitumour immune response.[4–6] There has been a rapid increase in monotherapy and dual-therapy Food Drug and Administration (FDA)-approved indications for the seven current FDA-approved ICIs (table 1, figure 1).

The 1-year absolute risk of cardiac events, including non-immune-related events, ranged from 6.6% to 9.7% for patients with melanoma and lung cancer receiving ICIs (table 2).[7] Most patients undergoing ICI therapy experience at least one IRAE.[8] Cardiovascular IRAEs occur with an incidence of 1.14%–5%,[4 7 9 10] but have the highest mortality rate among IRAEs up to 50% (table 2).[9–13] Immune checkpoints suppress T cell-mediated autoimmune activation in myocardium. Possible cardiovascular IRAE aetiologies include activation of local T cells, cross-reaction of antitumour T cells with myocardial antigens or systemic immune activation.[6 14 15] Cardiovascular IRAEs include myocarditis (0.3%–1.4% of patients on ICI therapy), arrhythmias (3.6%–4.8%), pericardial disease (1.74%), vasculitis (0.27%), acute coronary

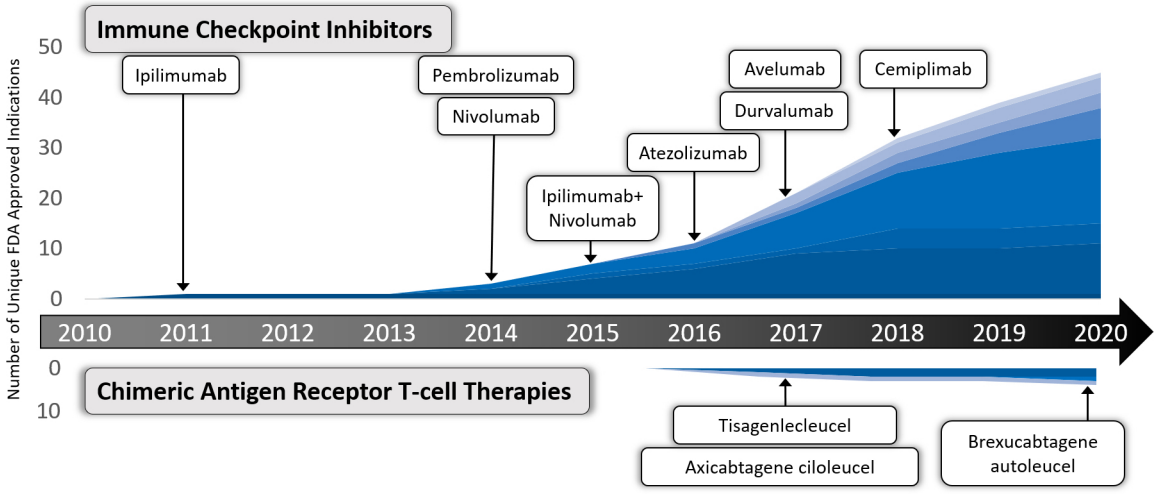

Figure 1 Timeline of Food Drug and Administration (FDA)-approved immunotherapies. Since the approval of the first immune checkpoint inhibitor (ICI) in 2001, there was been an exponential increase in FDA-approved agents and the number of FDA-approved target malignancies. Here, the number of unique FDA-approved malignancy-based indications for each FDA-approved therapy is plotted in categories of ICI (top) and chimeric antigen receptor T-cell therapies (bottom). Arrows indicate year of initial FDA approval for each individual medication.

syndrome (ACS) (0.95%–7%) and heart failure (HF, 1.6%) (figure 2, table 2).[7 12 13 16]

Risk factors

Cardiovascular IRAE risk factors are poorly understood. Combination therapy is associated with increased incidence, severity and mortality of ICI-associated myocarditis compared with monotherapy.[14] Concomitant non-cardiac IRAEs confer increased risk of ICI-associated myocarditis, particularly myositis (reported OR (ROR) 25, 95% CI 18.7 to 34.9), encephalitis (ROR 2.9, 95% CI 1.4 to 6.3) and hepatitis (ROR 2.9, 95% CI 1.9 to 4.5).[17] In a single-centre study, myocarditis was associated with pre-existing cardiovascular disease, including HF and ACS, and increased age (>80 years).[13] Investigations are needed

