Available online at www.sciencedirect.com

ScienceDirect

Chronic Diseases and Translational Medicine 5 (2019) 6−14

www.keaipublishing.com/en/journals/cdtm/

www.cdatm.org

Perspective

Managing cardiotoxicity associated with immune checkpoint inhibitors

Sireesha Upadhrasta [a], Hadi Elias [a], Keval Patel [b], Lei Zheng [c,*]

[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*

Received 9 December 2018

Available online 21 March 2019

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.[1,2] These pathways can be misused by tumor cells to escape immunologic antitumor responses. Studies by Allison et al[3] 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).

Peer review under responsibility of Chinese Medical Association.

Production and Hosting by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.cdtm.2019.02.004

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 al[24] 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 al[25,26] 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] Läubli et al[28] 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.

Table 1
List of ICIs, approval year, mechanism of action and current clinical indications.

Drug	Year approved	Mechanism of action	Target	Indications
Pembrolizumab (Keytruda)	2014	A mAb that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response leading to T cell proliferation and cytokine production.	PD-1	Melanoma NSCLC HNSCC cHL PMBCL Urothelial carcinoma Microsatellite instability-high cancer Gastric cancer Cervical cancer HCC
Nivolumab (Opdiv)	2014	A mAb that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response leading to T cell proliferation and cytokine production.	PD-1	Metastatic melanoma NSCLC Advanced RCC cHL HNSCC Urothelial carcinoma Metastatic colorectal cancer HCC
Atezolizumab (Tecentriq)	2016	A mAb that binds to PD-L1 and blocks its interaction with both PD1 and B7.1 receptors, which suppresses T-cell activity and cytokine production.	PD-L1	Metastatic urothelial carcinoma NSCLC
Avelumab (Bavencio)	2017	A mAb that binds to PD-L1 and blocks its interaction with both PD1 and B7.1 receptors, which suppresses T-cell activity and cytokine production.	PD-L1	Metastatic Merkel cell carcinoma Metastatic urothelial carcinoma
Durvalumab (Imfinzi)	2017	A mAb that binds to PD-L1 and blocks its interaction with both PD1 and B7.1 receptors, which suppresses T-cell activity and cytokine production.	PD-L1	Metastatic urothelial carcinoma NSCLC
Ipilimumab (Yervoy)	2011	A mAb that binds to CTLA-4 and blocks interaction of CTLA-4 with its ligands CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells.	CTLA-4	Metastatic melanoma

ICIs: immune checkpoint inhibitors; mAb: monoclonal antibody; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; PD-L2: programmed cell death ligand 2; NSCLC: non-small-cell lung cancer; HNSCC: head and neck squamous cell carcinoma; cHL: classical Hodgkin lymphoma; PMBCL: primary mediastinal B-cell lymphoma; HCC: hepatocellular carcinoma; RCC: renal cell carcinoma; CTLA-4: cytotoxic T lymphocyte associated antigen 4; CD: cluster of differentiation.

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.[29] The second mechanism involves expansion of T-cells targeting a common antigen shared by the tumor and the heart. Johnson et al[30] 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.[29,30] 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 cardiomuscular 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 al[30] 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 al[40] 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 al[40] 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 preformed.	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 (1.06)
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-exiting risk factors might affect the incidence of ICI mediated cardiotoxicity. In a case-series by Mahmood et al,[43] 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[44] 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[46] and Johnson et al[47] 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 $\geq$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.[51] 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 al[55] 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.

References

1. Varricchi G, Galdiero MR, Tocchetti CG. Cardiac toxicity of immune checkpoint inhibitors: cardio-oncology meets immunology. *Circulation*. 2017;136:1989−1992.
2. Mahoney KM, Freeman GJ, McDermott DF. The next immune-checkpoint inhibitors: PD-1/PD-L1 blockade in melanoma. *Clin Ther*. 2015;37:764−782.
3. Allison JP, Hurwitz AA, Leach DR. Manipulation of costimulatory signals to enhance antitumor T-cell responses. *Curr Opin Immunol*. 1995;7:682−686.

