Review Article

Cardiotoxicity of FDA-approved immune checkpoint inhibitors: A rare but serious adverse event

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Abstract

Refractory cancer represents a challenge for oncologists in providing treatment options without excessive toxicity and has led to the investigation of immune mechanisms. Immune checkpoint inhibitors (ICIs) directly interfere with the tumor cells' ability to evade the innate and adaptive immune system by targeting specific proteins such as cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), programmed cell death protein-1 (PD-1), and programmed cell death protein-ligand 1 (PD-L1), which are involved as negative regulators of T-cell function. Their growing success has led to the investigation for frontline treatment in several types of cancers. Even though these ICIs have demonstrated efficacy in the treatment of a variety of cancers, their use has been associated with the development of rare but severe adverse events. These events are the result of targeting specific checkpoint proteins on normal cells of the body as well as secondary downstream off-target effects on normal tissue. Similar to combined conventional cancer treatment, treating with combined ICIs are also associated with a higher risk of adverse events. Although cardiotoxicities related to immunotherapy are reportedly rare, they can be severe and associated with life-threatening conditions such as fulminant heart failure, hemodynamic instability, and cardiac arrest. Oncologists must carefully weigh the risk versus the therapeutic benefit of these agents in determining the best option for improving overall survival and minimizing morbidity and mortality of their patients. Our review focuses on the approved ICIs, their mechanism of action, their oncologic efficacy, and the associated potential for cardiovascular toxicity.

Keywords: *Anti-CTLA4, anti-PD1, anti-PDL1, cardiotoxicity, immune checkpoint inhibitors*

Introduction

Immune therapy utilizes the native immune system in oncologic treatment. The earliest report of immunotherapy goes back to the late 19th century when Dr. William Coley injected killed bacteria into a patient who had sarcoma and resulted in shrinkage of the tumor size.[1] The term "immunotherapy" refers to the agents that modify the function of the immune system in a particular way to achieve therapeutic benefits.

Immune checkpoint inhibitors (ICIs) are a class of immunotherapy that has been approved as a treatment option for solid tumors as well as hematological tumors [Table 1].[2-7]

They work by targeting specific checkpoint proteins and primarily include cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death receptor-1 (PD-1), and programmed cell death ligand-1 (PD-L1). Currently, agents against these three immune checkpoints are approved by the US Food and Drug Administration (FDA) and are increasingly used in clinical practice.[7] These agents inhibit the tumor cells from inactivating the immune system and lead to a restoration of the immune system role against the tumor cells and have been associated with increased survival in patients with typically poor outcomes.[26,27]

However, stimulation of the immune system is not without risk and is associated with multiorgan adverse events.[28] These adverse events occur with a variable frequency depending on the type of ICI, the type and location of cancer, and host characteristics, making it difficult to predict who will develop them.[29]

Conventional anticancer treatment and radiotherapy have well-established cardiovascular adverse events. However, the rare but life-threatening cardiovascular

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Table 1: Cardiotoxicity related to FDA-approved immune checkpoints inhibitors

Drug	Immune Checkpoint	FDA Approval	Study Population	Basis of Approval	Cardiotoxicity-Related Adverse Events
Ipilimumab	CTLA-4	Melanoma	676 patients with unresectable or metastatic melanoma, 403 received ipilimumab + (gp100), 137 received Ipilimumab, and 136 received gp100 alone	ORR 5.7% in the ipilimumab+gp100 arm, 10.9% in the ipilimumab arm, and 1.5% in the gp100 arm. MDR 11.5 months in the ipilimumab + gp100 arm, MDR not reached in the Ipilimumab or gp100 arm	Myocarditis in less than 9 weeks, 0.2% (1/471)[8] Cardiac arrest 0.3% (1/315)[9] Case reports Takotsubo-like syndrome[10] Asymptomatic LVD in less than 17 weeks[11] Pericarditis 12 weeks after the last dose[12]
Nivolumab	PD-1	Melanoma	120 patients had progression of disease on ipilimumab treatment and, if BRAF V600 mutation positive, a BRAF inhibitor	ORR 32%, 4 CR, and 34 PR. 33 patients (87%) had ongoing responses, durations ranging from 2.6 to 10 months, 13 patients with ongoing response ≥6 months	Asystole in 17 weeks[13] Myocarditis in 2-9 weeks, 0.06% (10/17620)[14] Case reports Myocarditis and myocardial fibrosis found in autopsy: lymphocytic myocarditis, after using ipilimumab followed by nivolumab[15] Complete heart block After a second infusion with nivolumab[16] Myocarditis after nine cycles of nivolumab in a patient with durable response[17] Pericarditis after 3 cycles[18] Pericarditis after five cycles of nivolumab[19]
			906 patients with resected, Stage IIIB/C or Stage IV	As adjuvant therapy, improved recurrence-free survival, fewer recurrences/ deaths, 34% (n=154)	
		Nonsmall cell lung cancer	582 patients with progression on platinum-based chemotherapy, 78% were tested for PD-L1 expression, 48% were negative	OS 12.2 months, the MRD 17 months. PFS: No significant difference between nivolumab and docetaxel	
		Renal cell carcinoma	410 patients with advanced renal cell carcinoma	Median OS was 25.0 months. Median PFS was 4.6 months	
		Classical Hodgkin lymphoma	95 patients relapsed or refractory cHL	ORR 65%, with 58% PR and 7% CR. median time-to-response 2.1 months; MDR was 8.7 months	

