Managing cardiotoxicity associated with immune checkpoint inhibitors

Sireesha Upadhraa, Hadi Eliasa, Keval Patelb, Lei Zhengc,*

a Department of Internal Medicine, Saint Agnes Hospital, Baltimore, MD 21229, USA
b Department of Internal Medicine, University of Maryland, Baltimore, MD 21201, USA
c Departments of Oncology and Surgery, The Pancreatic Cancer Precision Medicine Center of Excellence Program, The Bloomberg-Kimmel Institute for Cancer Immunotherapy, Baltimore, MD 21287, USA

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Abstract

Immuno-oncology is a fast evolving field of cancer therapy and immune checkpoint inhibitors (ICIs) are clearly a breakthrough in this field. Cardiotoxicity with conventional anti-cancer therapies has been well studied in the past and clear guidelines for management of these side effects are available in the literature. However, cardiotoxicity with novel agents such as ICIs has been fairly under-reported and/or underestimated and we are yet to formulate clear guidelines for management of these rare side effects. In the last few years, there has been an overall increase in the number of cases of cardiotoxicity related to ICIs. In this literature review, we describe the mechanism of action of the most widely used ICIs and their related cardiotoxicities. The increase in number of case reports about the potential of cardiotoxicities with these novel agents clearly indicates the need for a new insight into the field of cardio-immuno-oncology.

Keywords: Immune checkpoint inhibitor; Cardiotoxicity; Ipilimumab; Nivolumab; Pembrolizumab

Introduction

Immune system inhibitory pathways such as cytotoxic T lymphocyte associated antigen 4 (CTLA-4), programmed cell death ligand 1 (PD-L1), and programmed cell death 1 (PD-1) are natural checkpoints that dampen the anti-tumor responses of T cells and also play an important role in the prevention of autoimmune diseases. These pathways can be misused by tumor cells to escape immunologic antitumor responses. Studies by Allison et al helped better understand the exploitation of these pathways by tumor cells. One way that cancer cells can escape adaptive immunity is by clonal selection of non-immunogenic tumor cells during the immune editing process. Immune editing is a dynamic process that consists of immunosurveillance and tumor progression. It

* Corresponding author. 1650 Orleans Street, CRB1, Room 351, Baltimore, MD 21287, USA. Fax: +1 410 614 8217.
E-mail address: lzheng6@jhmi.edu (L. Zheng).
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highlights the dual role of immune system and further enhances the importance of immune checkpoints in preventing tumor progression.

Immune checkpoint inhibitors (ICIs) are anticancer drugs that work by disinhibiting T-cell activity by interfering with checkpoint molecules and thus result in T-cell activation and enhanced antitumor immune response.4,5 The development of ICIs has marked a new era in the field of oncology. Monoclonal antibodies targeting the aforementioned checkpoint molecules have shown promising results in terms of prognosis for solid tumors and hematological malignancies.6–8

Ipilimumab, first introduced in 2010, targeting CTLA-4 revolutionized the treatment of melanoma. Since then many other monoclonal antibodies have been introduced, targeting both PD-1 (nivolumab, pembrolizumab) and PD-L1 (atezolizumab, durvalumab, avelumab). These drugs have shown definite improvement in survival in different cancers (Table 1).9–12 However, increasingly, case reports have unveiled a wide range of side effects from activation of immune system with these agents.9,13–15 These side effects are more commonly referred to as immune-related adverse events (IRAEs). IRAEs are generally low grade and easily manageable when detected in a timely manner.

IRAEs could include a wide spectrum of organ systems such as skin, endocrine, gastrointestinal, pulmonary system and other rare toxicities include neurological, cardiac and renal system. The most commonly reported toxicities are rash, pruritus and vitiligo, hypothyroidism more than hyperthyroidism, diarrhea and episodes of hepatitis and pneumonitis. Both American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) have published recommendations for the management of some of the common IRAEs.16,17

Pathophysiology

Tumor cells use multiple mechanisms to avoid immune destruction: the first is by inhibition of T-cell activation through CTLA-4 and the second through the promotion of effector T-cell programmed cell death and inhibition of tumor cell apoptosis which is mediated by PD-1/PD-L1 interaction.18,19 ICIs target PD-1, PD-L1 and CTLA-4 thus inhibiting the tumor cells from inactivating the immune system which leads to restoration of its role against the tumor cells.5 This immune stimulation is associated with IRAEs which could occur at any time and it depends on the type of ICIs, type of cancer and the host characteristics.