4. Eigentler TK, Hassel JC, Berking C, et al. Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. *Cancer Treat Rev.* 2016;45:7−18.
5. Hurst JH. Cancer immunotherapy innovator James Allison receives the 2015 Lasker~DeBakey clinical medical research award. *J Clin Invest*. 2015;125:3732−3736.
6. Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature*. 2014;515:563−567.
7. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet*. 2016;387:1837−1846.
8. Nayak L, Iwamoto FM, LaCasce A, et al. PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma. *Blood*. 2017;129:3071−3073.
9. Varricchi G, Marone G, Mercurio V, Galdiero MR, Bonaduce D, Tocchetti CG. Immune checkpoint inhibitors and cardiac toxicity: an emerging issue. *Curr Med Chem*. 2018;25:1327−1339.
10. Maawy AA, Ito F. Future of immune checkpoint inhibitors. In: Ito F, Ernstoff M, eds. *Immune Checkpoint Inhibitors in Cancer*. St. Louis, MO: Elsevier, Inc; 2019:227−243.
11. Della Vittoria Scarpati G, Fusciello C, Perri F, et al. Ipilimumab in the treatment of metastatic melanoma: management of adverse events. *Onco Targets Ther*. 2014;7:203−209.
12. Lyon AR, Yousaf N, Battisti NML, Moslehi J, Larkin J. Immune checkpoint inhibitors and cardiovascular toxicity. *Lancet Oncol*. 2018;19:e447−e458.
13. Costa R, Carneiro BA, Agulnik M, et al. Toxicity profile of approved anti-PD-1 monoclonal antibodies in solid tumors: a systematic review and meta-analysis of randomized clinical trials. *Oncotarget*. 2017;8:8910−8920.
14. Heinzerling L, Ott PA, Hodi FS, et al. Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. *J Immunother Cancer*. 2016;4:50.
15. Tocchetti CG, Galdiero MR, Varricchi G. Cardiac toxicity in patients treated with immune checkpoint inhibitors: it is now time for cardio-immuno-oncology. *J Am Coll Cardiol*. 2018;71:1765−1767.
16. Brahmer JR, Lacchetti C, Thompson JA. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline summary. *J Oncol Pract*. 2018;14:247−249.
17. Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(suppl 4):iv264−iv266.
18. Walker LS, Sansom DM. The emerging role of CTLA4 as a cell-extrinsic regulator of T cell responses. *Nat Rev Immunol*. 2011;11:852−863.
19. Yang J, Riella LV, Chock S, et al. The novel costimulatory programmed death ligand 1/B7.1 pathway is functional in inhibiting alloimmune responses in vivo. *J Immunol*. 2011;187:1113−1119.
20. Grabie N, Gotsman I, DaCosta R, et al. Endothelial programmed death-1 ligand 1 (PD-L1) regulates CD8+ T-cell−mediated injury in the heart. *Circulation*. 2007;116:2062−2071.
21. Lucas JA, Menke J, Rabacal WA, Schoen FJ, Sharpe AH, Kelley VR. Programmed death ligand 1 regulates a critical checkpoint for autoimmune myocarditis and pneumonitis in MRL mice. *J Immunol*. 2008;181:2513−2521.
22. Wang J, Okazaki IM, Yoshida T, et al. PD-1 deficiency results in the development of fatal myocarditis in MRL mice. *Int Immunol*. 2010;22:443−452.
23. Waterhouse P, Penninger JM, Timms E, et al. Lymphoproliferative disorders with early lethality in mice deficient in CTLA-4. *Science*. 1995;270:985−988.
24. Tarrio ML, Grabie N, Bu D, Sharpe AH, Lichtman AH. PD-1 protects against inflammation and myocyte damage in T cell-mediated myocarditis. *J Immunol*. 2012;188:4876−4884.
25. Nishimura H, Okazaki T, Tanaka Y, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. *Science*. 2001;291:319−322.
26. Nishimura H, Nose M, Hiai H, Minato N, Honjo T. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity*. 1999;11:141−151.
27. Tivol EA, Borriello F, Schweitzer AN, Lynch WP, Bluestone JA, Sharpe AH. Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. *Immunity*. 1995;3:541−547.
28. Läubli H, Balmelli C, Bossard M, Pfister O, Glatz K, Zippelius A. Acute heart failure due to autoimmune myocarditis under pembrolizumab treatment for metastatic melanoma. *J Immunother Cancer*. 2015;3:11.
29. Tajiri K, Aonuma K, Sekine I. Immune checkpoint inhibitor-related myocarditis. *Jpn J Clin Oncol*. 2018;48:7−12.
30. Johnson DB, Balko JM, Compton ML, et al. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med*. 2016;375:1749−1755.
31. Brichard VG, Louahed J, Clay TM. Cancer regression and neurological toxicity cases after anti-MAGE-A3 TCR gene therapy. *J Immunother*. 2013;36:79−81.
32. Schooten E, Di Maggio A, van Bergen En Henegouwen PMP, Kijanka MM. MAGE-A antigens as targets for cancer immunotherapy. *Cancer Treat Rev*. 2018;67:54−62.
33. Yang S, Asnani A. Cardiotoxicities associated with immune checkpoint inhibitors. *Curr Probl Cancer*. 2018;42:422−432.
34. Semper H, Muehlberg F, Schulz-Menger J, Allewelt M, Grohé C. Drug-induced myocarditis after nivolumab treatment in a patient with PDL1- negative squamous cell carcinoma of the lung. *Lung Cancer*. 2016;99:117−119.
35. Geisler BP, Raad RA, Esaian D, Sharon E, Schwartz DR. Apical ballooning and cardiomyopathy in a melanoma patient treated with ipilimumab: a case of takotsubo-like syndrome. *J Immunother Cancer*. 2015;3:4.
36. de Almeida DVP, Gomes JR, Haddad FJ, Buzaid AC. Immune-mediated pericarditis with pericardial tamponade during nivolumab therapy. *J Immunother*. 2018;41:329−331.
37. Norwood TG, Westbrook BC, Johnson DB, et al. Smoldering myocarditis following immune checkpoint blockade. *J Immunother Cancer*. 2017;5:91.
38. Larkin J, Hodi FS, Wolchok JD. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373:1270−1271.
39. Wang DY, Salem JE, Cohen JV, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. *JAMA Oncol*. 2018;4:1721−1728.
40. Salem JE, Manouchehri A, Moey M, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an

