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Cardio-oncology (M Fradley, Section Editor)

Cardiovascular Complications Associated With Novel Cancer Immunotherapies

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Opinion statement

Immune therapies represent a quantum leap in the fight against cancer. Recently approved immune checkpoint inhibitors that target receptors involved in immune escape of cancer cells (including cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed cell death protein-1 (PD-1), and programmed cell death protein ligand-1 (PD-L1) are increasingly being used for therapeutic benefit in a number of cancers. The robust anti-cancer activity of these agents has been accompanied by the recognition of new adverse effects, often due to the over activation of immune system, that may limit their therapeutic benefit and adversely impact outcomes. Combination treatments in particular, such as approaches using two targeted immunotherapy agents, have higher risk of adverse effects. Our review focuses on the approved checkpoint inhibitor therapies and their potential for cardiovascular toxicity. While very few cases of autoimmune cardiotoxicity and myocarditis have been reported in clinical trials, severe, life-threatening episodes of heart failure and hemodynamic compromise associated with the use of immune checkpoint inhibitors have recently been reported in the literature. Early recognition, diagnosis, and management of autoimmune myocarditis represent an important clinical challenge with no current guidelines available for prevention, identification, and treatment of this serious condition. This area of cardio-oncology is evolving rapidly as more drugs

in this class are being discovered and pending approval. There is a need for future studies focused on prospective identification of biomarkers and clinical standards for treatment and long-term follow-up of cardiovascular toxicity to successfully continue the treatment of cancer while preventing the adverse outcomes with novel immune therapies.

Introduction

Cancer immunotherapy can broadly be defined as any biological substance used to manipulate the immune system to fight cancer [1]. Since its conception, when William Cooley injected cancer patients with streptococcal cultures in the 1890s, to 2010 when a clinical trial demonstrated anti-CTLA4 antibody extended the lives of melanoma patients, cancer immunotherapy has been a controversial topic [2]. In the most recent years, impressive successes in clinical studies led to the recognition of immunotherapy as the scientific breakthrough of the year in 2013, also marking a critical change of paradigm with targeting the immune system instead of targeting the tumor itself [3].

In a broad sense, this field encompasses a number of treatment approaches that utilize distinct components of immune system in fight against cancer. The main forms of immunotherapy strategies used, or in active clinical development today, include the following:

- Therapeutic monoclonal antibodies
- Immune checkpoint inhibitors
- Immune cell therapies
- Cancer vaccines
- Non-specific cancer immunotherapies (interleukins, interferons)

Monoclonal antibodies are synthetic proteins, typically designed to target a molecule expressed on the cancer cells, that can lead to tumor destruction by a number of mechanisms, including interfering with pro-survival signaling pathways and inducing apoptosis, activating complement system to cause cell death, or delivering toxic substances into tumor cells. With more than a dozen of monoclonal antibodies approved by the FDA and many more in the pipeline, monoclonal antibodies represent the fastest growing pharmaceutical industry market.

Manipulation of immune cells, primarily T lymphocytes, has also been explored in treatment of cancers, mostly by approach called adoptive cell transfer. In simple terms, T cells that infiltrate patient's tumor (tumor-infiltrating lymphocytes or TILs) are collected from tumor samples followed by the selection and selective expansion in the laboratory of the clones that show the greatest recognition of the cancer cells. The amplified, cytokine-activated population of TILs is then infused back to the patient. Another form of adoptive cell transfer uses chimeric antigen receptor (CAR) T cell therapy where patient's T cells are collected from the blood and genetically modified to express CAR protein. This receptor allows the modified T cells to attach to specific proteins on the surface of cancer cells, become activated, and attack the cancer cells. T cell therapies have seen significant progress in the recent years, in particular, in the treatment of blood malignancies, but have not yet translated into routine clinical practice [4]. Similarly, cancer vaccines and non-specific cancer immunotherapies represent areas of active work and we direct interested reader to recently published reviews [5].

