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Cardiovascular Toxicities Associated with Cancer Immunotherapies

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Abstract

Purpose of review—We review the cardiovascular toxicities associated with cancer immune therapies and discuss the cardiac manifestations, potential mechanisms, and management strategies.

Recent findings—The recent advances in cancer immune therapy with immune checkpoint inhibitors and adoptive cell transfer have improved clinical outcomes in numerous cancers. The rising use of cancer immune therapy will lead to a higher incidence in immune-related adverse events. Recent studies have highlighted several reports of severe cases of acute cardiotoxic events with immune therapy including fulminant myocarditis. We believe that immune-mediated myocarditis is a driving mechanism behind these cardiovascular toxicities and requires vigilant screening and prompt management with corticosteroids and immune-modulating drugs, especially with combination immune therapies.

Summary—While the incidence of serious cardiovascular toxicities with immune therapy appears low, these can be life-threatening especially when manifesting as acute immune-mediated

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Compliance with Ethical Standards

Conflict of Interest Daniel Y. Wang, Gosife Donald Okoye, and Thomas G. Neilan declare that they have no conflict of interest. Douglas B. Johnson reports being on the advisory board for BMS and Genoptix, and grants from Incyte.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

myocarditis. Further collaborative studies are needed to effectively identify, characterize, and manage these events.

Keywords

Immune therapy; Checkpoint inhibitors; PD-1; CTLA-4; Cardiovascular toxicities; Myocarditis

Introduction

Recent advances in immune therapy have revolutionized cancer treatment paradigms leading to substantially improved clinical outcomes for cancers with traditionally poor prognosis. Immune therapies have been approved as first-line treatments for metastatic melanoma and non-small cell lung cancer, and as second-line therapy for Hodgkin's lymphoma, head and neck, bladder, and renal cell cancers (see Table 1). In general, these novel therapies modulate and overcome cancer cell specific immune evasion. Distinct therapeutic classes include immune checkpoint inhibitors, chimeric antigen receptor (CAR) T cell therapy, and cancer vaccines. Activated T cell responses, however, may be non-specific to cancer cells and can target normal tissue leading to immune-related adverse events (irAEs). These toxicities most often affect the colon, lung, endocrine glands, skin, and liver, and are usually rapidly reversible with high-dose corticosteroids. However, limited recent reports of a spectrum of myocardial toxicities ranging from mild to fulminant among patients on immune checkpoint inhibitors suggest that immune-related cardiac effects may also be clinically relevant [10••]. With an expected increase in the usage of immune therapies along with prolonged survival, we expect a concomitant rise in the incidence of these cardiac side effects. Therefore, both oncologists and cardiologists will need to be vigilant for immune-mediated cardiotoxicity, and early detection strategies should be explored. In this review, we explore cancer immune therapy in the context of their cardiac-related adverse events and highlight potential mechanism and management.

Historical Perspective

While the field of cancer immune therapy has flourished in the last decade, it actually began over a century ago with observations by Dr. William B. Coley of spontaneous tumor regression in patients after infections, suggesting a connection with the immune system and cancer development. These findings culminated in the first immune therapy known as "Coley's toxins," a mixture of heat-killed cultures of *Streptococcus pyogenes* and *Serratia marcescens*, that was used as an injectable treatment for sarcoma patients [13]. While the use of this treatment was met with much skepticism during Dr. Coley's time and never gained widespread acceptance, our further understanding of cancer immunology has propelled the contemporary field of immune therapy into the forefront of modern cancer treatments.

Early Cytokine Immune Therapy

The earliest effective cancer immune therapies were cytokines in the form of high-dose interleukin-2 (IL-2) and interferon-alpha (IFN- α). IL-2 was identified as a T cell growth factor in 1976 and recombinant forms of IL-2 showed pre-clinical anti-tumor activity in

melanoma murine models [14]. Clinical trials led to high-dose IL-2 becoming the first FDA-approved immune therapy for renal cell carcinoma in 1992 and metastatic melanoma in 1998 [15]. Similarly, IFN- α therapy has exhibited anti-tumor effects in melanoma mouse models, presumably mediated through immune activation. IFN- α is currently approved for use in the adjuvant setting for high-risk, resected melanoma, and in combination with bevacizumab for advanced renal cell carcinoma.

Early clinical data revealed a high incidence of cardiovascular effects from high-dose IL-2 and IFN- α therapy ranging from severe hypotension (up to 65%), arrhythmias (up to 57%), and ischemia (up to 20%) [1, 2, 16, 17]. With high-dose IL-2 therapy, vascular leak syndrome and a myriad of cardiovascular complications resulting in hypotension and tachycardia can occur [16, 17]. Up to 10% of patients may have arrhythmias including atrial fibrillation, which can contribute to the hypotension. Rare cases of myocardial infarction or myocarditis have also been reported [1]. These findings highlight the substantial toxicities of IL-2, which is reserved for patients with excellent performance status and preserved organ function. While most of these changes result from cardiac stress and hemodynamic changes, pre-clinical studies suggest that IL-2 activated lymphocytes may also directly damage endothelial cells and cardiac myocytes [18].