The exact mechanism of cardiac IRAEs remains poorly understood; however, it is likely related to the direct inhibition of PD-1 and CTLA-4. Studies involving PD-1 deficient mice and CTLA-4 knockout mice, shed light into the fact that genetic manipulation of the PD-1 and CTLA-4 axis could be playing a role in the development of fatal myocarditis, although there is a notable difference in the mechanism of action of these agents.20–23

PD-1 is a co-inhibitory member of the B7/cluster of differentiation 28 (CD28) superfamily of molecules. It is expressed on the surface of activated T cells and interacts with its ligands PD-L1 and programmed cell death ligand 2 (PD-L2) to deliver inhibitory signals to T cell activation. Expression of PD-1 is induced by physiologic activation on T cells, B cells and macrophages. Studies done by Tarrio et al24 demonstrated that there was an increased inflammation, enhanced serum markers of immune damage and increased infiltration of CD8+ T cells in PD-1+/CD8+ T cells as compared to PD-1−/CD8+ T cells in a CD8+ T cell mediated adoptive transfer model. Other studies by Nishimura et al25,26 demonstrated that disruption of the gene encoding PD-1 in mice caused dilated cardiomyopathy. Genetic deletion of PD-L1/PD-L2 and treatment with anti-PD-L1 antibodies were shown to transform transient myocarditis into a lethal form of the disease. Studies in mouse models also showed a protective effect of PD-1 against inflammation and myocyte damage.20–22

CTLA-4 is an inhibitory co-receptor, expressed almost exclusively on T cells, and plays a key role in early stages of T cell activation. CTLA-4 antagonizes CD28 mediated co-stimulation by binding to CD80 (also known as B7.1) and/or CD86 (also known as B7.2).18 Overexpression of CTLA-4, dampens activation of T cells by competing CD28 in binding to CD80 and/or CD86.18 The importance of CTLA-4 has been demonstrated by animal studies involving CTLA-4 knockout mice. It was noted that CTLA-4 knockout mice developed severe/fatal myocarditis which was likely a result of the lymphocytic infiltration of cytotoxic T-cells.27 Lüblü et al28 were able to demonstrate that lymphocytic infiltrates involve the same T-cell lineage which was present in both tumor and myocardium using immunohistochemistry analysis. Endomyocardial biopsy and postmortem analysis confirmed cytotoxic T-cells, macrophages and signs of myocardial fibrosis, suggesting direct myocardial injury.
It can be inferred from these studies that there are at least two mechanisms of developing ICI-related myocarditis. The first mechanism is the breakdown of immune tolerance to the heart mediated by CTLA-4 and PD-1 pathways as described above. The second mechanism involves expansion of T-cells targeting a common antigen shared by the tumor and the heart. Johnson et al reported two cases of lethal myocarditis when combination of ipilimumab and nivolumab was used in treatment of melanoma. They found that selective T-cell activation happened in response to a common antigen, as T-cell populations infiltrating the myocardium were identical to those present in tumors and skeletal muscle. They also noted that high levels of muscle-specific antigens such as desmin and troponin were observed in the population group. Overall,
this leads to the inference that common antigens between tumor and heart exist and ICIs can enhance T-cell effector function and thus lead to lethal myocarditis.29,30

One of the first tumor-associated antigens recognized was the melanoma associated antigen-A (MAGE-A) antigen, and it has been expressed in multiple cancers and associated with poor prognosis. Although clinical trials involving anti-MAGE-A human leukocyte antigen (HLA)-A0201-restricted T-cell receptor (TCR) showed clinical regression of cancer, their use has been shown to be associated with neurotoxicity and cardiotoxicity.31,32 This was likely related to the homology between targeted antigens and cardiomyoskeletal proteins.32