This review focuses on a subgroup of immunotherapy agents, characterized by the common actions of their targets, immune checkpoint proteins, that in physiologic setting inhibit T cells and limit uncontrolled activation of immune response. As now demonstrated in clinical trials and practice, pharmacologic inhibition of checkpoint inhibitors can "release the brakes" and activate immune response against cancer with markedly improved survival [6]. At the same time, side effects shared among these potent anti-cancer agents often reflect activation of the immune system with inflammatory responses in different

organ systems including cardiovascular. Here, we summarize mechanisms and reported clinical scenarios of cardiovascular toxicities associated with immune checkpoint inhibitors with available evidence for diagnosis, management, and prognosis.

Mechanism of action of immune checkpoint inhibitors

Immune checkpoint inhibitors are important regulators of T cell signaling. Two inhibitory receptors, cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein-1 (PD-1), are expressed on the T cells and in physiologic conditions prevent over-activation and promote apoptosis of the cytotoxic T cells. The tumor cells can utilize these same receptors to escape the immune system and avoid destruction by T cells as schematically shown in Fig. 1. Presentation of tumor peptides to the immune system occurs via the antigen-presenting cell (APC) in the context of the major histocompatibility class (MHC) peptide which binds to the T cell receptor (TCR) and activates naïve T cells (Fig. 1a). T cells also express CD28 (which enhances their activation upon binding to co-stimulatory peptide B7 on the APC) and counter-acting CTLA-4, the binding of which inhibits and disables T cell activation. Following activation, T cells migrate to the tumor tissues to induce effector T cell responses that will result in tumor cell recognition and destruction.

There are two main mechanisms by which tumor cells evade the immune response: by binding to CTLA-4 and reducing naïve T cell activation (Fig. 1a), and by expressing programmed cell death protein ligand-1 (PD-L1) which binds to PD-1 on effector T cells and mediates T cell downregulation and apoptosis (Fig. 1b). The antibodies against immune checkpoint molecules bind and block this inhibitory signaling downstream from CTLA-4 (ipilimumab), PD-1 (pembrolizumab and nivolumab), and PD-L1 (atezolizumab) and thus enhance the cytotoxic host immune response to the cancer cell (Fig. 1a–b) [5]. There are four checkpoint inhibitor agents currently approved in the treatment of human malignancies [7]:

1. Ipilimumab: a CTLA-4 inhibitor, fully human IgG1 monoclonal antibody (mAb) that was first approved by FDA in 2011
2. Pembrolizumab: a humanized IgG4 mAb PD-1 inhibitor
3. Nivolumab: a fully human IgG4 PD-1 inhibitor, similar to pembrolizumab, but with reduced affinity for PD-1 compared to pembrolizumab
4. Atezolizumab: a humanized IgG1 mAb that binds to PD-L1 and blocks its interaction with both PD-1 and B7 receptors

Adverse effects associated with checkpoint inhibitors

The checkpoint inhibitors are generally well tolerated but they do have important immune-related adverse effects. As it may be expected by their mechanism