In IFN- α therapy, cardiac adverse reports have been reported but are less frequent as compared to high-dose IL-2. Moreover, in eight phase 1 trials involving IFN- α , no significant cardiotoxic adverse events were reported. In one small case series of 44 cancer patients treated with interferon, cardiotoxic effects ranged from arrhythmias (25/44), dilated cardiomyopathy (5/44), and ischemic heart disease manifested in MI (9/44) and sudden death (2/44) [2]. No relationship between cardiotoxic effects and dosage could be found. Most of these effects were ultimately reversible with cessation of treatment.

Immune Checkpoint Inhibitors

Ipilimumab (Anti-CTLA-4 Therapy)

The concept of immune checkpoints as potential targets for cancer treatment was introduced in the 1990s. Initial understanding of T cell biology revolved around the concept of a two-signal model which required T cell receptor (TCR) recognition and engagement by major histocompatibility complex (MHC) bound antigens (“signal 1”) as well as engagement by co-stimulatory molecules, CD28 and B7 (“signal 2”), for an effective immune response (Fig. 1) [19]. However, the discovery that CTLA-4, the first immune checkpoint identified, could directly antagonize T cell responses by opposing this CD28 co-stimulation shifted the focus from enhancing anti-tumor immune responses to removing inhibitors of T cell function [20–22]. Pre-clinical studies revealed that inhibition of CTLA-4 could enhance anti-tumor responses leading to the development and approval of ipilimumab, a monoclonal antibody to CTLA-4 [23, 24]. With its landmark approval, ipilimumab represented the first drug to demonstrate a survival benefit in metastatic melanoma, a uniformly deadly cancer with a historical long-term survival of less than 10% [25]. Since the first clinical trials, 5–10-year follow-up data with ipilimumab has shown a doubling of that long-term survival to approximately 21% [26]. The clinical trial experience with ipilimumab revealed a distinct class of toxicities, termed immune-related adverse events (irAEs), including colitis,

hepatitis, endocrinopathies, and dermatitis. While these irAEs were frequent and clinically significant leading to reversible morbidity with courses of high-dose corticosteroids, they rarely led to mortality (~1%) [27•].

Cardiac adverse events were uncommon in the initial studies of ipilimumab. One patient treated with single-agent high-dose ipilimumab (10 mg/kg) developed fatal myocarditis [28•]. There has been a range of notable cardiac-related side effects reported post-marketing. A multicenter retrospective study ($n=752$) revealed one patient with fatal concurrent myocardial fibrosis and hepatitis who received ipilimumab for metastatic melanoma[3]. Other case reports revealed a case of reversible left ventricular dysfunction, one case of late onset pericardial effusion, constrictive pericarditis with biopsy-proven pericarditis, a case of cardiac tamponade which responded to high-dose corticosteroids, and one case of Takotsubo cardiomyopathy with apical ballooning on echocardiography (Table 1) [4–6].

Anti-PD-1 Therapy

After the clinical success of anti-CTLA-4 therapy with ipilimumab in melanoma, intensive research efforts identified other immune checkpoints. Two such molecules were programmed death 1 (PD-1) and its ligand, PD-L1, which were initially discovered to inhibit T cell proliferation in murine models [29]. Similar to the CTLA-4/B7 interaction, binding of PD-1, expressed on activated T cells, to PD-L1, expressed on cancer or stromal cells, leads to T cell exhaustion. However, unlike CTLA-4 and B7, which interact at the level of the lymph nodes between T cell and antigen presenting cells (APCs), PD-1 and PD-L1 interact at the level of the tumor microenvironment (Fig. 2). Blockade of PD-1 was shown to reverse the “exhausted” T cell phenotype and produce anti-tumor responses in murine models [30]. Subsequent clinical trials with nivolumab and pembrolizumab, both anti-PD-1 monoclonal antibodies, successfully demonstrated a clinical benefit and improved overall survival compared with conventional therapies in various tumor types including melanoma, renal cell, and non-small cell lung cancer [31–36].

From these clinical trials of anti-PD-1, there have been several reports of clinically significant cardiotoxic effects, including cases of pericarditis, hypertension, atrial and ventricular arrhythmias as well as a case of fatal case of a myocardial infarction [32, 37–39]. Case reports and case series have confirmed these findings outside the clinical trial setting [7, 8] (Table 1). One case series of 496 melanoma patients treated with anti-PD-1 therapy revealed a 1% incidence of cardiac disorders which ranged from a case of fatal ventricular arrhythmia due to myocarditis, various arrhythmias (atrial flutter, ventricular arrhythmia), asystole due to cardiomyopathy, hypertension, myocarditis, and left ventricular dysfunction [9]. These events occurred at various times ranging from 2 to 17 weeks after treatment; the non-fatal cases improved or resolved with treatment with corticosteroids or supportive medications. Other case reports include autoimmune myocarditis with varying degrees of severity, from steroid-reversible disease to fulminant myocarditis [40, 41]. At this time, there does not appear to be any known association with the particular anti-PD-1 drug (pembrolizumab or nivolumab), tumor response, tumor type, or specific clinical features

that predispose these patients to these serious cardiac adverse events. Ultimately, clinically significant cardiac events are infrequent with single-agent immune checkpoint inhibition.