Table 1 continued on next page

Table 1: Continued

Drug	Immune Checkpoint	FDA Approval	Study Population	Basis of Approval	Cardiotoxicity-Related Adverse Events
		Squamous cell carcinoma of the head and neck	361 patients with recurrent or metastatic HNSCC with disease progression on or within 6 months of receiving platinum-based chemotherapy	Median OS was 7.5 months	
		Urothelial carcinoma	270 patients with metastatic carcinoma progressed on platinum-containing chemotherapy	ORR 19.6%, seven patients had CR and 46 had PR. MDR was 10.3 months with responses ongoing at data cutoff	
		Hepatocellular carcinoma	154 patients who progressed on or were intolerant to sorafenib	ORR 14.3%, with three patients CR and 19 patients PR. The range of response duration 3.2 to 38.2+ months; Response ≥6 months, 91% of responders; response ≥12 months, 55% of responders	
		Mismatch repair deficient and microsatellite instability-high metastatic colorectal cancer	53 patients with locally determined dMMR or MSI-H metastatic CRC, and 74 patients of metastatic disease, who had disease progression on fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy	ORR 28%, 1 CR and 14 PR, response ≥6 months, 67% of responders; Response ≥12 months, 55% of responders in 53 population. ORR 32% among 74 population	
Nivolumab in combination with ipilimumab	PD-1 and CTLA-4	Melanoma	142 patients, stratified by BRAF V600 mutation status, 109 patients with BRAF V600 wild-type melanoma	ORR 60%, PFS of 8.9 months	Case reports Myocarditis 0.27% (8/2974)[14] Myocarditis with heart failure with low EF in 22 weeks[20]
Pembrolizumab	PD-1	Melanoma	834 patients who had no more than one line of prior systemic therapy and not received ipilimumab	Median PFS was 5.5 and 4.1 months when administered in 2 weeks and 3 weeks, respectively. ORR 34%, 33% when administered in 2 weeks and 3 weeks, respectively	Myocarditis in a week, 3.8% (1/26)[21] Cardiac arrest in 20 weeks[20] Hypertension 2 weeks, 0.6% (3/496)[13] Stable angina 2 weeks, 0.4% (2/496)[13] Sinus tachycardia[13] Case reports Myocarditis after 15 weeks of starting pembrolizumab[22] Cardiac arrest within 20 weeks[20]
		Nonsmall cell lung cancer	305 patients who had no prior treatment, 1033 patients who were previously treated for metastatic NSCLC	PFS of 10.3 months of 305 patients, median survival was 10.4 months of 1033 patients	