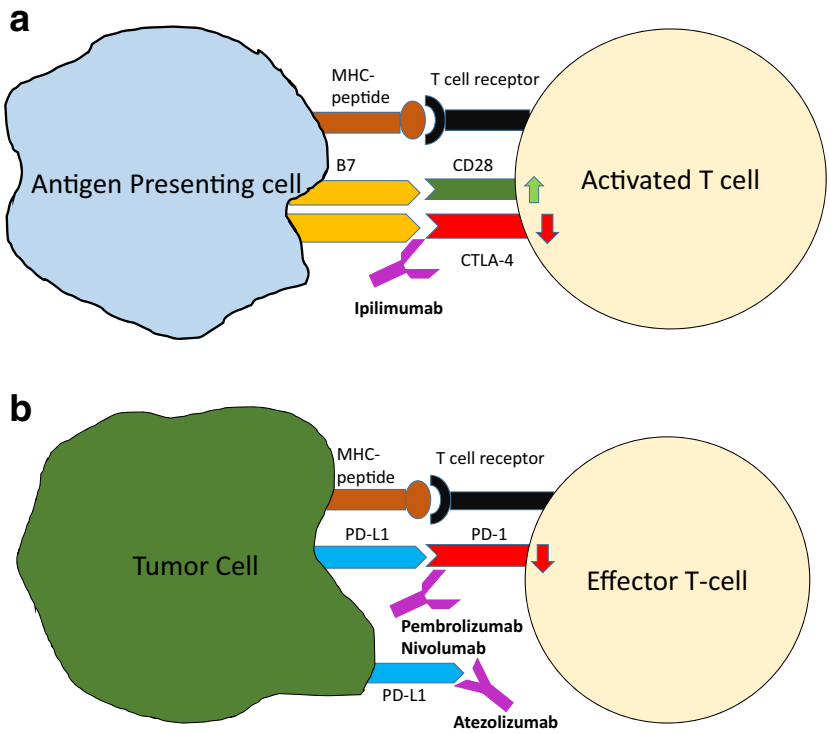

Fig. 1. **a** Activation phase. The binding of the MHC-peptide molecule along with co-signaling from the binding of B7/CD28 leads to activation (expressed as an *upward-facing green arrow*) of the naïve T cell. CTLA-4 expressed on activated T cells has a higher binding affinity to B7. The CTLA-4/B7 complex leads to decreased activation (expressed as a *downward-facing red arrow*) of the T cells causing the cancer cells to escape immune-mediated destruction. Ipilimumab is a monoclonal antibody which inhibits CTLA-4/B7 complex formation. **b** Effector phase. The activated T cells migrate and bind to the tumor cells. The tumor cells express PD-L1 which binds to PD-1 on the effector T cells leading to their inactivation and apoptosis. Nivolumab and pembrolizumab are monoclonal antibodies to PD-1 and prevent PD-1/PD-L1 interaction. Atezolizumab is a monoclonal antibody against the PD-L1 receptor and it also prevents PD-1/PD-L1 interaction. *APC* antigen-presenting cell, *MHC-peptide* major histocompatibility class peptide molecule, *B7* co-signaling molecule, *CD 28* cluster of differentiation molecule 28, *CTLA-4* cytotoxic T lymphocyte-associated antigen 4, *PD-1* programmed cell death protein 1, *PD-L1* programmed cell death protein ligand-1

of action, side effects often present as uncontrolled activation of the immune system skewing the fine balance between self-tolerance and auto-immunity. Using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) [8], fatigue, musculoskeletal pain, rash, pruritus, nausea, vomiting, and diarrhea were the most frequent grades 1–2 adverse events noted in the initial checkpoint inhibitors clinical trials (Table 1). The frequency varied depending on the drug used: 64–80% of patients treated in ipilimumab clinical trial experienced grades 1–2 toxicity, 23% grades 3–4, and 0.86% had fatal outcomes [9, 10], while in pembrolizumab clinical study, grades 1–2 toxicity occurred in up to 79% and grades 3–4 in 13% of patients [9]. Patients treated with atezolizumab had more reported side effects, with grade 1 and 2 toxicities reported in 96%, grades 3 to 4 in 50%, and fatal outcomes in 0.9% of patients [7].

The severity and frequency of adverse events was considerably higher when a combination of drugs was used compared to monotherapy. Fifty-five percent of