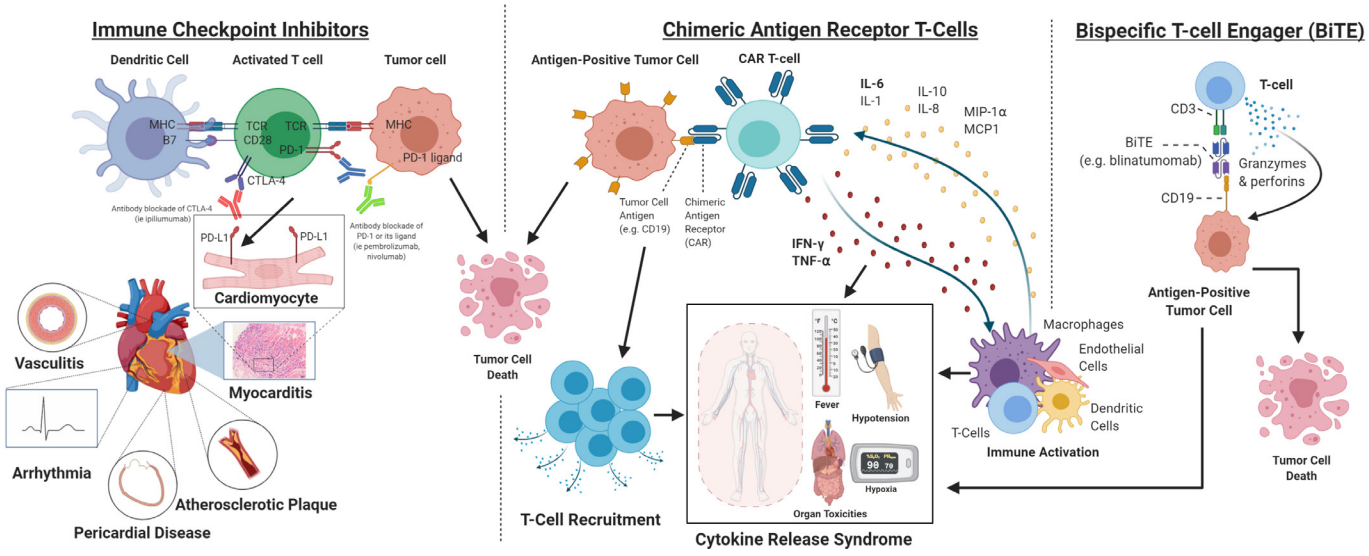

Figure 2 Mechanisms of immune checkpoint inhibitors and chimeric antigen receptor T-cell therapies. (A) Mechanism of immune checkpoint inhibitors: dendritic cells, other antigen-presenting cells and tumour cells have surface MHCs and co-inhibitor receptors (B7 or PD-1 ligand) that bind to activated T cells via TCR, CTLA-4 and PD-1 receptors, respectively. Immune checkpoint inhibitors are monoclonal antibody antagonists to CTLA-4, PD-1 and PD-L1. Inhibition in tumour cells allows activated T cell-mediated tumour cell death. Inhibition of this pathway in the myocardium is thought to be driven by PD-L1 receptors on cardiomyocytes. Inhibition of this regulatory pathway leads to myocarditis, vasculitis, atherosclerosis, arrhythmias and pericardial disease. (B) Mechanism of CAR T-cell therapy and cytokine release syndrome. Autologous T cells are genetically engineered to express a chimeric antigen receptor that binds with an antigen-positive tumour cell leading to cell death. (C) Mechanism of bispecific T cell engager (BiTE) therapy. BiTE molecule links two single chain variable fragments that bind the CD3 receptor on T cells and the CD19 receptor on the target tumour cells. By bringing these cells in close physical proximity, the T cell is activated to attack tumour cells. Similar to CAR T-cell mechanism, this T cell activation can precipitate CRS and the associated cardiotoxicities. Additionally, CAR T-cells can cause immune activation with production of multiple cytokines and T cell recruitment leading to cytokine release syndrome characterised by fever, hypotension, hypoxia and multiorgan toxicity. CAR, chimeric antigen receptor; CTLA-4, cytotoxic T lymphocyte associated protein-4; MHC, major histocompatibility complex; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1TCR, T cell receptor. Created with BioRender.com.

Table 1 FDA-approved indications and toxicities for immune checkpoint inhibitors

Drug	FDA approved indications	FDA labelled cardiotoxic effect
Ipilimunab	Melanoma	Pericarditis (incidence<1%) Myocarditis (incidence 0.2%)
Nivolumab	Melanoma, NSCLC, SCLC, RCC, classical Hodgkin lymphoma, head and neck SCC, Urothelial carcinoma, HCC, dMMR and MSI-h metastatic CRC, oesophageal SCC	Myocarditis (incidence<1%), ventricular arrhythmia
Pembrolizumab	Melanoma, NSCLC, oesophageal SCC, SCLC, SCC of the head and neck, classical Hodgkin lymphoma, Urothelial carcinoma, gastric or gastro-oesophageal junction, MSI-h or dMMR solid tumours, Cervical cancer, Merkel cell carcinoma, HCC, tumour mutational burden-high solid tumours, cutaneous SCC, PMBCL, RCC, endometrial carcinoma, MSI-h or dMMR CRC	Cardiac failure (incidence 0.4%)
Atezolizumab	Urothelial carcinoma, NSCLC, PD-L1-positive triple-negative breast cancer, HCC, small cell lung cancer, melanoma	Myocardial infarction
Durvalumab	Urothelial carcinoma, NSCLC, SCLC	Myocarditis (incidence<1%)
Avelumab	Merkel cell carcinoma, urothelial carcinoma, RCC	Myocarditis
Cemiplimab	Advanced SCC	Myocarditis (case reports)

Each FDA-approved agent has been approved for multiple unique malignancies. All agents are labelled with warnings of known cardiotoxicities.
CRC, colorectal cancer; dMMR, mismatch repair-deficient; FDA, Food Drug and Administration; HCC, hepatocellular carcinoma,; MSI-h, high microsatellite instability; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; PMBCL, primary mediastinal large B-cell lymphoma; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung cancer.

to identify high-risk patients, including concurrent cardiotoxic chemotherapies or targeted therapies, tumour types and underlying cardiovascular disease.

ICI-ASSOCIATED MYOCARDITIS

ICI-associated myocarditis presentations range from asymptomatic biomarker elevation to cardiogenic shock. Symptomatic ICI-associated myocarditis commonly presents with shortness of breath, chest pain or palpitations.[12] Over 40% of patients have concurrent severe IRAEs, particularly myositis (25%) and myasthenia gravis (10%).[10 12] Onset is common after two to three infusions with up to 80% occurring within 3 months of initiation,[7 9 10 12 13] but range from days to years (table 2). Given the non-specific presentation and timing, a high index of suspicion for ICI-associated myocarditis is required.

Monitoring and diagnosis

Baseline ECG and biomarkers, including troponin and brain natriuretic peptide (BNP), followed by ongoing monitoring for new cardiovascular symptoms are recommended with ICI therapy (figure 3).[2] While evidence is limited for risk stratification, routine biomarker monitoring may be pursued in select individuals. ICI therapy is not contraindicated with underlying cardiovascular disease, but patients should be medically optimised prior to therapy. Cardiac biomarkers are sensitive; troponin and BNP are elevated in 94% and 66% of cases of ICI-associated myocarditis, respectively. Additionally, higher admission and peak troponin level were associated with increased major adverse cardiac events (MACE).[9] Although ECG is abnormal in 89% of cases, diagnostic utility is limited due to increased ICI-associated arrhythmias distinct from myocarditis.[9]

Echocardiography is the first-line imaging modality for suspected ICI-associated myocarditis, but should be interpreted with caution as left ventricular ejection fraction (LVEF) is normal in up to 50% of cases.[9] Beyond LVEF, reduction in global longitudinal strain is associated with the presence (14.1%±2.8% myocarditis vs 20.5%±1.9% control, p<0.001) and severity of myocarditis (1.5-fold and 4.4-fold increased risk of MACE in reduced and preserved LVEF, respectively).[18]

Cardiac magnetic resonance imaging (CMR) further characterises myocardium using late gadolinium enhancement (LGE) and T2-weighted short-T1 inversion recovery imaging of oedema, but has limited sensitivity in ICI-associated myocarditis. In an international registry of ICI-associated myocarditis (n=103), only 48% of all patients had LGE compared with 90% in other causes of acute myocarditis.[19] LGE was distributed in subendocardial, transmural, subepicardial, mid-myocardial and diffuse patterns, and independent of LVEF, with 43% of LGE in preserved LVEF. LGE was not associated with symptoms, outcomes, ECG or echocardiographic findings. Importantly, timing alters CMR sensitivity in ICI-associated myocarditis. CMR administered >4 days after admission showed greater rates of LGE compared with earlier (72.0% vs 21.6%, OR 9.35, p<0.001).[20]

Endomyocardial biopsy is the diagnostic gold standard in ICI-associated myocarditis, but the invasive nature and procedural risks limit widespread use. Accordingly, diagnosis is based on clinical and biomarker assessment, aided with echocardiography and CMR.