Table 1 continued on next page

Table 1: Continued

Drug	Immune Checkpoint	FDA Approval	Study Population	Basis of Approval	Cardiotoxicity-Related Adverse Events
		Squamous cell carcinoma of the head and neck	174 patients with recurrent or metastatic HNSCC who had disease progression on or after platinum-containing chemotherapy	ORR 16%. MDR not reached at the time of analysis. The range of duration of response 2.4 months to 27.7 months. Response ≥6 months, 23 (82%) had responses among the 28 responding patients	
		Classical Hodgkin lymphoma	210 adult cHL patients	ORR 69%. PR in 47%, CR in 22%. MDR was 11.1 months	
		Urothelial carcinoma	370 patients, 270 received pembrolizumab	Median follow-up time of 7.8 months, ORR 28.6%. MDR not reached (range 1.4, 17.8 months). On other study, ORR was 21% for pembrolizumab and 11% for chemotherapy	
		Gastric or gastroesophageal junction adenocarcinoma	259 patients, 55% (*n*=143) had tumors expressing PD-L1 and either MSS or undetermined MSI or MMR status	ORR 13.3%; duration of response, 2.8+to 19.4+months; Response ≥6 months, 58% of responders; Response ≥12 months, 26% of responders	
		Microsatellite instability-high or mismatch repair deficient solid tumors	149 patients with MSI-H or dMMR cancers	ORR 39.6%, 11 CR, and 48 PR. Response ≥6 months for 78%	
Atezolizumab	PD-L1	Urothelial carcinoma	310 patients had disease progression during or following a platinum platinum-containing chemotherapy, 32% have PD-L1 expression	ORR 14.8%, response ≥6 months, 37/46 of responders; response ≥12 months, 6/46 of responders. ORR 26.0% of 100 patients whose had PD-L1 expression	Congestive heart failure[23] Cardiac arrest,[24] constrictive pericarditis[25]
		Nonsmall cell lung cancer	1137 patients with NSCLC, two clinical trials: OAK and POPLAR	Median OS 13.8 months in OAK, Median OS 12.6 months in POPLAR	
Durvalumab	PD-L1	Urothelial carcinoma	182 patients who progressed on platinum-containing chemotherapy	ORR 17.0%, ORR 26.3% in 95 patients with a high PD-L1 expression, ORR 4.1% in 73 patients with a low or negative PD-L1 expression	Immune-mediated myocarditis<1%
		Nonsmall cell lung cancer	713 patients with unresectable, Stage III NSCLC	Median PFS 16.8 months in durvalumab arm and 5.6 months in placebo arm	
Avelumab	PD-L1	Merkel cell carcinoma	1738 patients with metastatic Merkel cell carcinoma	ORR 33%, 11% CR, and 22% PR. response duration 2.8-23.3 + months. 86% of responses durable for ≥6 months	Immune-mediated myocarditis <1%
		Urothelial carcinoma	242 patients with locally advanced or metastatic disease	ORR 13.3%, (*n*=30) followed for ≥13 weeks, ORR 16.1%, (*n*=26) followed for ≥6 months	

CR: complete responses; MDR: median duration of response; OS: overall survival; ORR: overall survival rate; PR: partial responses; PFS: progression-free survival; FDA: US Food and Drug Administration; LVD: left ventricular dysfunction; HNSCC: squamous cell carcinoma of the head and neck; MMR: mismatch repair; dMMR: mismatch repair deficient; MSI-H: microsatellite instability-high; MSS: microsatellite stable; EF: ejection fraction; NSCLC: non-small-cell lung cancer; cHL: classical Hodgkin lymphoma; CRC: colorectal cancer.

toxicities associated with ICIs are now being recognized with growing interest. ICIs can affect various aspects of cardiovascular function,[30] with reported toxicities as rhythm disturbances (bradycardia/tachycardia), cardiomyopathy with congestive heart failure, hypertension, and pericardial/myocardial disease.[31]

Development and approval of new checkpoint inhibitors are expected, thus emphasizing a growing need for follow-up and monitoring to elucidate the long-term cardiovascular safety profile. Ultimately, the goal is to continue uninterrupted effective cancer therapy while preventing severe adverse side effects. Our objectives are to review the mechanism of ICIs, their oncologic efficacy, and their known associated cardiovascular toxicity.

Methods

A MEDLINE search for cardiovascular toxicities associated with immunotherapy, in particular, ICIs approved by the FDA, was performed. We performed a comprehensive review articles, key research papers, and case reports establishing the incidence, diagnosis, monitoring, and management of cardiovascular toxicities related to ICIs until May 2018. For newly approved agents, package inserts information and reported data from the FDA website were obtained.

Mechanism of Action of Immune Checkpoint Inhibitor Treatment

In viral infections, T-cells can identify and attack infected host cells by the presence of nonself-antigens. Similarly, neoplastic cells are targeted by T-cells as a part of normal immune surveillance. This enables the immune system to target non-self-antigens, which are presented by antigen-presenting cells (APCs) to the T-cells. A set of stimulatory and inhibitory receptors regulate the function of the cytotoxic T-cells.