Table 1. FDA-approved immune checkpoint inhibitors for treatment of malignancies

Drug	Molecular target	Oncologic indications	Common adverse effects
Ipilimumab [12]	CTLA-4	Unresectable or metastatic melanoma, adjuvant treatment of patients with cutaneous melanoma including who have undergone total lymphadenectomy	Fatigue, diarrhea, pruritus, rash, immune-related colitis, hepatitis, and endocrinopathies
Nivolumab [13]	PD-1	BRAF V600 mutation-positive unresectable or metastatic melanoma, BRAF V600 wild-type unresectable or metastatic melanoma, unresectable or metastatic melanoma in combination with ipilimumab, metastatic NSCLC, advanced RCC, classical Hodgkin's lymphoma, recurrent or metastatic squamous cell carcinoma of the head and neck	Immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, rash, encephalitis, complications of allogenic HSCT, embryo-fetal toxicity *Increased frequency of irAEs with combination therapy of ipilimumab and nivolumab like myocarditis and myositis [16••]
Pembrolizumab [14]	PD-1	Unresectable or metastatic melanoma, metastatic NSCLC, metastatic or recurrent HNSCC	Immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, embryo-fetal toxicity
Atezolizumab [15]	PDL-1	Locally advanced or metastatic urothelial carcinoma, metastatic NSCLC	Immune-related pneumonitis, hepatitis, colitis, endocrinopathies, myasthenic syndrome/myasthenia gravis, GBS or meningoencephalitis, ocular toxicity, pancreatitis, infection, embryo-fetal toxicity

CTLA-4 cytotoxic lymphocyte-associated antigen-4, *PD-1* programmed cell death protein-1, *PD-L1* programmed cell death protein ligand-1, *GBS* Guillain-Barre syndrome, *BRAF* b-raf proto-oncogene, *irAE* immune-related adverse effects, *NSCLC* non-small cell lung cancer, *HNSCC* head and neck squamous cell carcinoma, *RCC* renal cell carcinoma, *HSCT* hematopoietic stem cell transplant

patients treated with ipilimumab-nivolumab combination experienced grade 3 and 4 adverse events compared to 16% of patients receiving nivolumab only [11]. Immune effects, including pneumonitis, colitis, hepatitis, rash, and endocrinopathies, represented majority of the severe adverse effects that often required discontinuation of therapy either permanently or temporarily [17]. The incidence of immune-related cardiovascular toxicity is rare and the initial trials of immune checkpoint inhibitors reported cardiac events in 0.09% patients receiving ipilimumab, nivolumab, or both [16••].

Recently, with increasing recognition and reports of rare but potentially fatal cases of immune myocarditis and associated heart failure in clinical practice, a new review of clinical trial data was performed and reported increased likelihood of severe myocarditis with ipilimumab and nivolumab combination at 0.27% compared to 0.06% with nivolumab alone (five fatal events vs one event) [16••]. The presumed mechanism for autoimmune myocarditis is that shared targeted antigen may exist among the tumor cells and the cardiac myocytes that become target of activated T cells leading to myocardial lymphocytic infiltration and clinical picture of heart failure and conduction abnormalities. Recent report by Johnson and colleagues provides the first molecular evidence in support of this theory [16••]: using the genetic sequencing analysis,

the authors found a high degree of sequence sharing of the highly variable complementarity-determining region-3 (CDR3) among the T cells, tumor cells, and the cardiac myocytes.

Case reports of immunotherapy-mediated cardiotoxicity

At present, there are no recommendations regarding cardiovascular assessment, diagnosis, or monitoring of cardiac effects associated with immune checkpoint inhibitors that could guide practicing physicians. We searched the PubMed, Ovid, and Cochrane database using the terms myocarditis, acute heart failure, checkpoint inhibitor, autoimmune cardiotoxicity, cytotoxic T lymphocyte-associated antigen-4, programmed cell death protein-1, and programmed cell death protein ligand-1 through Dec 2016. Seven reports, with 15 cases of cardiotoxicity related to immune checkpoint inhibitors, were identified and their common characteristics summarized below and in Table 2.

Clinical features

The clinical presentations of cardiotoxicity may vary from non-specific symptoms to signs of overt acute heart failure that progress in a fulminant fashion, requiring inotropic support. Reported common clinical features were dyspnea, fatigue, peripheral edema, bilateral rales, chest pain, arrhythmia, and syncope. Most patients had conduction abnormalities on presentation which frequently (5 out of 15 reported cases) progressed towards complete heart block [9, 16••] and cardiac arrest [9]. Cardiac function reports varied from preserved LVEF [16••] to various degrees of cardiac dysfunction and cardiogenic shock.