Combination Immune Therapy

As the mechanisms of anti-CTLA and anti-PD-1 therapy are distinct, pre-clinical models supported the combination to synergistically improve anti-tumor responses [42]. The first combination immune therapies involved ipilimumab and nivolumab in melanoma. These trials demonstrated a significant improvement in clinical responses as compared to single-agent therapy (58% in the combination, 44% in nivolumab alone, and 19% in ipilimumab alone) [28•]. However, this efficacy was juxtaposed against higher frequency of serious immune-related side effects (55% in the combination, 16% in nivolumab alone, and 27% in ipilimumab alone). There was at least one case of fatal ventricular arrhythmia in the combination arm of an earlier phase II study of ipilimumab and nivolumab [43]. In general, these side effects were generally reversible with cessation of treatment and corticosteroids.

Emerging data suggest that fulminant myocarditis can result from combination of ipilimumab and nivolumab treatment. Two patients with metastatic melanoma developed myositis with rhabdomyolysis, early progressive and refractory cardiac electrical instability, and myocarditis with a robust presence of T cell and macrophage infiltrates [10••]. Both patients died despite prompt high-dose corticosteroids use and, in one case, treatment with infliximab. T cell infiltrates were only seen in striated muscle (both skeletal muscle and myocardium) and in the tumor metastases, but not in other tissue types. Characterization of the TCR revealed indications of shared high-frequency TCRs targeting tumor, heart and skeletal muscle suggesting possible T cell cross-reactivity targeting a common antigen.

Another case report identified LV dysfunction in a patient treated with combination nivolumab and ipilimumab [11]. The patient presented with heart failure symptoms with a significant reduction in LVEF from 50 to 15% after three infusions of the combination immune therapy. Biopsy confirmed the diagnosis of immune-mediated myocarditis. However, his LVEF improved to 40% after 2 months of high-dose corticosteroids and medical treatment of his heart failure.

A review from a large safety database from the manufacturer of ipilimumab and nivolumab, Bristol-Myers Squibb, revealed that myocarditis occurred more frequently (0.27 vs. 0.06%) and severely (0.17 vs <0.01% fatal cases) with combination therapy with ipilimumab and nivolumab than with nivolumab monotherapy [10••]. Of note, these data were collected retrospectively from a single manufacturer where no prospective standardized screening of cardiac issues was performed, so this likely represents an underrepresentation of the true incidence. Further efforts on pharmacovigilance should be promoted with screening methods detailed below. In addition, as numerous companies have developed checkpoint inhibitor, these data need to be assessed with other drugs.

Pathophysiology of Immune Checkpoint Inhibitor-Induced Cardiovascular Events

The underlying pathophysiology for these immune-mediated cardiovascular events is unknown, but the development of myocarditis is now an established side effect related to checkpoint inhibition. Pre-clinical data suggest that both CTLA-4 and PD-1 play critical

roles regulating immune homeostasis in the myocardium. CTLA-4^{-/-} mice develop severe autoimmune myocarditis mediated by CD8⁺ T cells, which is rapidly fatal after birth [22, 44]. PD-1-deficient mice are also predisposed to spontaneous myocarditis, likely due to cytotoxic activity of effector T cells against cardiac myocytes [45–49]. Interestingly, in BALB/c genetic background, PD-1^{-/-} mice develop spontaneous dilated cardiomyopathy due to autoantibodies to cardiac troponin, which suggests a possible antibody-mediated etiology in some genetic backgrounds [48, 49]. PD-1 deficiency in the autoimmune MRL-Fas^{lpr} mice, a model for lupus, led to the development of fatal myocarditis with T cell and macrophage infiltration into the myocardium with evidence of heart-specific autoantibodies [46, 47]. In our own cases, we did not observe any evidence of antibody deposition, although these diverse mechanisms suggest that distinct immune processes may be triggered by immune checkpoint inhibitors. Ultimately, further studies are needed to clarify the pathophysiology of immune checkpoint inhibitors, as single agents or in combination therapy, in relation to myocarditis.