Tumor cells use two main mechanisms to escape immune destruction; the first mechanism is by inhibition of the activation of the T-cells through CTLA-4. This antigen exerts its function when it is expressed on the surface of CD4+ and CD8+ T-cells. It has a higher affinity for costimulatory receptors CD80 and B7 on APCs than the T-cell costimulatory receptor CD28[32] [Figure 1a]. The expression of CTLA-4 is regulated by the degree of the T-cell receptor (TCR) activation and cytokines such as interleukin-2 (IL-2) and interferon gamma (INF-γ). The binding of CTLA-4 to B7 leads to inactivation of the T-cell, which helps the tumor cell escape the immune system. CTLA-4 hence acts as a key regulator of T-cell activation.

The second mechanism is through the promotion of effector T-cell programmed cell death and inhibition of tumor cell apoptosis [Figure 1b]. This mechanism has mediated the function of PD-L1, which is a transmembrane protein ligand that is expressed on the surface of many tissues including tumor cells. The binding of PD-L1 with PD-1 leads to inhibition of tumor cell apoptosis and effector T-cell death as well as its conversion to regulatory T-cells.[33] PD-L1 has also been shown to be involved in the inhibition of B7, suggesting a common pathway between CTLA-4 and PD-1. The expression of this molecule is regulated by the function of certain cytokines such as INF-γ and IL-2, which enacts as a physiological brake of effector T-cell function.[34]

Immune Checkpoint Inhibitors

Immune checkpoints are proteins that regulate the function of the native immune system. They are expressed on both B-cells and T-cells. They can be categorized into two main mechanisms: stimulatory and inhibitory. The inhibitory checkpoints are the main target for ICIs. Currently, the FDA has approved ICIs for clinical use that target CTLA-4, PD-1, and PD-L1.

Ipilimumab was the first ICIs approved by the FDA in 2011 for the treatment of melanoma.[35] It inhibits CTLA-4, which is an immune checkpoint protein that inhibits T-cell activation.[36] [Figure 1c].

Nivolumab and pembrolizumab are ICIs approved in 2015 against PD-1, which is a transmembrane protein that binds to PD-L1 inhibiting tumor cell death. ICIs targeted against PD-L1 including atezolizumab, avelumab, and durvalumab have also been approved for clinical use. They exert their effect by inhibiting the binding of PD-L1 to PD-1, which blocks the apoptosis of T-cells [Figure 1d].

Recently, there are studies investigating additional immune checkpoint proteins including BTLA-B and T-cell lymphocyte attenuator (BTLA), which inhibits T-cell function by binding not only to the B7 protein on APCs but also to tumor necrosis factor family receptors. Its blockade leads to enhancement of CD8+ T-cell function.[37]

TIM-3–T-cell immunoglobulin and mucin domain-3 (TIM-3) is another molecule which is expressed on T-helper cells, cytotoxic CD8+ T-cells, interferon gamma, and dendritic cells. It works by binding to its ligand galectin-9 that is found mostly on tumor cells. Its blockade leads to hyperproliferation of the T-cells and shrinkage of tumor cells in animal models.[38]

VISTA-V-domain Ig suppressor of T-cell activation (VISTA) is a part of the B7 family, and it is expressed mostly in hematopoietic cells as well as the tumor cell. Sharing homology to PD-L1, it works to activate T-cell function and facilitates infiltration of T-cells into tumors.[39]

Lymphocyte activation gene 3 (LAG3) expresses mostly on B-cells and to lower extent on T-cells. LAG3 protein functions by binding to major histocompatibility complex (MHC) class II, which inhibits T-cell differentiation and function. Combined treatment with LAG3 protein inhibitor and nivolumab showed promising