Table 2. Published case reports of cardiotoxicity related to immune checkpoint inhibitors

References	Therapeutic agent	Number of cases	Cardiovascular adverse effects
Heinzerling et al. [9]	Ipilimumab, nivolumab or their combination, and pembrolizumab	8	Myocarditis, heart failure, cardiomyopathy, myocardial fibrosis, cardiac arrest
Johnson et al. [16••]	Nivolumab and ipilimumab combination	2	Myocarditis and myositis
Koelzer et al. [10]	Ipilimumab followed by nivolumab	1	Myocarditis and myocardial fibrosis
Laubli et al. [18]	Pembrolizumab	1	Myocarditis
Behling et al. [17]	Nivolumab	1	Complete heart block
Geisler et al. [19]	Ipilimumab	1	Cardiomyopathy with Takotsubo-like syndrome
Semper et al. [20]	Nivolumab	1	Myocarditis

Similarly, in our recent experience (Mohebtash et al. submitted for publication) of a patient with metastatic melanoma treated with ipilimumab and nivolumab combination, shortness of breath was a presenting heart failure symptom occurring 10 days after the administration of the first cycle of immunotherapy. This patient developed acute heart failure, generalized volume overload, and respiratory decompensation requiring ventilator support. New interventricular delay was present on the electrocardiogram on presentation and progressed to advanced heart block within several days. In published reports, the average onset of symptoms varies widely, ranging from 2 to 32 weeks (median of 10 weeks), from the first dose of the immune checkpoint inhibitor. Similar to our experience, earlier symptom onset has been reported with combination of ipilimumab and nivolumab, as early as 13 days following therapy initiation [16••]. In more than half of the reports (8 out of 15 cases), grade 3 and 4 involvement of other organ system was noted, most often autoimmune hepatitis and myositis. While reports mention other side effects, we identified no clear distinguishing prodrome which could predict the development of myocarditis. Our patient had developed severe rash, about a week after receiving immunotherapy combination, that was treated with systemic steroids and discontinuation of immunotherapy. Development of progressive heart failure despite discontinuation of immunotherapy may indicate that activation of immune system, and its cardiovascular toxicity consequences, persists beyond the treatment and provides a rational for the use of immunosuppression in the treatment of acute heart failure and cardiogenic shock in these patients.

Another common clinical feature is the rapid progression of hemodynamic instability with heart and multi-organ failure that highlights the importance of early recognition of symptoms to assure patient transfer to intensive care setting for invasive hemodynamic monitoring and support.

Diagnosis

In patients receiving immune checkpoint inhibitors who present with signs or symptoms of heart failure, rapid and comprehensive cardiovascular evaluation is indicated to assess severity of cardiac compromise, hemodynamic stability, and presence of electrical abnormalities that pose immediate threat. EKG should be performed early and telemetry monitoring considered in patients with mild abnormalities. Rhythm abnormalities such as atrial fibrillation, varying degrees of conduction delay, and supraventricular tachyarrhythmias need to be closely monitored and treated accordingly. Complete heart block is of a particular concern and appearance of intraventricular conduction delay may herald the development of complete heart block. Signs of heart failure and electrical instability should prompt consideration of patients transfer to tertiary care hospitals with intensive care units capable of advanced cardiac support.

Early exclusion of other etiologies of heart failure should be considered with diagnostic tests including coronary angiogram, cardiac function imaging, and biomarkers including cardiac troponin and NT-proBNP.