Treatment

ICI-associated myocarditis is a potentially fatal complication of ICI therapy with mortality approaching 50% (table 2).[9–11 13] Importantly, among survivors with reduced LVEF approximately half completely recover LVEF.[10] Limited by the lack of randomised controlled trials, current treatment strategies are based on expert consensus. The 2018 American Society for Clinical Oncology (ASCO) guidelines define severity as grades 1–4 (figure 3).[2]

ICI-associated myocarditis management includes stopping ICIs, immunosuppression and supportive therapy. The risk of restarting ICIs after myocarditis recovery is unknown and permanent discontinuation is recommended for severity greater than grade 1.[2 21] ICIs have a long half-life (ipilimumab 14.5 days, pembrolizumab 25.0 days, nivolumab 26.7 days and atezolizumab 27.0 days); in severe cases, plasmapheresis can clear antibodies from the bloodstream.[15]

Corticosteroids are the backbone of immunosuppression in ICI-associated myocarditis. ASCO guidelines recommend oral

Table 2 Major studies of cardiovascular immune-related adverse events

Study	Type of study	No. of patients	Cardiotoxicities	Onset (days) mean (Range)	Outcomes
A. Registries of ICI cardiotoxicities					
Escudier *et al* [12]	Case series of ICI-related cardiotoxicity	30	Myocarditis (79%) Atrial fibrillation (30%) Conduction disorder (17%) Ventricular arrhythmia (27%) Takotsubo-like cardiomyopathy (14%)	65 (2–454)	CV death (26.7%) Cardiac arrest (6.7%) Ventricular arrhythmia (26.7%)
Mahmood *et al* [9]	Multicentre registry of ICI myocarditis	35	Myocarditis (100%)	34 (21–75)	CV death (17%) Cardiogenic shock (8.6%) Cardiac arrest (2.9%) Complete heart block (8.6%)
Moslehi *et al* [10]	WHO VigiBase Pharmacovigilance	101	Myocarditis (100%)	27 (5–155)	Death (46%)
Salem *et al* [11]	WHO VigiBase Disproportionality analysis	442	Myocarditis (28%)	30 (1–240)	Death (50%) Cardiogenic shock (15.6%) Cardiac arrest (9%)
			Pericardial disease (21%)	30 (0–330)	Death (21.1%) Cardiogenic shock (3.2%) Cardiac arrest (4.2%)
			Vasculitis (19%)	55 (21–98)	Death (6.1%) Cardiogenic shock (0%) Cardiac arrest (1.2%) Impaired vision (27.8%)
			Supraventricular arrhythmias (50%)	14 (1–925)	Death (23.9%%) Cardiogenic Shock/Arrest (2%)
B. Registries of patients on ICI therapy					
Oren *et al*[13]	Single-centre registry of ICI use	3326	MI (7%) Stroke (7%)		
			Myocarditis (0.36%)	138 (18–138)	Death (42%)
			Pericardial disease (1.74%)	195 (3–1143)	Death (26%)
			Vasculitis (0.27%)	243 (6–1026)	Death (0%)
Drobni *et al* [16]	Single-centre case-control study of ICI use	2842	MI (0.95%) Coronary revascularisation (0.87%) Ischaemic stroke (0.91%)	NA	CV events (2.32%)
D'Souza *et al*[7]	Danish registry of patients with ICI use	Lung cancer+PD1i			
		743	Arrhythmia (3.6%) Heart failure (1.6%) Myocarditis (1.4%)	133 (2–455) 194 (23–376) 75 (34–149)	CV events (5.9%) CV death (2.4%)
		Malignant melanoma+PD1i			
		145	Arrhythmia (4.8%) Heart failure (<2%) Myocarditis (<2%)	178 (20–326) NA NA	CV events (6.2%) CV death (2.8%)
		Malignant melanoma+CTLA-4i			
		212	Arrhythmia (3.8%) Heart failure (<1%) Myocarditis (<1%)	211 (74–416) NA NA	CV event (9.0%) CV death (5.7%)

(A) Summary of registry studies of patients with known ICI-associated cardiovascular toxicities. Myocarditis and arrhythmias were the most commonly identified cardiotoxicities. Among patients with cardiotoxicities, there was highly variable timing of onset and high mortality. (B) Large-scale retrospective studies of all patients undergoing ICI therapy that characterised incidence of cardiotoxicities.

CTLA-4i, cytotoxic T lymphocyte antigen-4 inhibitor; CV, cardiovascular; ICI, immune checkpoint inhibitor; MI, myocardial infarction; PD1i, programmed death-1 inhibitor.

or intravenous high-dose corticosteroids (prednisone 1–2 mg/kg) for 4–6 weeks depending on severity of symptoms and clinical response (figure 3, table 3).[2] An international multicentre registry of 126 ICI-associated myocarditis cases found that early, high-dose corticosteroids were associated with improved outcomes. Early corticosteroid administration (<24 hours since admission) was associated with lower rates of MACE compared with 24–72 or >72 hours (7.0%, 34.3% and 85.1%, respectively, p<0.001). High-dose corticosteroids (greater than methylprednisolone 500 mg/day) was associated with a reduced risk of MACE independent of timing (HR 0.27, 95% CI 0.09 to 0.84, p=0.024).[22] Randomised controlled trials are needed to define the optimal timing and dose of corticosteroid therapy in ICI-associated myocarditis.