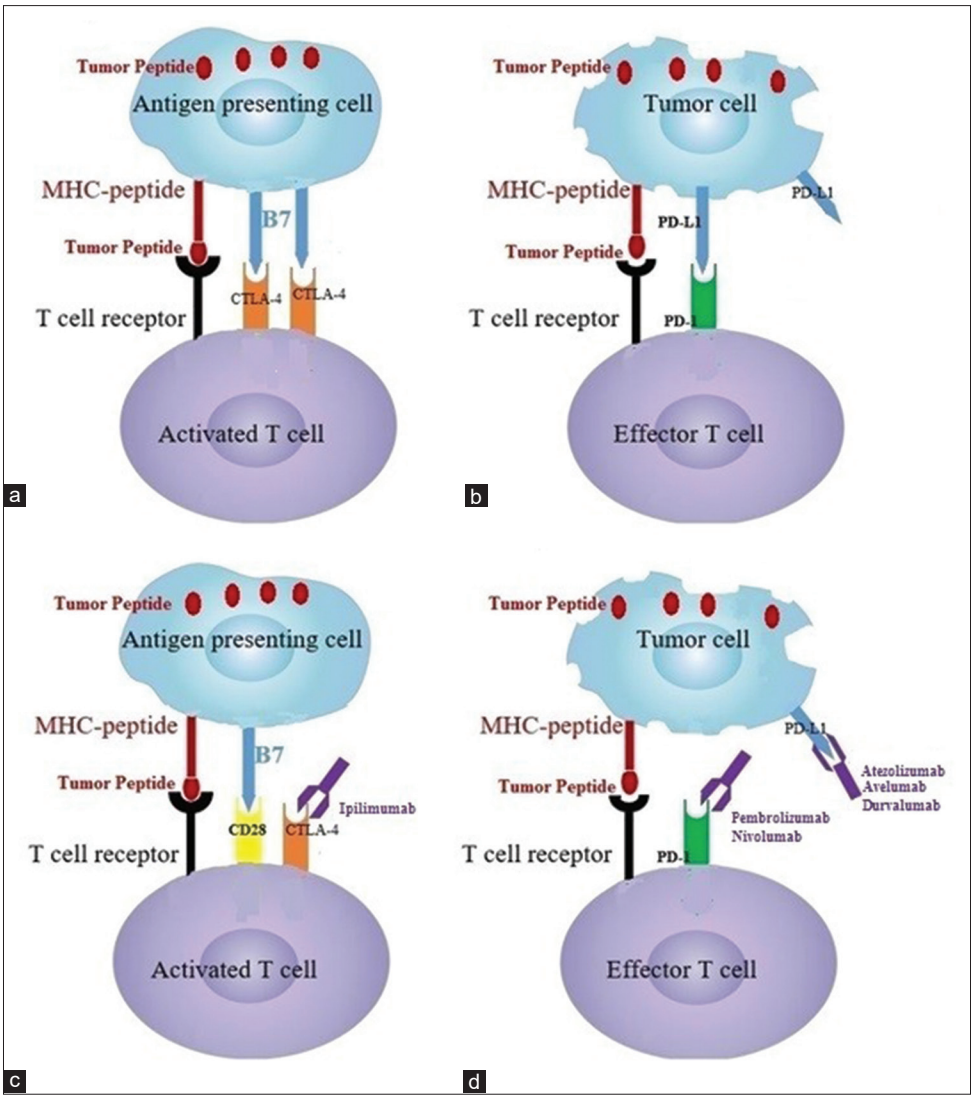

Figure 1: The mechanism used by the tumor cells to evade the immune system (a and b). The mechanism of action of immune checkpoint inhibitors to inhibit the tumor cells from evading the immune system (c and d).

results in patients with advanced melanoma who had failed previous treatment with a PD-1 inhibitor monotherapy.[40]

Tumor cells utilize complex mechanisms to evade immunosuppressive pathways blocked by a single signaling checkpoint molecule. Combination ICIs have been used to target multiple pathways to improve outcomes.[41,42] The combination of anti-CTLA-4 and anti-PD-1, in particular, has been shown to enhance antitumor activity and patient survival.[9,43]

Cardiac Toxicity of Checkpoint Inhibitors in Patients with Cancer

ICIs have shown an increase in overall response rate and overall survival in different types of refractory metastatic cancers; however, these agents can cause significant cardiotoxicities. Based on the reported data, these events could develop within 2–32 weeks after starting treatment.[44]

Many adverse cardiac manifestations related to immune therapy have been described, including myocarditis/pericarditis, dysrhythmias including heart block and cardiac arrest, and cardiomyopathy.