Echocardiography is frequently the first choice to establish the degree of LV dysfunction and monitor changes over time in particular in the intensive care unit setting. Cardiac MR (CMR) with tissue characterization provides valuable insight in patients with suspected myocarditis. The presence of gadolinium enhancement pattern consistent with myocarditis may establish the diagnosis in particular in patients with less severe symptoms; however, CMR may not be feasible in patients requiring invasive hemodynamic or respiratory support and/or requiring intravenous pacemakers. In unstable patients, right heart catheterization should be performed early with endomyocardial biopsy that represents the gold standard for the diagnosis of autoimmune myocarditis. The biopsy may show intense patchy lymphocytic infiltrates within the myocardium often involving the atrioventricular nodes and cardiac sinuses with or without evidence of fibrosis. Immunohistochemical staining should be obtained for presence of diagnostic CD3+, CD4+, and CD8+ T cells and antibody-mediated reaction excluded by absence of CD20-positive cells. Additional stainings have been reported and may be considered such as CD68 macrophage marker and FOXP3 regulatory T cell apoptosis marker [10, 16••, 18]. PCR analysis of the biopsy sample can help exclude viral causes of myocarditis.

Treatment

Clinical presentation dictates therapeutic approaches and a high degree of suspicion for drug-induced cardiotoxicity is warranted in patients on immune checkpoint therapy presenting with heart failure symptoms. Initial treatment of unstable patient includes respiratory and hemodynamic support including intravenous pacing in the case of advanced conduction abnormalities. In stable patients, presenting with less severe picture of heart failure, diuresis and initiation of heart failure therapies should be considered. For patients presenting with arrhythmias and conduction delays, low threshold should be used for the insertion of intravenous pacemaker as risk of progression to complete heart block appears to be high.

With regard to specific therapy, immunosuppression is the mainstay of treatment of drug-mediated toxicity. Early initiation of high-dose prednisone at a dose of 1–2 mg/kg/day is presently recommended for any grade 3 and 4 adverse effects and cardiac toxicity should be treated by extrapolation from these guidelines [21]. Immunotherapy is stopped until symptoms resolve or, for grade 3 and 4 adverse effects, indefinitely. Infliximab has been used in the treatment of patients with severe steroid-refractory immune side effects including colitis, hepatitis, and pneumonitis and should be considered if there is an inadequate response to steroids within 3–5 days. Higher doses of steroids have not shown added benefit in the treatment of the autoimmune toxicities [21]. In our patient who presented with cardiogenic shock and had documented T cell infiltration on endomyocardial biopsy, we successfully used anti-thymocyte globulin (ATG) in consultation with the heart failure transplant team.

ATG was given in addition to steroid therapy and following heart transplant protocol with improvement in hemodynamic status and LVEF on the echocardiogram.

Prognosis

Data regarding the prognosis of patients who develop autoimmune myocarditis during or after immune checkpoint inhibitor therapy are very limited. Frequent fatal outcomes in published case series should be interpreted with caution and attention to possible reporting bias. Pre-existing cardiovascular disease, use of dual checkpoint inhibition, and poor response to steroid therapy have been reported in cases with adverse outcomes [22•] but larger and prospective surveillance will be critical to identify more specific prognostic indicators.

Conclusions

Cardiotoxicity is a rare and serious adverse effect of immune checkpoint therapy. Rare and isolated cases of myocarditis have been reported in early nivolumab and pembrolizumab clinical trials [16••]; however, with more widespread use of these agents in clinical practice, increasing numbers of heart failure and fatal cardiotoxicities have been recognized and reported. Our review addresses important gaps such as familiarizing cardiology providers with mechanisms of action of immune checkpoint inhibitors and raises the awareness of the immune side effects of these agents. We captured cardiac events in patients receiving cancer treatment using literature search and then summarized common features, treatment, and outcomes to help orient practicing physicians about the importance of early recognition, diagnosis, and treatment. The indications for immune therapies are rapidly expanding and more than 600 studies registered with clinicaltrials.gov are currently enrolling patients into studies using immune checkpoint inhibition. Inclusion of cardiovascular assessment and prospective collection of cardiovascular phenotypes, imaging, and biomarkers into ongoing and future studies will enable us to identify predictors of cardiotoxicity risk. In addition to clinical investigations, genetic and molecular analyses are critically needed to provide insight into toxicity mechanisms and to guide us towards molecular risk stratification and even treatment.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

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.

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