Epidemiology

Clinical presentation

Cardiac involvement from ICI therapy is variable and potential toxicities include myocardial, pericardial, and conduction system involvement. Prevalence is much higher in patients on combination immunotherapy. Pericardial disease, Takotsubo cardiomyopathy, and conduction abnormalities including complete heart block have also been reported with ICI use, although they occur less frequently as compared to myocarditis (Table 2).11,12,33–37

Signs and symptoms vary depending on the type of cardiac toxicity and the degree of involvement. Patient could present with pericardial pain in case of pericarditis, shortness of breath in the setting of pulmonary edema from myocarditis or palpitations, pre-syncope and syncope in the setting of arrhythmias.

Cardiac IRAEs are known to occur less frequently than IRAEs in other organ systems and are known to be clinically challenging to diagnose and treat when they do occur.

Myocarditis related to ICI use has emerged as an important IRAE from a review of recent case reports, clinical trials and safety databases. In 2016, Johnson et al30 reported two cases of patients with melanoma in whom fatal myocarditis developed after the first dose of ipilimumab and nivolumab. Pharmacovigilance studies show that myocarditis occurred in 0.27% of patients treated with combination of ipilimumab and nivolumab. Other studies have looked into the safety databases of Bristol-Myers-Squibb to identify the occurrence of these events in patients treated with nivolumab, ipilimumab, or both. Among 20,594 patients treated with ICIs, 18 drug-related myocarditis cases (0.09%) were reported. Patients who received combination ICIs had more severe and frequent myocarditis than those who received nivolumab alone (0.27% vs. 0.06%).12,30 Although combination ICI therapy has shown a significant anti-tumor effect in the treatment of multiple cancers, discontinuation has been required in nearly 40% of treated patients due to cardiac side effects.38

Prevalence

In 2018, a meta-analysis to evaluate the adverse drug reactions associated with ICIs was published. The analyzed data were from large academic medical centers, the global World Health Organization (WHO) pharmacovigilance program and all published ICI clinical trials in cancer patients internationally that used anti-PD-1/PD-L1 and anti-CTLA-4 agents. Out of 613 ICI-related fatal events reported from 2009 through January 2018 in WHO pharmacovigilance database (Vigilyze), 52 were cardiac IRAEs, including 3 caused by anti-CTLA-4 antibody, 27 caused by anti-PD-1/PD-L1 antibody, and 22 caused by the combination of anti-CTLA-4 antibody and anti-PD-1/PD-L1 antibody. Myocarditis had the highest fatality rate at 52 (39.7%) of 131 reported cases. Retrospective review of 3545 patients treated with ICIs at 7 academic centers revealed a 0.6% fatality rate; cardiac and neurologic events were especially prominent (43%).39

In Table 3, we present a brief analysis of adverse drug reactions (ADRs) for the six commonly used ICIs, contained within VigiBase, the WHO global database for ADRs. A total of 106,025 ADRs were reported, 2215 (2.09%) were cardiac. Among the cardiac ADRs, myocarditis accounted for 14.1% (312 cases), followed by pericardial disease including pericarditis, pericardial effusions and cardiac tamponade cases which accounted for 13.6% (302 cases). These were followed by conduction abnormalities (152 cases, 6.86%) and stress cardiomyopathy (16 cases, 0.72%). From this brief analysis, it appears myocarditis is the most common type of cardiac toxicity with immune checkpoint inhibitors. Combination ICIs and associated ADRs were not part of our analysis; however, studies by Salem et al40 have verified the increased incidence of cardiac IRAEs with combination therapy. Further details on the proportions of cardiac ADRs for each specific immunotherapy agent are listed in Table 3 (data obtained from VigiAccess).41