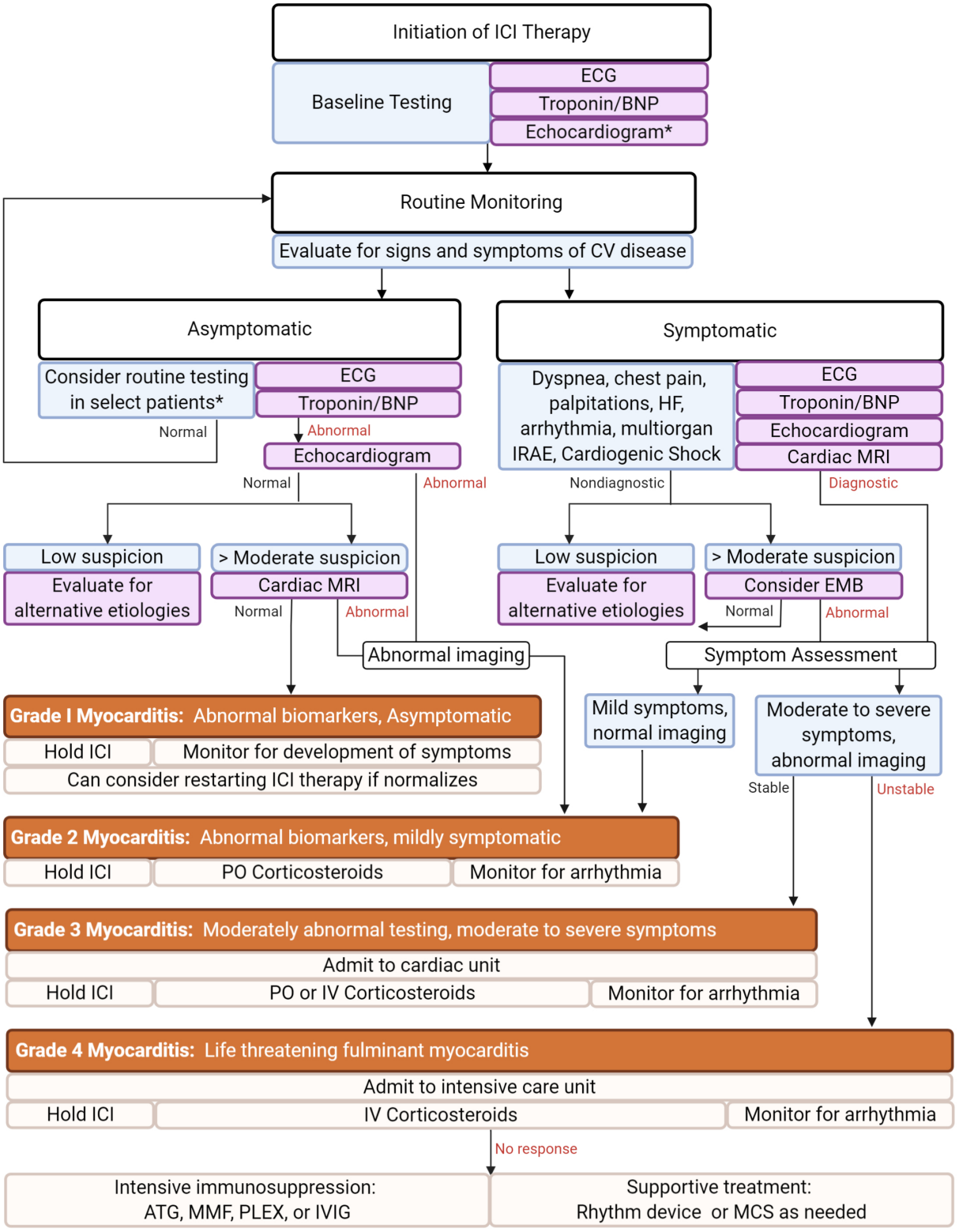

Figure 3 Proposed algorithm for treatment of ICI-associated myocarditis. All patients should undergo baseline biomarker and ECG testing prior to initiation of therapy. Throughout therapy, particularly in the first 3–6 months, patients should be evaluated for signs and symptoms of myocarditis. Asterisk (*) indicates that select asymptomatic patients should undergo baseline echocardiogram and routine biomarker testing. These patients may include those at increased cardiovascular risk, history of cardiotoxic therapeutics or those on combination therapy. Patients with low suspicion for ICI myocarditis should undergo evaluation for alternative aetiologies of symptoms and biomarker changes, including an ischaemic evaluation. Severity of ICI-associated myocarditis is classified as grade 1–4 depending on symptoms, biomarker and imaging findings. Treatment with immunosuppression is given according to the grade of severity. Based on 2018 ASCO guidelines.[2] Lavender-coloured boxes represent diagnostic tests. ATG, antithymocyte globulin; BNP, brain natriuretic peptide; EMB, endomyocardial biopsy; HF, heart failure; ICI, immune checkpoint inhibitor; IRAE, immune-related adverse event; IV, intravenous; IVIG, intravenous immunoglobulin; MCS, mechanical circulatory support; MMF, mycophenolate mofetil; PLEX, plasma exchange; PO, per oral. Created with BioRender.com.

Table 3 Immunosuppression used in treatment of ICI-associated myocarditis

Pharmacotherapy	Mechanism of action	Example dose	Proposed duration
Corticosteroids Prednisone	Suppression of lymphocyte activity, inhibition of cytokine production, sequestration of CD4+ T lymphocytes	1–2 mg/kg/day per oral	4–6 weeks taper
Methylprednisolone		1 g/day intravenous	3–5 days followed by per oral taper above
Antithymocyte globulin	Rapid T lymphocyte depletion, complement-mediated cell lysis	500 mg intravenous daily	3–5 days
Mycophenolate mofetil	Inhibits T and B cell proliferation by depleting guanosine nucleotides	1 g intravenous twice daily	5 days
Abatacept	CTLA-4 agonist Inhibits T cell co-stimulation upstream of ICI targets	500 mg intravenous every 2 weeks	5 doses
Plasmapheresis	Removal of monoclonal antibody drug from plasma	NA	5 days
Intravenous immunoglobulin	Multifactorial; neutralising antibodies for autoantibodies; reduction of cytokine release; expansion of T regulatory cells	2 g/kg	5 days
Infliximab*	Anti-TNF-α Downregulation of cytokines and T lymphocyte apoptosis	5–10 mg/kg intravenous	1–2 doses

In patients with severe ICI-associated myocarditis refractory to corticosteroid therapy, additional immunosuppressive agents have been proposed. Doses and frequency of agents have been adapted from treatment of cellular rejection in cardiac transplant. Infliximab should be avoided in patients with heart failure due to increased mortality. Adapted from Khunger *et al*.[6]

*Contraindicated in moderate-to-severe heart failure; associated with increased risk of mortality.

CTLA-4, cytotoxic T lymphocyte antigen 4; ICI, immune checkpoint inhibitor; NA, not available; TNF, tumour necrosis factor.

Adjuvant immunosuppressive agents are used in fulminant, grade 4 ICI-associated myocarditis. ICI-associated myocarditis and cardiac allograft cellular rejection have similar histological appearances and may have similar mechanisms. Therefore, antirejection drugs and protocols have been adapted to treat ICI-associated myocarditis (figure 3), including mycophenolate, antithymocyte globulin, abatacept and infliximab (table 3).[2 6 9] However, infliximab should be avoided due to reports of increased cardiovascular mortality, particularly with moderate-to-severe HF.[23]

ICI-associated myocarditis can progress to cardiogenic shock, life-threatening arrhythmias and death. Inpatient monitoring of grade 3 or 4 ICI-associated myocarditis patients is needed to monitor for decompensation and arrhythmias requiring temporary or permanent pacemaker placement. Advanced mechanical circulatory support, including intra-aortic balloon pump, Impella (Abiomed, Danvers, Massachusetts, USA) or extracorporeal membrane oxygenation, may be considered in cardiogenic shock. Decisions for invasive management of arrhythmias or haemodynamic complications are complex, incorporating likelihood of cardiac recovery, comorbidities, underlying malignancy and associated prognosis, and require a multidisciplinary approach.