Suggested mechanisms of toxicity

ICIs in contrast to conventional cancer treatments have unique adverse events as they influence immune checkpoints, which play an essential role in maintaining self-regulation of the immune system. Their therapeutic targets can alter immunologic tolerance and give rise to inflammatory side effects, known as immune-related adverse events (IRAEs).[45]

Cardiotoxicities related to immunotherapies is likely caused by the direct inhibition of CTLA-4 and PD-1. PD-1 prevents normal tissue inflammation and protects against myocyte injury associated with inflammatory processes.[46]

The deletion of PD-1 gene in mice was accompanied by an increased incidence of spontaneous myocarditis and cardiomyopathy.[47] Similarly, CTLA-4-deficient mice developed severe myocarditis resulting from lymphocytic infiltration with cytotoxic T-cells, which are more pathogenic than normal T-cells.[48]

In humans, lymphocytic myocarditis was suspected to be the main mechanism responsible for these cardiovascular side effects. One of the first cases reported in 2013 was secondary to Ipilimumab.[49] The subsequent pathologic analysis focused on identifying the lineage of these lymphocytic infiltrates. Using immunohistochemistry analysis, Laubli et al. showed same T-cell lineage in both the tumor and the myocardium.[22] The first large case series of myocarditis related to combined checkpoint inhibitors with ipilimumab and nivolumab was published in 2016 and again reported on the nature of the T-cell involvement.[20] There was increased interest in the possible mechanisms of cardiotoxicity from a study published by Johnson et al. in 2016.[14] Their study pointed at a potential mechanism of a common epitope shared by the heart and the tumor and also the effect of the potential loss of function of PD1, which is known to have protective effects in cardiomyocytes.

Myocarditis

Ipilimumab has been reported to cause myocarditis. In phase III clinical trial of 475 patients taking ipilimumab as adjuvant therapy for stage III and IV melanoma, one patient died due to myocarditis.[8]

The results from 20,594 patients treated with nivolumab vs. nivolumab + ipilimumab, reported in Bristol–Myers Squibb safety database, evaluated adverse cardiac events. In the nivolumab arm, 10 (0.06%) patients reported myocarditis versus eight (0.27%) in the combination arm. However, fatal events occurred more frequently in the combination arm, five (0.17%) versus one (<0.01%) in the nivolumab arm.[14]

Fatal myocarditis with cardiomyopathy was reported in another patient treated with pembrolizumab.[13] In another study of nivolumab, fatal myocarditis was reported in a patient with metastatic clear cell renal cell carcinoma after 2 weeks of starting the treatment.[50]

Severe myocarditis has been reported to be more frequent during combination treatment. Heinzerling et al. reported eight patients treated with ipilimumab and/or anti-PD1 (nivolumab or pembrolizumab) that had myocarditis.[20] Smoldering myocarditis was also reported in a 49-year-old patient receiving nivolumab and ipilimumab following several weeks of treatment.[51]

Even separate treatment intervals may confer increased cardiac risk. A 35-year-old female patient who received ipilimumab followed by nivolumab was found to have lymphocytic myocarditis on autopsy.[15]

Pembrolizumab-associated immune-mediated myocarditis was reported in a case of a 73-year-old woman treated for metastatic uveal melanoma who developed severe acute heart failure,[22] as well as in a patient who received one dose of pembrolizumab for Merkel-cell carcinoma.[21]

Recently, 32 cases of ICI related myocarditis (2013–2017) from eight-center institutional registry were compared to 105 patients on ICI that did not develop myocarditis. Nearly, all the patients that developed myocarditis had troponin elevation (94%). The majority of patients with myocarditis had an abnormal ECG on clinical presentation (89%). Most of the findings related to combination therapy and outcomes were not robust, likely due to limitations in sample size and selection bias. Troponin T was higher in patients with myocarditis that developed major adverse cardiovascular events (MACE). An initial higher mean equivalent dose of methylprednisolone (2.06 mg/kg) was related to no MACE. Lower steroids doses were associated with higher troponin values and a higher incidence of MACE.[52]

A recent brief communication of a case series obtained from VigiBase (WHO database) analyzed 101 cases of severe myocarditis following treatment with ICI. Myocarditis-related fatality was higher in patients that received treatment with a combination of anti-PD-1 or anti-PD-L1 plus anti-CTLA-4 compared to monotherapy with anti-PD-1 or PD-L1 (67% vs. 36%; $P = 0.008$).[53]

Pericarditis

Pericardial diseases including acute pericarditis and cardiac tamponade have been described during ipilimumab treatment.[12]

There are case reports of nivolumab causing pericardial effusions that lead to tamponade physiology. Although still unclear, it is thought that the pericardial effusions that develop from nivolumab may be due to the phenomenon of pseudoprogression that is seen with immunotherapy.[18,19]