A similar study published in 2018 by Salem et al40 evaluated the IRAEs associated with ICIs through analysis of VigiBase. The association between ICIs and
### Table 2
Summary of approach and treatment strategies for ICI induced cardiotoxicities.12

| Cardiac toxicity | Clinical presentation | Mechanism of cardiotoxic effects | Clinical approach | Clinical management |
|------------------|-----------------------|----------------------------------|-------------------|-------------------|
| **Myocarditis**  | Presentation can be challenging. Can present with HF, pulmonary edema, cardiogenic shock, multiorgan failure, ventricular arrhythmias. | Not fully understood. Post-mortem analysis has shown inflammatory cell infiltrate, increase in extracellular space volume, and loss of cardiomyocytes. Studies have confirmed the presence of both CD4-positive and CD8-positive T cells. | Depends on the presentation (asymptomatic to fulminant myocarditis). Diagnostic tests include EKG, biomarkers, cardiac imaging (ECHO or cardiac MRI). If still uncertain, endomyocardial biopsy can be performed. | 1st: Stop ICI depending on the severity of toxicity. 2nd: IV methylprednisolone 500–1000 mg daily until clinically stable, followed by oral prednisone 1 mg/kg daily, and wean as tolerated. For non-steroid responders, consider mycophenolate mofetil or infliximab, anti-thymocyte globulin or intravenous immunoglobulin. 3rd: Use of conventional cardiac treatments per standard ACC guidelines. |
| **Pericardial disease** | Can occur in isolation with typical pericardial pain or alongside with myocardial involvement with perimyocarditis, and can be complicated by pericardial effusion and tamponade. | Not fully understood. | Diagnostic tests include EKG, cardiac biomarkers and cardiac imaging. | 1st: Stop ICI therapy, and consider re-challenging with ICI therapy only if clinically stable and when clinical pericarditis is excluded. 2nd: Consider intravenous methylprednisolone 500–1000 mg daily until clinically stable, followed by oral prednisone 1 mg/kg once daily, and wean as tolerated. |
| **Arrhythmias** | Can present in wide ranges, from complete atrioventricular block (third degree heart block) to atrial and ventricular tachyarrhythmias. | Underlying myocarditis with inflammation being the substrate for triggered arrhythmias, inflammation of the His-Purkinje system being the trigger for re-entry arrhythmias, increased systemic inflammation leading to arrhythmias without myocarditis. | Diagnostic test: EKG | 1st: Stop ICI therapy, and consider re-challenging with ICI therapy only if clinically stable and after myocarditis is excluded. Immune suppression is not applicable in the absence of myocarditis. 2nd: Management of arrhythmias per ACC guidelines. |

ICIs: immune checkpoint inhibitors; HF: heart failure; CD: cluster of differentiation; EKG: electrocardiogram; ECHO: echocardiogram; MRI: magnetic resonance imaging; IV: intravenous; ACC: American College of Cardiology.

### Table 3
Incidence of ADRs as reported within the VigiAccess/VigiBase from the World Health Organization global database for ADRs.

| Drug             | Total ADRs, n | Cardiac ADRs, n (%) | Proportion of cardiac ADRs |
|------------------|---------------|---------------------|----------------------------|
|                  |               | Myocarditis, n (%)  | Pericardial disease, n (%) | Conduction abnormalities, n (%) | Stress cardiomyopathy, n (%) |
| Pembrolizumab    | 25,028        | 497 (1.99)          | 80 (16.10)                 | 80 (16.10)                  | 34 (6.84)                  | 5 (1.00) |
| Nivolumab        | 49,506        | 1103 (2.23)         | 148 (13.40)                | 155 (14.10)                | 71 (6.44)                 | 6 (0.54) |
| Atezolizumab     | 3627          | 94 (2.59)           | 10 (10.60)                 | 16 (17.00)                 | 6 (6.38)                  | 1 (0.10) |
| Avelumab         | 505           | 16 (3.17)           | 4 (25.00)                  | 2 (12.50)                  | 2 (12.50)                 | 0 (0.00) |
| Durvalumab       | 1329          | 34 (2.56)           | 4 (11.80)                  | 7 (11.80)                  | 0 (0.00)                  | 0 (0.00) |
| Ipilimumab       | 26,030        | 471 (1.81)          | 69 (14.60)                 | 42 (8.92)                  | 39 (8.28)                 | 4 (0.85) |
| Total            | 106,025       | 2215 (2.09)         | 312 (14.10)                | 302 (13.60)                | 152 (6.86)                | 16 (0.72) |