ICI-ASSOCIATED ATHEROSCLEROSIS

Recent investigations have focused on ICI-associated immune dysregulation and atherosclerotic cardiovascular disease (ASCVD). The proposed connection was first noted as a 1% incidence of ACS in a meta-analysis of 22 ICI trials in lung cancer.[24] Recently, a single-centre study of 3326 patients on ICIs showed a 7% incidence of each ACS and stroke.[13] In fact, in a matched cohort study, ICI therapy conferred a threefold increased risk of ASCVD (HR 3.3, 95% CI 2.0 to 5.5, p<0.001).[16]

Initially, the increased risk of ACS was attributed to other ICI-associated complications, such as vasculitis or coronary vasospasm, rather than atherosclerotic plaque rupture. However, recent advances demonstrate an important role for activated T cells in vulnerable plaques that may be modulated by ICI therapy. Large vessel atheroma in humans and mice with melanoma undergoing ICI treatment demonstrated no change in ^{18}FDG-PET-positive vascular inflammation. However, the intraplaque immune response shifted from macrophage to T cell-predominant with increased necrotic core and endothelial activation indicating plaque vulnerability to rupture.[25]

Beyond the acute risk of ACS, ICIs lead to atherosclerosis progression and ASCVD risk.[16] PD-1 expression modulates the arterial wall immune response; disruption via PD-1 inhibition leads to atherosclerosis progression. Single-cell analysis of human atheroma with recent ACS showed a distinct pattern of T cell activation. In particular, increased PD-1 expression may accelerate atherosclerosis and ACS in patients with pre-existing ASCVD.[26] Importantly, concurrent statin or corticosteroid use was associated with reduced aortic atherosclerotic plaque progression.[16] Therefore, cardiac care for the oncology patient must become proactive with aggressive risk factor modification at initiation of therapy and close cardiovascular monitoring.[27]

Other ICI-associated cardiotoxicities

ICI-associated pericardial disease, including pericarditis, myopericarditis and pericardial effusion, have been most commonly reported in lung cancer.[11] In a single-centre retrospective study of patients with non-small cell lung cancer, pericardial effusions were increased with ICIs compared with chemotherapy (3.3% vs 1.6%, respectively).[28] Clinical features include new onset chest pain, pericarditis-related ECG changes and pericardial effusion on imaging. Notably, mortality in ICI-associated pericarditis is 21%—significantly higher than non-ICI-associated pericarditis.[11] Therapeutic options, including non-steroidal anti-inflammatories, steroids or colchicine, have not been studied in this population and merit consideration.

ICI-associated arrhythmias are the most common cardiotoxicity and portend significant mortality, particularly sudden cardiac death.[7 11 12] ICI-associated arrhythmias include conduction delays, ventricular and supraventricular arrhythmias.[12 29] Only 17% of supraventricular arrhythmias are isolated, with the overwhelmingly majority associated with concurrent IRAEs, including colitis (26.1%), thyroiditis (13.1%), pneumonitis (13.1%) and myocarditis (12.2%).[11] In contrast, local ventricular

or conduction system inflammation likely causes conduction delays and ventricular arrhythmias. In patients with palpitations or syncope, evaluation includes ECG, ambulatory ECG monitoring and evaluation for myocarditis or other IRAEs.

ICI-associated vasculitis, including polymyalgia rheumatica and temporal arteritis, presents relatively delayed with median onset 55 days (table 2). Although mortality is comparatively low, impaired vision occurred in 27.8% of cases.[11] The ASCO guidelines recommend corticosteroid treatment to prevent vision loss.[4]

CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY

CAR T-cell therapy is a cell-based immunotherapy whereby patient's cells are genetically engineered to target tumour-specific proteins to induce tumour-cell apoptosis (figure 2).[30] Currently, three CD19-directed CAR T-cell therapies (axicabtagene ciloleucel, brexucabtagene autoleucel, tisagenlecleucel) are FDA-approved for diffuse large B-cell lymphoma (DLBCL), acute lymphoblastic leukaemia (ALL) and mantle cell lymphoma. CAR T-cell therapy in solid malignancies is under investigation.[31] Despite significant clinical efficacy,[32] life-threatening toxicities, including haemodynamic instability and cardiotoxicity, complicate CAR T-cell therapy.

Cardiotoxicity pathophysiology

On engagement with target antigen domains, CAR T-cells elicit a strong immune response critical to their therapeutic effect. Activation of CAR T-cells leads to massive systemic release of cytokines, including IL-6, TNF-α and IFN-γ, causing prostaglandin activation and triggering cytokine release syndrome (CRS).[33] CRS manifests as fever, tachycardia, hypotension, hypoxia and multiorgan dysfunction[34 35] and can be associated with cardiotoxicity.[36]

IL-6 is a primary driver of inflammation in CRS, leading to increased B and T cell activity and release of acute phase reactive proteins.[37] A marked rise in IL-6 accompanies CAR T-cell-associated cardiotoxicity in CRS.[15] Elevated IL-6, previously studied in diabetes, is associated with cardiovascular complications including myocardial ischaemia, atherosclerosis, HF and hypertension.[38] IL-6 may similarly lead to CAR T-cell-associated cardiotoxicity.[39]

Cardiotoxicity presentation

Cardiovascular toxicity following CAR T-cell therapy is often accompanied by CRS, neurotoxicity and graft versus host disease.[40] Among CAR T-cell-associated cardiovascular events reported to the FDA Adverse Events Reporting System from 2017 to 2019 (n=196), CRS was present in two-thirds of patients.[41] The most common study-defined MACE were arrhythmias (77.6%), HF (14.3%) and myocardial infarction (0.5%). The most frequently reported system-specific adverse event, immune effector cell-associated neurotoxicity syndrome (ICANS)—previously named CAR T-cell-related encephalopathy syndrome—was associated with a combined measure of CRS and cardiovascular events.[41]

Retrospective studies of CAR T-cell therapy have characterised cardiotoxicity (table 4). Cardiovascular events include decompensated HF, arrhythmia, ACS, stroke, prolonged QTc[42] and cardiovascular death. In an adult study of CAR T-cell therapy (n=137), all MACE (n=17) occurred with grade ≥2 CRS and 95% occurred with elevated troponin.[39] In another retrospective study (n=145), high-grade CRS was strongly associated with

Table 4 Major studies of cardiotoxicity following chimeric antigen receptor (CAR) T-cell therapy

Study	Population (indication) (n)	Therapy	Developed CRS (%)	Adverse CV event (%)
Shalabi *et al*[45]	Paediatrics, young adults (r/r B-cell malignancies) (n=52)	Investigational CD19-directed CAR T	71	>10% LVEF decrease or new-onset grade ≥2 LV dysfunction (12%) Hypotension requiring pressors (17%)
Lefebvre *et al*[43]	Adults (DLBCL, ALL, CLL) (n=145)	CD19-directed CAR T	72	CV death (1.4%) Symptomatic HF (15%) Non-fatal ACS (1.4%) New Afib (7.6%) New other arrhythmia (1.4%)
Alvi *et al 2019*[39]	Adults (DLBCL, MM, transformed follicular, other) (n=137)	CD19-directed CAR T (or investigational CAR T)	40% (only CRS ≥grade 2)	CV death (11%) New-onset HF (11%) HF decompensation (3.6%) Any new arrhythmia (12%)
ELIANA— Maude *et al*[w8]	Paediatrics, young adults (r/r B-ALL) (n=75)	Tisagenleceucel (CD19-directed CAR T)	77%	Cardiac arrest (4%) Heart failure (2.7%) DIC (2.7%)
ZUMA-1—Locke *et al*[40]	Adults (r/r B-ALL) (n=101)	Axicabtagene ciloleucel (CD19-directed CAR T)	93%	Cardiac arrest (1%) Hypoxia (33.6%)
Burstein *et al*[46]	Paediatrics (ALL) (2–27 years old) (n=93)	CD19-directed CAR T	Not reported (100% among patients requiring inotropic support)	Hypotension requiring pressors (no echocardiography performed) (4%) Hypotension requiring pressors (normal echocardiography) (10%) Hypotension requiring pressors (echocardiographic dysfunction) (10%)