Adoptive Cell Transfer

Another novel approach to leverage immunity for cancer treatment involves adoptive cell transfer (ACT), where a patient's own T cells are engineered to specifically target tumor cells. The principles of ACT are based on initial studies where pre-existing tumor infiltrating lymphocytes (TILs) were collected, expanded, and then re-introduced into a patient immune microenvironment concurrently with systemic IL-2. Through these methods, ACT with autologous TILs has been shown to achieve a response rate of 53% with complete responses in 24% in 101 patients with melanoma [50]. However, the success with autologous TILs has been largely limited to melanoma as obtaining tumor-reactive TILs is difficult in other cancer types; furthermore, responses in other solid tumors have rarely been observed [51]. Further advances in ACT with genetic engineering of modified TCRs or CAR into T cells have expanded the use of ACT into several other cancer types. Today, intensive research efforts are underway to expand this technology.

Genetically modified TCRs allow for higher affinity towards tumor antigens that are normally not well-engaged by wild-type TCRs. These tumor-associated antigens are often produced from cancer-germline (or cancer/testis) genes that are restrictively expressed in immunologically protected germline cells of the testes and trophoblasts, but become abnormally expressed in various cancers. Common cancer-germline antigens include NYESO-1 and MAGE-A3, which are highly expressed on various cancers [52,53]. In early trials, there was a response rate of 45 and 67% in melanoma and synovial cell sarcoma patients, respectively. The majority of adverse events with treatment are related to preparative therapy or IL-2, but there has been occasional evidence of cross-reactivity towards other normal cells with fatal consequences. In one case series, the use of genetically modified TCR against MAGE-A3, another cancer-germline antigen, led to development of fatal cardiogenic shock in two patients [12]. Mechanistic studies revealed no evidence of MAGE-A3 expression on cardiac tissue, but significant myocardial damage with T cell infiltration which targeted titin, an unrelated myocardial protein [54]. A similar case was reported with modified MART-1 TCR in a metastatic melanoma patient who experienced irreversible neurologic damage and cardiac arrest 6 days after T cell infusion

[55]. While infused T cells were found in cardiac tissue, no cross-reactivity was seen with cardiomyocytes suggesting an alternative mechanism likely related to a cytokine release syndrome.

CAR T cell therapy has shown the greatest benefit in hematopoietic malignancies such as B cell acute lymphoblastic leukemia (B-ALL) where CD19, a ubiquitously expressed antigen on malignant cells and differentiated B cells, has been targeted. In heavily pre-treated B-ALL patients, 70–90% of patients experience complete responses to CAR T cell therapy, where traditionally <10% of patients survive beyond 5 years [56, 57]. Like other novel immune therapies, CAR T cell therapy produces its own unique toxicity profile. In particular, cytokine release syndrome (CRS), a systemic inflammatory response that correlates with the in vivo activation and proliferation of CAR T cells, has been a hallmark adverse event of this therapy. Clinically, cardiovascular manifestations of CRS include hypotension, arrhythmias (including tachycardia), decreased left ventricular systolic ejection fraction, troponinemia, and QT prolongation [58–60]. The pathophysiology for cardiac dysfunction is unclear, but resembles cardiomyopathy seen in stress and sepsis. In one dramatic case of cardiac dysfunction, a patient treated with CAR T cell therapy experienced cardiac arrest 7 days after infusion with subsequent reduction in LVEF to <25% from a normal baseline [59]. While the onset of these cardiac side effects can be rapid and severe, they are typically reversible.

Review of Myocarditis

As immune-mediated myocarditis has been a defining feature of cardiotoxicity in immune therapy, it will be critical to fully characterize the nature of myocarditis to determine preventive and treatment strategies. In general, myocarditis is an inflammatory disease of the heart muscle or myocardium. Myocarditis can have many etiologies and has a highly variable presentation that ranges from the incidental findings of an abnormal cardiac biomarker to clinical manifestations that include fatigue, chest pain, heart failure, arrhythmias, heart block, cardiogenic shock, and even sudden death. The range of presentations likely reflects the variability of disease involvement (focal or diffuse) and severity (mild to severe).

Because of the variability of clinical presentation, there are no specific findings for myocarditis and myocarditis is often a diagnosis of exclusion. When myocarditis is suspected, a range of tests from electrocardiogram (EKG), biomarkers, chest radiology, cardiac imaging, and cardiac sampling may be suggested. An EKG is cheap and widely available but the EKG findings are non-specific and can be normal even in significant myocarditis. Cardiac troponin I and troponin T are cardiac-specific makers of cardiomyocyte damage (including in cases of ongoing myocardial inflammation as in myocarditis). Both EKG and troponin measurements are recommended as initial diagnostic tests in cases of suspected myocarditis [61, 62]. Other cardiac biomarkers including BNP or NT-proBNP are markers of myocardial stretch but may be normal in milder forms of myocarditis.