ADR: adverse drug reactions.
cardiovascular IRAEs has been studied using odds ratios and information component (IC; an indicator value for disproportionate Bayesian reporting that compares observed and expected values to find drug-adverse effect combinations that have been reported more often than one would expect. A value of >0 for the lower end of the IC 95% credibility interval [IC025] is deemed significant). Drug-related adverse events were most described with myocarditis (reporting odds ratio, 11.21 [95% CI: 9.36–13.43]; IC025, 3.20), pericardial disease (reporting odds ratio, 3.80 [95% CI: 3.08–4.62]; IC025, 1.63), and vasculitis (reporting odds ratio, 1.56 [95% CI: 1.25–1.94]; IC025, 0.03).42

Risk factors

It is still uncertain which, if any, pre-existing risk factors might affect the incidence of ICI mediated cardiotoxicity. In a case-series by Mahmood et al., myocarditis appeared to be more common in individuals with pre-existing cardiovascular risk factors; however, 70% of the patients who developed myocarditis had a normal left ventricular ejection fraction before initiating therapy. It was also noted that myocarditis presented early, most commonly 30 days after initiating ICIs and 81% presented within 3 months. In contrast, Moslehi et al. recently reported on the absence of concomitant cardiovascular or anti-diabetic drugs in 75% of all cases of myocarditis and suggested that pre-existing cardiac disorders or cardiovascular risk factors would not predispose patients to develop ICI-associated myocarditis.

Nonetheless, there is enough concerning data, so developing a surveillance protocol for the early phases and post initiation of ICI therapy is imperative. Unfortunately, as described above a normal pre-treatment echocardiogram does not reliably predict who will develop myocarditis. Follow-up of patients with repeat echocardiogram (ECHO), cardiac biomarkers and/or cardiac MRI in the initial and later phases of ICI therapy would be beneficial in the evaluation of late onset cardiotoxicity.

Patients with autoimmunity can develop subclinical or subacute myocarditis. It has been noted that patients with autoimmune disorders are usually excluded from clinical trials with ICI therapy. Approximately 14% of patients with lung cancer have a concurrent diagnosis of autoimmune disease.45 Menzies et al. and Johnson et al. demonstrated that 20%—30% of patients with pre-existing autoimmune diseases experienced an autoimmune flare after being treated with anti-PD-1 antibodies or anti-CTLA-4 antibodies. However, the authors concluded that ICI therapy was feasible for patients with certain types of pre-existing autoimmune conditions.

Interestingly, researchers observed that although men are more likely to derive benefit from cancer immunotherapy than women, they are also more affected by IRAEs than women.40,42,48 Conversely, autoimmune diseases affect women more than men and the prevalence of cardiovascular disease or risk factors is higher in men than women, especially in the pre-menopausal age group. Further studies should ensure inclusion of women for a clear assessment of sex dysmorphism in ICI-related IRAEs.42

Diagnosis and management

Diagnosis

Cardiotoxicity associated with ICI use is known for its wide range of clinical presentations depending upon the extent of cardiac involvement (i.e. local vs. diffuse). This makes it unfavorable for early diagnosis; however, with increasing awareness of cardiotoxicity as an important IRAE, certain general characteristics of their presentations can be used as clinical markers of disease onset. For example, myocarditis associated with ICI use has almost always presented with an elevation in cardiac biomarkers such as troponin and creatinine kinase MB (CK-MB).33,49 The degree of troponin elevation could also correlate with major adverse cardiac events (MACE) outcomes as shown in a prospective observational study by Mahmood et al.43 There was a 4-fold increased risk of MACE with troponin T of ≥1.5 ng/ml (hazard ratio: 4.0; 95% confidence interval: 1.5 to 10.9; P = 0.003). Additionally, patients who experienced MACE myocarditis were found to have a higher admission, peak and discharge troponin T value. The diagnostic accuracy for troponin T and MACE was highest for discharge/final troponin T (area under the curve [AUC]: 0.81; P = 0.004) and fair for admission and peak troponin T (AUC: 0.76, P = 0.010; and AUC: 0.76, P = 0.010, respectively).