Dysrhythmias

The data on cardiovascular adverse events of PD-L1 inhibitors are limited. A few cases of cardiac arrest have been reported in the literature.[54] Cardiac arrest was reported in one case in ipilimumab arm of a study of 945 patients.[9] It was described as IRAEs in a patient during nivolumab treatment among 496 patients with metastatic melanoma treated with nivolumab or pembrolizumab.[13]

Complete heart block was reported after the second infusion with nivolumab. This conduction impairment was part of autoimmune myositis.[16]

Cardiomyopathy

Asymptomatic left ventricular dysfunction was reported 4 months after completion of the second course of treatment with ipilimumab.[11] Ipilimumab has also been reported to cause Takotsubo cardiomyopathy.[10]

Life-threatening autoimmune cardiomyopathy was reported in a 72-year-old patient treated with ipilimumab and nivolumab, which resolved completely after discontinuation the treatment.[55] Thus, early identification and intervention is essential in preventing and potentially restoring normal cardiac function.

Monitoring

The role for cardiac imaging or cardiac biomarkers in the early detection of myocarditis related to immunotherapy is not well addressed. Limited clinical observations have led the Society for Immunotherapy of Cancer and more recently the American Society of Clinical Oncology (ASCO), to add electrocardiogram (ECG) and troponin to their consensus recommendations on how to monitor these patients.[56] These recommendations can be summarized by obtaining ECG and also troponin at baseline and then weekly for 6 weeks, especially in patients with underlying known structural heart disease. They admitted that this might not be a cost-effective approach, but strongly encouraged testing if cardiopulmonary symptoms developed.

Cardiac biomarkers including troponins and brain natriuretic peptides should be tested in all suspected cases. MRI studies are positive in about third of the cases showing myocardial edema. Left ventricular systolic dysfunction is seen in about two-thirds of these patients by echocardiography.[56,57]

Management

The general treatment of cardiac toxicities involves first hemodynamic stabilization using the standard of care cardiovascular therapies. The treatment of myocardial inflammation with steroids and immunomodulatory agents such as intravenous immunoglobulin (IVIG) has been used with variable response. Inflammatory side effects can be controlled with the administration of high-dose glucocorticoids.[57]

Clinically severe, prolonged, and even fatal events have occurred in rare instances. Adverse events can lead to discontinuation of therapy in nearly 40% of patients.[9,43] Commonly, the discontinuation of ICIs is warranted for Grade 4 toxicities, whereas dose interruption and initiation of high-dose corticosteroids are recommended for Grade 3 toxicities. Some refractory cases may require infliximab or other immunosuppressive agents.[57]

Future Directions

Despite being a rare event, catastrophic cardiovascular toxicity in the form of fulminant myocarditis related to ICIs is associated with high mortality, about 27%–45%.[53,58] There are still many questions that need to be answered to care for these patients optimally. This includes figuring out if differences in T-cell subsets activated by different ICIs have any role in defining the severity of cardiovascular toxicity and if these findings will translate into a distinct clinical response to steroids or immunomodulators therapies.[59]

The use of these agents in high-risk groups, such as patients with a previous history of autoimmune disease or prior organ transplant, requires in-depth discussions with the patients and providers to weigh the risks and benefits of continued treatment.[60]

Cardiac toxicities may be underrepresented due to a lack of reported data in the postmarketing phase. They can be fatal, especially when they manifest as acute immune-mediated myocarditis. These cases, though rare, require the use of a screening algorithm that can appropriately identify patients who would benefit from these agents with minimal risk of severe toxicity. The increased popularity of these agents in clinical practice necessitates the urgency of developing such a model. Identifying the risk of cardiac events may lead to better treatment modalities and may allow patients to continue their ICI without interruption. Further prospective studies are needed to identify and manage the cardiotoxicity events of these agents effectively.

Conclusions

ICIs provide a promising treatment for various cancers through specific immune mechanisms. They have shown great promise in prolonging overall survival and remission in otherwise refractory cancers. However, the adverse cardiac effects of immunotherapy can lead to serious complications and mortality.

Given the increased use of ICIs approved by the FDA, close observation and long-term follow-up are needed to ensure the safety of these agents. Multidisciplinary collaboration between oncologists and cardiologists is recommended to optimize the use of these agents to optimize individualized patient care.

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Conflicts of interest

The authors disclosed no conflicts of interest.

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