Definitive diagnosis is generally based upon an invasive endomyocardial biopsy (EMB) in which histology reveals inflammatory infiltrates in the myocardium not typical of

ischemic damage from coronary artery disease [63]. Cardiovascular magnetic resonance (CMR) imaging can serve as the imaging test of choice and may be used for diagnosis. Specifically, CMR can be used to provide standard measures of cardiac size and function; however, it is the unique tissue characterization provided by CMR especially after the administration of gadolinium-based contrast agents that facilitates the noninvasive diagnosis of myocarditis. Specifically, myocarditis is associated with increased capillary permeability, increased myocardial water content, and cellular necrosis. These pathognomic features are detected on CMR by measuring T1, T2 and detecting late gadolinium enhancement in the cardiac muscle. A combination of these CMR criteria has a sensitivity of 76% and specificity of 96% for myocarditis [64, 65]. Therefore, using current consensus criteria a diagnosis is based heavily on an integrated assessment of clinical, imaging, and laboratory findings and is generally a diagnosis of exclusion.

Management of Immune-Mediated Myocarditis for Oncologist and Cardiologists

With our understanding of myocarditis, the monitoring and screening for immune-mediated myocarditis and cardiovascular toxicities will prove to be challenging. However, given the recent reports of fatal, fulminant myocarditis in combination immune therapies, ongoing clinical trials involving combination immune therapies have begun to include further cardiovascular screening such as baseline EKGs to address screening for these cardiovascular side effects. Additionally, it is the practice at some institutions to obtain not only baseline EKGs, but also baseline and weekly cardiac biomarkers such as troponin I in the first few weeks of patients treated with combination immune therapies such as ipilimumab and nivolumab. At this time, there are no specific guidelines regarding exclusion criteria related to prior cardiovascular health.

As the use of immune therapies continues to rise and expand in oncology, practicing clinicians must be vigilant for immune-mediated myocarditis. Symptoms such as chest pain, dyspnea, palpitation, and peripheral edema should lead to further cardiac investigation. Prompt evaluation for myocarditis including EKG and cardiac biomarkers should be initiated. If the initial findings are highly suspicious for immune-related myocarditis, a prompt referral to a cardiologist should be made with escalation to noninvasive imaging such as echocardiogram and CMR. An EMB should be considered if indicated as above. Other etiologies of these symptoms such as immune-related pneumonitis and pulmonary embolism or acute coronary syndromes should also be evaluated concomitantly.

While there currently are no consensus guidelines for management of immune-mediated myocarditis in the setting of cancer immune therapy, we advocate the early screening of patients receiving combination immune therapy with cardiac troponins given the variable presentation of this potentially fatal side effect (see Fig. 3). If there is an asymptomatic elevation in cardiac troponins, holding immune therapy and monitoring the cardiac troponin will inform clinicians on the nature of the elevation. Furthermore, our experience has shown that once a diagnosis of immune-mediated myocarditis from immune therapy is highly suspected or made clinically, treatment should be prompt and based on the severity of the

presentation. As some patients may present with severe, fulminant disease in acute heart failure or other cardiovascular compromise, immunosuppressive therapy in the form of high-dose glucocorticoids should be rapidly initiated (i.e., methylprednisolone 1000 mg per day for 3 days followed by prednisone 1 mg/kg). Additional immunosuppressive therapy is generally warranted in these cases as has been suggested for other severe irAEs. While infliximab is a familiar choice as an adjunctive immunosuppressant for other immune-related adverse events (pneumonitis, colitis), it has been associated with heart failure and is contraindicated at higher doses than 5 mg/kg in patients with moderate or severe heart failure (New York Heart Association class III/IV) [66]. In the presence of moderate to severe heart failure, we would consider instead using anti-thymocyte globulin or tacrolimus (given their efficacy in cardiac allograft rejection) in addition to high-dose steroids. Concurrently, standard heart failure and anti-arrhythmic management should also be initiated. Ultimately, the optimal treatment algorithm for this entity has yet to be defined.

For adoptive cell transfer and specifically for CAR T cell therapy, the use of tocilizumab, an anti-interleukin-6 receptor antibody, has significantly reduced the severity and incidence of CRS without affecting excellent clinical outcomes [58–60]. Originally approved for rheumatologic disorders, tocilizumab has not been FDA approved for CRS, but is widely used in managing this toxicity in CAR T cell therapy.

Future Directions

There are still many unknowns regarding the cardiac-related adverse events in cancer immune therapy. Pre-clinical and early clinical insights have helped to focus next steps in research and clinical care. First, a better estimation of the true incidence of these events are needed in both the clinical trial and post-marketing setting. This involves careful screening and monitoring protocols of patients receiving combination immunotherapy. Second, subclinical cardiac adverse events that occur on treatment may have lasting effects as these patients live longer. Third, further research must be focused on the acute management of these often, rapidly fatal cardiotoxic events. This will require a collaborative effort from cardiologist, oncologists, and immunologists to develop consensus guidelines that can control and reverse the havoc released on the myocardium by the immune system. Lastly, a better understanding of the pathophysiology that trigger these events and the general relationship between the immune system and myocardium is needed. This knowledge will help us more safely move into the new world of combination immune therapies.