observational, retrospective, pharmacovigilance study. *Lancet Oncol*. 2018;19:1579−1589.
41. VigiAccess (n.d.). http://www.vigiaccess.org/. Accessed December 3, 2018.
42. Varricchi G, Galdiero MR, Mercurio V, Bonaduce D, Marone G, Tocchetti CG. Pharmacovigilating cardiotoxicity of immune checkpoint inhibitors. *Lancet Oncol*. 2018;19:1545−1546.
43. Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol*. 2018;71:1755−1764.
44. Moslehi JJ, Salem JE, Sosman JA, Lebrun-Vignes B, Johnson DB. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. *Lancet*. 2018;391:933.
45. Khan SA, Pruitt SL, Xuan L, Gerber DE. Prevalence of autoimmune disease among patients with lung cancer: implications for immunotherapy treatment options. *JAMA Oncol*. 2016;2:1507−1508.
46. Menzies AM, Johnson DB, Ramanujam S, et al. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. *Ann Oncol*. 2017;28:368−376.
47. Johnson DB, Sullivan RJ, Menzies AM. Immune checkpoint inhibitors in challenging populations. *Cancer*. 2017;123:1904−1911.
48. Abdel-Rahman O. Does a patient's sex predict the efficacy of cancer immunotherapy? *Lancet Oncol*. 2018;19:716−717.
49. Reddy N, Moudgil R, Lopez-Mattei JC, et al. Progressive and reversible conduction disease with checkpoint inhibitors. *Can J Cardiol*. 2017;33:1335.e13−1335.e15.
50. Gianni M, Dentali F, Grandi AM, Sumner G, Hiralal R, Lonn R. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. *Eur Heart J*. 2006;27:1523−1529.
51. Blauwet LA, Cooper LT. Myocarditis. *Prog Cardiovasc Dis*. 2010;52:274−288.
52. Escudier M, Cautela J, Malissen N, et al. Clinical features, management, and outcomes of immune checkpoint inhibitor−related cardiotoxicity. *Circulation*. 2017;136:2085−2087.
53. Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. *J Am Coll Cardiol*. 2014;63:2751−2768.
54. Mornoş C, Petrescu L. Early detection of anthracycline-mediated cardiotoxicity: the value of considering both global longitudinal left ventricular strain and twist. *Can J Physiol Pharmacol*. 2013;91:601−607.
55. Ganatra S, Neilan TG. Immune checkpoint inhibitor-associated myocarditis. *Oncologist*. 2018;23:879−886.
56. Aquaro GD, Perfetti M, Camastra G, et al. Cardiac MR with late gadolinium enhancement in acute myocarditis with preserved systolic function: ITAMY study. *J Am Coll Cardiol*. 2017;70:1977−1987.
57. Kushnir I, Wolf I. Nivolumab-induced pericardial tamponade: a case report and discussion. *Cardiology*. 2017;136:49−51.
58. Jain V, Bahia J, Mohebtash M, Barac A. Cardiovascular complications associated with novel cancer immunotherapies. *Curr Treat Options Cardiovasc Med*. 2017;19:36.
59. Frigeri M, Meyer P, Banfi C, et al. Immune checkpoint inhibitor-associated myocarditis: a new challenge for cardiologists. *Can J Cardiol*. 2018;34:92.e1−92.e3.

Edited by Pei-Fang Wei