A growing number of retrospective studies have found cardiotoxicities associated with CAR T-cell therapy across both paediatric and adult cohorts. The rates of CRS, which commonly co-occurs with cardiotoxicity, are also noted across studies.
DLBCL, diffuse large B-cell lymphoma; ALL, acute lymphocytic leukaemia; CLL, chronic lymphocytic leukaemia; MM, multiple myeloma; LVEF, left ventricular ejection fraction; LV, left ventricle; CV, cardiovascular; HF, heart failure; ACS, acute coronary syndrome; Afib, atrial fibrillation; DIC, disseminated intravascular coagulation.

increased risk of MACE. MACE (n=31) occurred at a median of 11 days with a wide range (IQR=6–151), underscoring a need for longitudinal cardiovascular monitoring.[43] In a retrospective cohort of 116 patients treated with CD19-directed CAR T-cells undergoing serial echocardiograms, 10% of patients developed new or worsening cardiomyopathy with a median LVEF decline from 58% to 37% and a median of 12.5 days following therapy.[44]

Paediatric CAR T-cell therapy populations are also susceptible to cardiotoxicity. Among paediatric and young adult patients (n=52) with haematological malignancies treated with CD19-28ζ CAR T-cells, patients developed CRS (n=37) left ventricular dysfunction (n=6) and hypotension requiring vasoactive agents (n=9). Notably, 31% of patients with troponin measurements and CRS had elevated troponin and reduced LVEF.[45]

Monitoring and treatment

While CAR T-cell therapy has no absolute contraindications, cardiovascular toxicity risk is not uniform. Increased age, hyperlipidaemia, coronary artery disease and outpatient medications including beta-blockers, ACE inhibitors and angiotensin receptor blockers were associated with cardiomyopathy, but not cancer type, prior anthracycline use or mediastinal radiation.[44] In paediatric patients with ALL, hypotension requiring vasopressors was more likely in those with higher tumour burden, lower baseline LVEF or diastolic dysfunction.[46] Because of the common association of CRS, co-occurring inflammatory toxicities, such as ICANS, may increase cardiotoxicity risk.[41]

Monitoring, diagnosis and treatment of cardiotoxicity during CAR T-cell therapy remains challenging (figure 4). In a case report, a patient with cardiomyopathy and refractory DLBCL with planned CAR T-cell therapy underwent CardioMEMS (Abbott Medical, Abbott Park, Illinois, USA) implantation prior to lymphodepletion. CardioMEMS, conventionally used for outpatient HF management, was repurposed for invasive haemodynamic monitoring throughout hospitalisation.[47] This novel application demonstrated a proof of concept for haemodynamic guidance in high-risk patients during CRS.

No randomised controlled trials have evaluated interventions to reduce cardiovascular morbidity in CAR T-cell therapy, but given their strong association, early intervention of CRS may prevent cardiotoxicity. Tocilizumab, an FDA-approved IL-6 receptor antagonist, prevents symptomatic CRS progression.[30 48] Each 12-hour delay from CRS onset to tocilizumab administration was associated with a 1.7-fold increased risk of MACE.[39] Both in vitro and clinical data suggest that tocilizumab does not impair CAR T-cell efficacy.[49 50] Siltuximab, a monoclonal IL-6 targeted antibody, has similarly been used off-label to prevent CRS progression in CD19-directed CAR T-cell therapy.[w1]