Conclusion

As cancer immune therapy continues to improve clinical outcomes in patients, cardiac-related adverse events, especially immune-mediated myocarditis, remain a challenge to predict, diagnose, and treat. These cardiac events, while rare, may lead to significant morbidity and even mortality. Collaborative research efforts to manage these events will be critical moving forward.

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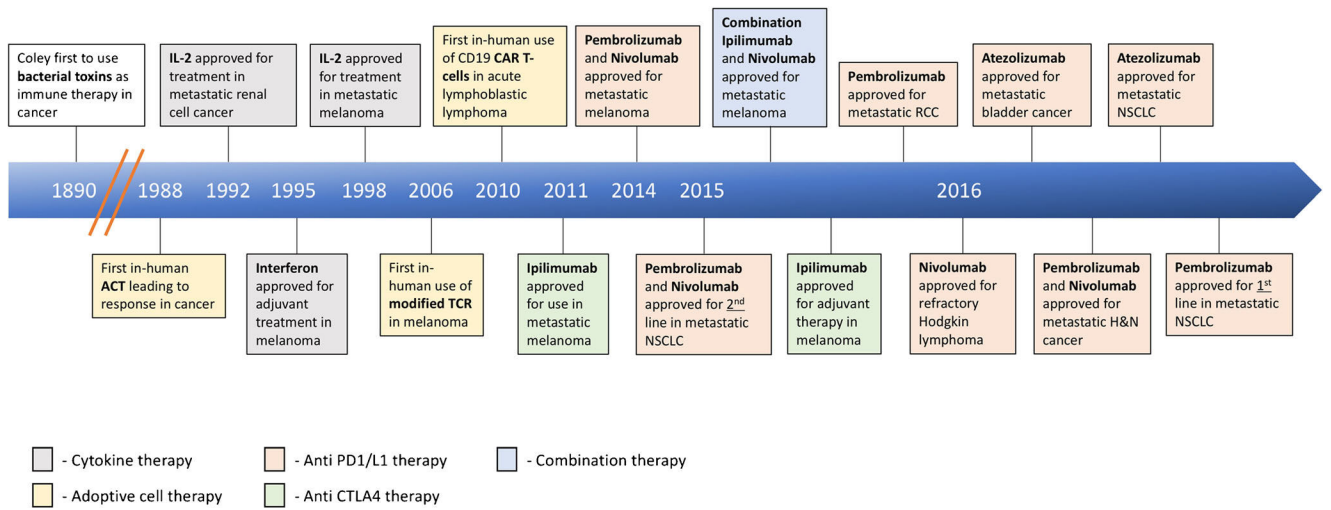


Fig. 1.
Timeline of breakthroughs in cancer immune therapy

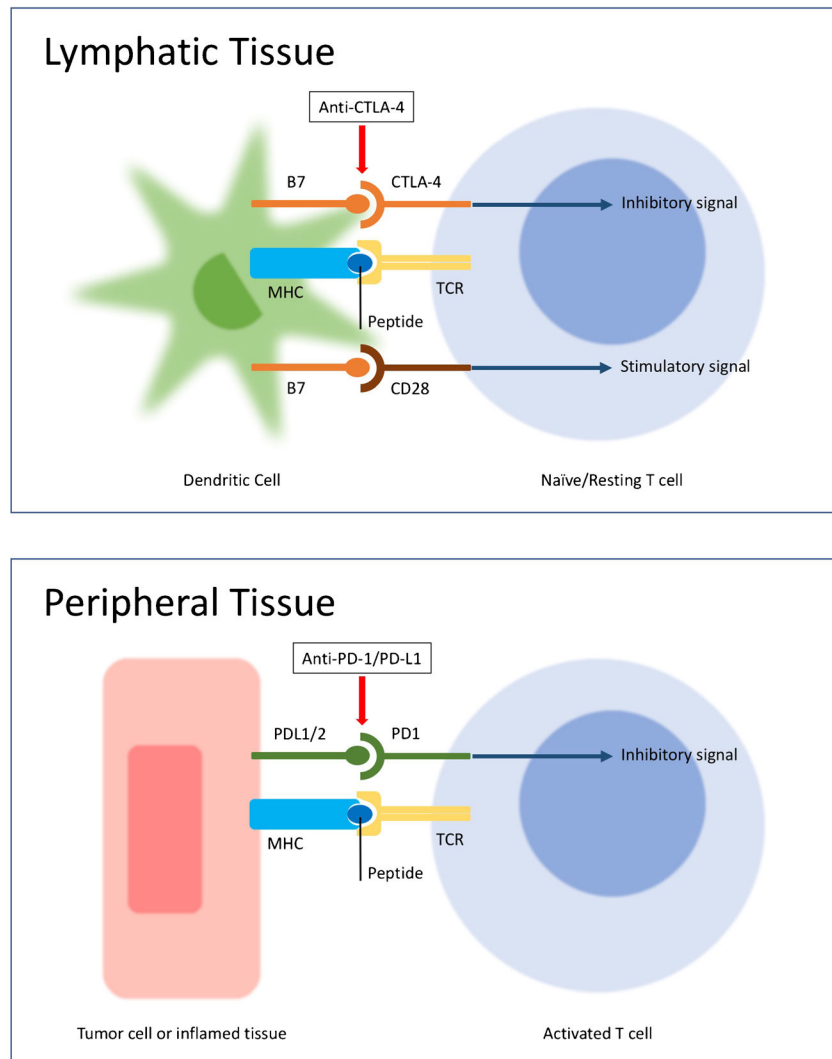


Fig. 2. Mechanism of checkpoint inhibition in **a** lymphatic tissue and **b** peripheral tissue