Electrocardiogram (EKG) and echocardiogram are readily available diagnostic tools for diagnosis of myocarditis. Nonspecific T-wave changes are the most common EKG abnormalities seen in myocarditis; however, new onset conduction blocks including complete heart blocks, arrhythmias, ST elevations mimicking ST elevation myocardial infarction (STEMI) and new onset Q waves may also be seen.50 The sensitivity of EKG in myocarditis is only 47%;
however, it is important to note that data pertaining to myocarditis related EKG changes in the setting of ICI therapy are limited.34 In a recent retrospective study, new EKG changes and systolic dysfunction were observed in up to 40% and 79% respectively, of all patients diagnosed with ICI-associated cardiotoxicity.33,52 Evidence supports the use of longitudinal global strain measured by echocardiogram to detect cardiotoxicity in patients undergoing chemotherapy.53,54

The role of cardiac MRI in the diagnosis of cardiac toxicity is debatable. While some studies have not found cardiac MRI to be particularly useful in the diagnosis of ICI-mediated cardiotoxicity, they still continue to recommend its use to differentiate ICI-related myocarditis from other etiologies of cardiac dysfunction.34 However, it is important to note that recent studies by Ganatra et al55 showed that cardiac MRI is highly sensitive and specific and can be used as a primary modality for diagnosis of suspected ICI associated myocarditis. Both T1/T2 weighted images and gadolinium based images compare similarly in the diagnosis of ICI mediated cardiotoxicity.55,56

Histological analysis of endomyocardial biopsy in patients with ICI-related myocarditis found lymphocytic infiltrates within the myocardium, cardiac sinus, and the atrioventricular nodes explaining the complete heart block demonstrated in these patients. Increased expression of CD8+ T cells and CD68+ macrophages were also observed suggesting direct myocardial injury by hyperactivated cytotoxic T cells as a possible mechanism of myocardial injury.33 It is important to note that endomyocardial biopsy, although has diagnostic value, has very limited clinical value due to the invasiveness of the procedure.

Management

Glucocorticoid therapy has been shown to improve left ventricular function measured as ejection fraction by 50% in the setting of ICI mediated cardiotoxicity.33 There are various proposed treatment regimens ranging from 30 mg of oral prednisone daily for isolated pericardial disease to 1000 mg of intravenous methylprednisolone daily for fulminant myocardial disease.33,57 Alternatively, oral prednisone at an initial dose of 1—2 mg/kg daily followed by a slow taper has been shown to be of benefit in patients without fulminant myocarditis.33,58 Other immunosuppressive regimens that can be used in steroid non-responders include plasmapheresis, intravenous immunoglobulins, anti-thymocyte globulin (ATG), mycophenolate mofetil, tacrolimus and infliximab.37,49,58,59 Data supporting the use of these therapies are lacking which largely limits their use in the treatment of cardiac toxicities.

It is of paramount importance to develop guidelines for early diagnosis and management of cardiotoxicity associated with ICIs. Currently, there are no definite treatment guidelines for these potentially fatal side effects although high dose steroids remain the cornerstone of therapy, as with IRAEs of any other organ system. Algorithms for diagnosing and managing IRAEs including ICI-related myocarditis have been proposed.30,55

Cardio-immuno-oncology: the future prospective

Time has come for cardiologists, oncologists and immunologists to work in close collaboration to diagnose and manage cardiotoxicity associated with ICI use, in a timely manner. The use of ICIs in the treatment of different cancers is predicted to increase in the near future and it is safe to assume so will cardiotoxicity. It is imperative to spread awareness about the manifestations of cardiotoxicity amongst clinicians. Close follow-up of patients on ICI with serial cardiac biomarkers, EKGs and cardiac echocardiograms should be incorporated into guideline management recommendations for patients receiving ICI therapy. It is important to acknowledge that the lack of prospective and cohort studies is a limitation as currently most of the data are observed from case reports and case series. Continued research in understanding the pathophysiology of ICI-related cardiotoxicity has the potential to help develop new therapeutic modalities. Future studies are needed to assess the long-term cardiotoxicity of ICIs. Together, we can make a difference!

Conflicts of interest

None declared.

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