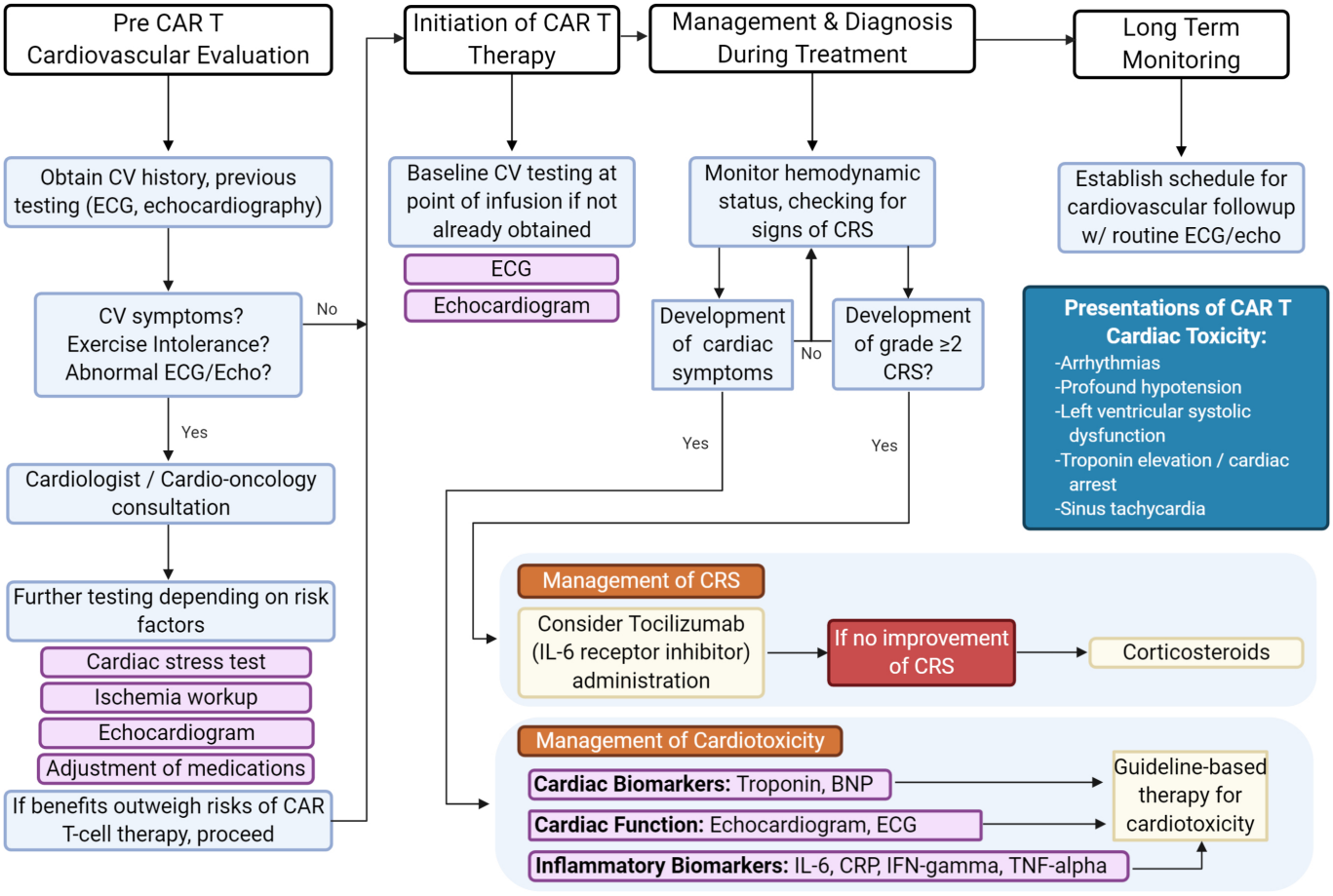

Figure 4 Proposed algorithm for evaluation and treatment of chimeric antigen receptor (CAR) T-cell therapy-associated cardiotoxicity. The optimal cardiovascular management of CAR T-cell patients prior to, during and following therapy is an area of active research, and formal guidelines have not yet been developed. Based on current evidence, we propose an algorithm for individualised care of CAR T-cell patients depending on their level of baseline risk factors and their clinical course during treatment. Lavender boxes represent diagnostic tests. BNP, brain natriuretic peptide; CRP, C reactive protein; CRS, cytokine release syndrome; CV, cardiovascular; IL-6, interleukin-6; IFN, interferon; TNF, tumour necrosis factor. Created with BioRender.com.

Corticosteroids are used in severe, refractory CRS. Corticosteroids abrogate the inflammatory cascade, interfering with T-cell function and inducing T-cell apoptosis,[w2] but do not alter clinical response to therapy.[w3] Further research is needed to improve cardiovascular outcomes and monitoring protocols during and following CAR T-cell therapy, particularly in high-risk patients.

BISPECIFIC T CELL ENGAGER THERAPY

Bispecific T cell engager (BiTE) molecules link two single-chain variable fragments targeting T cell and tumour cell antigens to bring them into close physical proximity (figure 2).[w4] Binding and colocation cause T cell activation and cytokine release. Blinatumomab, targeting CD3 and CD19, was the first FDA-approved BiTE agent in 2017 for B cell precursor ALL.[w5] Although cardiovascular effects of BiTE therapy have not been specifically studied, blinatumomab causes CRS with likely similar cardiovascular effects as in CAR T-cell therapy. In the TOWER trial investigating blinatumomab, CRS and ACS occurred in 2.6% and 2.2% of patients, respectively.[w6] However, a real-world study of blinatumomab showed grade 3–4 CRS in 19% of patients.[w7] Ongoing surveillance for adverse cardiovascular effects is warranted for this evolving immunotherapy.

CONCLUSION

Immunotherapy has emerged as an important and diverse class of treatments for advanced malignancies; with improved survival rates, both use and duration of treatment has increased significantly over the past decade. For FDA-approved indications alone, the percentage of patients with cancer eligible for ICIs increased from 1.5% in 2011 to 42.6% in 2018.[3] Although uncommon, myocarditis is a significant and potentially severe complication of immunotherapy. Like recent findings linking these agents to accelerated atherosclerosis, such therapies have the potential for more insidious, long-term effects that are only starting to be recognised. With CAR T-cell and BiTE therapy, the overlapping and detrimental effects of CRS on the cardiovascular system require further mechanistic study to develop effective diagnostic and treatment strategies. International multicentre collaborations are needed to identify high-risk individuals, develop monitoring guidelines and optimise treatment strategies to improve the care of patients with immunotherapy-associated cardiotoxicities for current and future therapies.

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REFERENCES

1 Zaha VG, Meijers WC, Moslehi J. Cardio-Immuno-Oncology. *Circulation* 2020;141:87–9.
2 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. *JCO* 2018;36:1714–68.
3 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020;70:7–30.
4 Hu J-R, Florido R, Lipson EJ, *et al*. Cardiovascular toxicities associated with immune checkpoint inhibitors. *Cardiovasc Res* 2019;115:854–68.
5 Tajiri K, Ieda M. Cardiac complications in immune checkpoint inhibition therapy. *Front Cardiovasc Med* 2019;6:3.
6 Khunger A, Battel L, Wadhawan A, *et al*. New insights into mechanisms of immune checkpoint inhibitor-induced cardiovascular toxicity. *Curr Oncol Rep* 2020;22:65.
7 D'Souza M, Nielsen D, Svane IM, *et al*. The risk of cardiac events in patients receiving immune checkpoint inhibitors: a nationwide Danish study. *Eur Heart J* 2020. doi:10.1093/eurheartj/ehaa884. [Epub ahead of print: 09 Dec 2020].
8 Michot JM, Bigenwald C, Champiat S, *et al*. Immune-Related adverse events with immune checkpoint blockade: a comprehensive review. *Eur J Cancer* 2016;54:139–48.
9 Mahmood SS, Fradley MG, Cohen JV, *et al*. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol* 2018;71:1755–64.
10 Moslehi JJ, Salem J-E, Sosman JA, *et al*. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. *Lancet* 2018;391:933.
11 Salem J-E, Manouchehri A, Moey M, *et al*. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. *Lancet Oncol* 2018;19:1579–89.
12 Escudier M, Cautela J, Malissen N, *et al*. Clinical features, management, and outcomes of immune checkpoint Inhibitor-Related cardiotoxicity. *Circulation* 2017;136:2085–7.
13 Oren O, Yang EH, Molina JR, *et al*. Cardiovascular health and outcomes in cancer patients receiving immune checkpoint inhibitors. *Am J Cardiol* 2020;125:1920–6.
14 Johnson DB, Balko JM, Compton ML, *et al*. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med* 2016;375:1749–55.
15 Herrmann J. Adverse cardiac effects of cancer therapies: cardiotoxicity and arrhythmia. *Nat Rev Cardiol* 2020;17:474–502.
16 Drobni ZD, Alvi RM, Taron J, *et al*. Association between immune checkpoint inhibitors with cardiovascular events and atherosclerotic plaque. *Circulation* 2020;142:2299–311.
17 Guha A, Al-Kindi S, Jain P, *et al*. Association between myocarditis and other immune-related adverse events secondary to immune checkpoint inhibitor use. *Int J Cancer* 2020;147:1753–4.
18 Awadalla M, Mahmood SS, Groarke JD, *et al*. Global longitudinal strain and cardiac events in patients with immune checkpoint Inhibitor-Related myocarditis. *J Am Coll Cardiol* 2020;75:467–78.
19 Goitein O, Matetzky S, Beinart R, *et al*. Acute myocarditis: noninvasive evaluation with cardiac MRI and transthoracic echocardiography. *AJR Am J Roentgenol* 2009;192:254–8.
20 Zhang L, Awadalla M, Mahmood SS, *et al*. Cardiovascular magnetic resonance in immune checkpoint inhibitor-associated myocarditis. *Eur Heart J* 2020;41:ehaa051
21 Dolladille C, Ederhy S, Sassier M, *et al*. Immune checkpoint inhibitor rechallenge after immune-related adverse events in patients with cancer. *JAMA Oncol* 2020;6:865–71.
22 Zhang L, Zlotoff DA, Awadalla M, *et al*. Major adverse cardiovascular events and the timing and dose of corticosteroids in immune checkpoint inhibitor-associated myocarditis. *Circulation* 2020;141:2031–4.
23 Cautela J, Zeriouh S, Gaubert M, *et al*. Intensified immunosuppressive therapy in patients with immune checkpoint inhibitor-induced myocarditis. *J Immunother Cancer* 2020;8:e001887.
24 Hu Y-B, Zhang Q, Li H-J, *et al*. Evaluation of rare but severe immune related adverse effects in PD-1 and PD-L1 inhibitors in non-small cell lung cancer: a meta-analysis. *Transl Lung Cancer Res* 2017;6:S8–20.
25 Poels K, Van Leent MMT, Boutros C. Immune checkpoint inhibitor therapy aggravates T Cell–Driven plaque inflammation in atherosclerosis. *JACC: CardioOncology* 2020;2:599–610.
26 Fernandez DM, Rahman AH, Fernandez NF, *et al*. Single-Cell immune landscape of human atherosclerotic plaques. *Nat Med* 2019;25:1576–88.