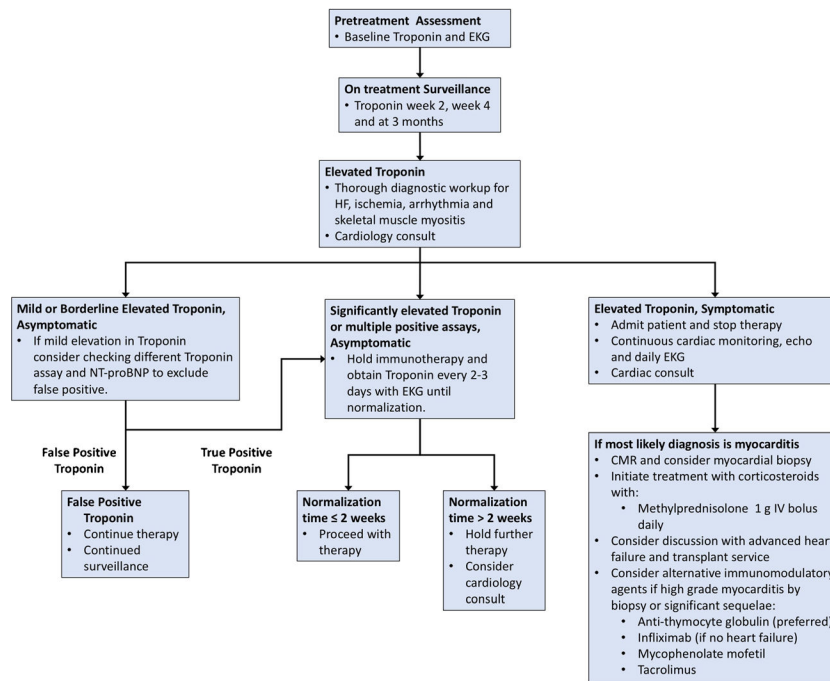


Fig. 3.
Proposed mechanism for management of immune-mediated myocarditis

Table 1
Summary of case reports and series of cardiovascular toxicities associated with cancer immune therapies

Ref	# of pts	Age/sex	Tumor type	Stage	Prior Tx	Cancer treatment	Onset ^a	Clinical presentation
[1]	8	22–67 (mean 41)/both	Melanoma/RCC	IV	N/A	IL-2	<= 4 days	Various
[2]	44	N/A/both	Various	IV		N/A	N/A	N/A
[3]	1	61/F	Melanoma	IV	MAGE-A3 vaccination, EFN-alpha, PRAME vaccination	Ipilimumab	16	N/A
[4]	1	60/M	Melanoma	IV	Adjuvant ipilimumab	Ipilimumab	18	Palpitations
[5]	1	59/M	Melanoma	IV	None	Ipilimumab	21	Chest pain and dyspnea
[6]	1	83/F	Melanoma (vaginal)	IV	None	Ipilimumab	12	Chest pain and dyspnea
[7]	1	69/F	Melanoma (choroidal)	IV	N/A	Nivolumab	8	General malaise and palpitations
[8]	1	73/F	Melanoma (uveal)	IV	Dacarbazine, ipilimumab	Pembrolizumab	15	Dyspnea
[9]	5	49–87/both	Melanoma	IV	Various	Nivolumab, pembrolizumab	2–17	N/A
[10••]	2	65/F	Melanoma	IV	N/A	Ipilimumab and nivolumab	2	atypical chest pain, dyspnea, and fatigue
		63/M	Melanoma	IV	N/A	Ipilimumab and nivolumab	2	Fatigue, myalgias
[11]	1	72/M	Melanoma	IV	N/A	Ipilimumab and nivolumab	6	Dyspnea, peripheral edema and anasarca
[12]	2	63/M	Melanoma	IV	Adjuvant EFN dendritic cell vaccine, ipilimumab	ACT with MAGE-A3 TCR	<1	Chills, nausea, abdominal pain then cardiopulmonary arrest
		57/M	Multiple myeloma	N/A	Lenalidomide/Dex, Bortezomib/ Dex, D-PACE (Dex, Cisplatin, Doxorubicin, Cyclophosphamide, etoposide)	ACT with MAGE-A3 TCR	<1	Hypotension, hypoxia, AMS

Ref	Cardiovascular side effects	Labs	Imaging	Histology	Intervention	Tumor response	Outcome of side effect	Notes
[1]	Hypotension (5), ischemia (2), atrial/	Normal to elevated	Non-obstructive and obstructive CAD,	Transmural myocardial necrosis,	N/A	N/A	Fatal	

Ref	# of pts	Age/sex	Tumor type	Stage	Prior Tx	Cancer treatment	Onset ^a	Clinical presentation
				non-infectious myocarditis				
[2]	ventricular arrhythmias (4), CKMB myocarditis (6) Atrial/ventricular arrhythmia (25), ischemia/MI (9), congestive heart failure (1), 1st degree AVB (2), cardiomyopathy (5), sudden death (2)	N/A	N/A	N/A	N/A	N/A	N/A	
[3]	Myocarditis	N/A	N/A	Myocardial fibrosis	N/A	PD	Fatal	Presented with concurrent immune-related hepatitis
[4]	Paroxysmal atrial fibrillation, left BBB, left ventricular dysfunction, ischemia	N/A	LVEF reduction from 55–60% to 40–45% with abnormal septal motion on echocardiogram, mildly decreased uptake in the anterior segment after stress on pharmacological stress test	N/A	Initiated on lisinopril and carvedilol	N/A	Resolved to normal LVEF after 5 months	Second ipilimumab treatment
[5]	Pericarditis, pericardial effusion	Normal troponin	Pericardial thickening and moderate pericardial effusion on CT	Acute fibrinous pericarditis without malignancy or microorganism	Pericardioecetosis and window, indomethacin, IV steroids to oral taper	N/A	Resolved	Concurrent adrenal insufficiency, hypothyroidism, colitis
[6]	Subacute “Takotsubo-like” cardiomyopathy, transient supraventricular/ventricular tachycardia	Elevated troponin (0.98 ng/ml) and ESR (65 mm/hr)	Akinetic apex on echocardiogram with preserved EF, non-obstructive CAD, focal FDG uptake in ballooned LV apex on PET-CT	N/A	Beta-blocker	N/A	Resolved	
[7]	Myocarditis	Positive rapid troponin, elevated CK and CKMB	Diffuse hypokinesis of the left ventricle, LVEF 30% on echocardiogram, normal coronary arteries on angiography	Infiltration of CD8+ T cells in myocardium	Oral steroid taper	SD	Return to normal EF	
[8]	Acute heart failure, myocarditis	Elevated BNP and troponin	LVEF of 30% with marked ventricular dyssynchrony on echocardiogram, no findings consistent with myocarditis or ischemia on cardiac MRI	Infiltration of CD8+ T cells in myocardium	Oral steroid taper, candesartan, bisoprolol, spironolactone, torsemide	SD	Resolved, EF returned to 52%	
[9]	Stable angina, sinus tachycardia, ventricular arrhythmia, asystolia, hypertension, atrial flutter, myocarditis,	N/A	N/A	N/A	V/PO steroids (1/1), metoprolol (1), antihypertensives (1)	PD (3), PR (1) N/A (1)	Resolved except for one death	

Ref	# of pts	Age/sex	Tumor type	Stage	Prior Tx	Cancer treatment	Onset ^a	Clinical presentation
[10••]	cardiomyopathy, LV systolic dysfunction Myocarditis, myositis, intraventricular conduction delay, complete heart block, refractory ventricular tachycardia Myocarditis, myositis, intraventricular conduction delay, complete heart block	Elevated CK, CKMB, and troponin Elevated CK, CKMB, and troponin	Preserved EF (73%) Low normal EF (50%)	Infiltration of T cells in myocardium, cardiac sinus, AV nodes, and skeletal muscle	IV steroids IV steroids, infliximab	N/A N/A	Fatal Fatal	Evidence of selective clonal T cell populations in the tumor and myocarditis, myositis, intraventricular skeletal muscle
[11]	Myocarditis and cardiomyopathy	N/A	LVEF reduction from 50% to 15% on echocardiogram, no evidence of ischemia on cardiac MRI or angiography	Infiltration of lymphocytes with fibrosis in myocardium	Oral steroid taper, ramipril, metoprolol, spironolactone, and furosemide	PR	EF improved to 40%	
[12]	Cardiopulmonary arrest due to acute myocardial infarction	Elevated troponin, CKMB, and cytokines	N/A	Autopsy revealed severe coronary disease and myocardial infarction, T cell infiltration of the myocardium with necrosis	None	N/A	Fatal	Concurrent neutropenic fever, anemia, and cytokine release syndrome
	Cardiogenic shock	Elevated troponin and cytokines	N/A	Cardiac myonecrosis with T cell infiltrate in myocardium	IV steroids, vasopressors	N/A	Fatal	Concurrent neutropenic fever, and C. difficile infection

Ref/reference, Tx treatment

^aWeeks after initiation of therapy