27 Kondapalli L, Bottinor W, Lenneman C. By releasing the brakes with immunotherapy, are we accelerating atherosclerosis? *Circulation* 2020;142:2312–5.
28 Canale ML, Camerini A, Casolo G, *et al*. Incidence of pericardial effusion in patients with advanced non-small cell lung cancer receiving immunotherapy. *Adv Ther* 2020;37:3178–84.
29 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;34:1059–68.
30 Neelapu SS, Tummala S, Kebriaei P, *et al*. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol* 2018;15:47–62.
31 Martinez M, Moon EK. Car T cells for solid tumors: new strategies for finding, infiltrating, and surviving in the tumor microenvironment. *Front Immunol* 2019;10:128.
32 Singh AK, McGuirk JP. Car T cells: continuation in a revolution of immunotherapy. *Lancet Oncol* 2020;21:e168–78.
33 Frey N, Porter D. Cytokine release syndrome with chimeric antigen receptor T cell therapy. *Biol Blood Marrow Transplant* 2019;25:e123–7.
34 Oved JH, Barrett DM, Teachey DT. Cellular therapy: immune-related complications. *Immunol Rev* 2019;290:114–26.
35 Leick MB, Maus MV. Toxicities associated with immunotherapies for hematologic malignancies. *Best Pract Res Clin Haematol* 2018;31:158–65.
36 Asnani A. Cardiotoxicity of immunotherapy: incidence, diagnosis, and management. *Curr Oncol Rep* 2018;20:44.
37 Hunter CA, Jones SA. Il-6 as a keystone cytokine in health and disease. *Nat Immunol* 2015;16:448–57.
38 Qu D, Liu J, Lau CW, *et al*. Il-6 in diabetes and cardiovascular complications. *Br J Pharmacol* 2014;171:3595–603.
39 Alvi RM, Frigault MJ, Fradley MG, *et al*. Cardiovascular events among adults treated with chimeric antigen receptor T-cells (CAR-T). *J Am Coll Cardiol* 2019;74:3099–108.
40 Locke FL, Ghobadi A, Jacobson CA, *et al*. Long-Term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol* 2019;20:31–42.
41 Guha A, Addison D, Jain P, *et al*. Cardiovascular events associated with chimeric antigen receptor T cell therapy: cross-sectional FDA adverse events reporting system analysis. *Biol Blood Marrow Transplant* 2020;26:2211–6.
42 Lee DW, Kochenderfer JN, Stetler-Stevenson M, *et al*. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. *The Lancet* 2015;385:517–28.
43 Lefebvre B, Kang Y, Smith AM, *et al*. Cardiovascular Effects of CAR T Cell Therapy. *JACC CardioOncol* 2020;2:193–203.
44 Ganatra S, Redd R, Hayek SS, *et al*. Chimeric antigen receptor T-cell Therapy-Associated cardiomyopathy in patients with refractory or relapsed non-Hodgkin lymphoma. *Circulation* 2020;142:1687–90.
45 Shalabi H, Sachdev V, Kulshreshtha A, *et al*. Impact of cytokine release syndrome on cardiac function following CD19 CAR-T cell therapy in children and young adults with hematological malignancies. *J Immunother Cancer* 2020;8:e001159.
46 Burstein DS, Maude S, Grupp S, *et al*. Cardiac profile of chimeric antigen receptor T cell therapy in children: a single-institution experience. *Biol Blood Marrow Transplant* 2018;24:1590–5.
47 Kanelidis AJ, Raikhelkar J, Kim G, *et al*. CardioMEMS-Guided CAR T cell therapy for lymphoma in a patient with anthracycline-induced cardiomyopathy. *JACC CardioOncol* 2020;2:515–8.
48 Le RQ, Li L, Yuan W, *et al*. Fda approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. *Oncologist* 2018;23:943–7.
49 Singh N, Hofmann TJ, Gershenson Z, *et al*. Monocyte lineage-derived IL-6 does not affect chimeric antigen receptor T-cell function. *Cytotherapy* 2017;19:867–80.
50 Gardner RA, Ceppi F, Rivers J, *et al*. Preemptive mitigation of CD19 CAR T-cell cytokine release syndrome without attenuation of antileukemic efficacy. *Blood* 2019;134:2149–58.

References

w1. Maude SL, Teachey DT, Porter DL, et al. CD19-targeted chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. *Blood* 2015;**125**:4017-23.
w2. Herold MJ, McPherson KG, Reichardt HM. Glucocorticoids in T cell apoptosis and function. *Cellular and Molecular Life Sciences* 2006;**63**:60-72.
w3. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *New England Journal of Medicine* 2017;**377**:2531-44.
w4. Huehls AM, Coupet TA, Sentman CL. Bispecific T-cell engagers for cancer immunotherapy. *Immunology & Cell Biology* 2015;**93**:290-6.
w5. FDA Approval letter for blinatumomab.
https://wwwaccessdatafdagov/drugsatfda_docs/nda/2014/125557Orig1s000Approvpdf.
W6. Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *New England Journal of Medicine* 2017;**376**:836-47.
w7. Apel A, Ofran Y, Wolach O, et al. Safety and efficacy of blinatumomab: a real world data. *Annals of Hematology* 2020;**99**:835-8.
w8. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *New England Journal of Medicine* 2018;**378**:439-48.