JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2018, 48(1) 7–12
doi: 10.1093/jjco/hyx154
Advance Access Publication Date: 13 November 2017
Review Article

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Review Article

Immune checkpoint inhibitor-related myocarditis

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Received 12 July 2017; Editorial Decision 7 September 2017; Accepted 30 September 2017

Abstract

Immune checkpoint inhibitors have demonstrated significant clinical benefit in many cancers. The clinical benefit afforded by these treatments can be accompanied by a unique and distinct spectrum of adverse events. Recently, several fatal cases of immune checkpoint inhibitor-related myocarditis were reported. Although its frequency is comparatively lower than that of other immune-related adverse events, myocarditis can lead to circulatory collapse and lethal ventricular arrhythmia. Immune checkpoints, cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1), play important roles in establishing peripheral tolerance to the heart. Evidence from studies using genetically engineered mouse models suggests that CTLA-4 signaling terminates proliferation and promotes anergy during the primary response to cardiac self-peptide recognition. PD-1 signaling restrains autoreactive T cells that enter the peripheral tissues and recognize cardiac-peptide, maintaining them in an anergic state. Patients affected by immune checkpoint inhibitor-related myocarditis often experience rapid onset of profound hemodynamic compromise progressing to cardiogenic shock. Early diagnosis is mandatory to address specific therapy and correct the timing of circulatory support. However, the diagnosis of myocarditis is challenging due to the heterogeneity of clinical presentations. Owing to its early onset, nonspecific symptomatology and fulminant progression, especially when these drugs are used in combination, oncologists should be vigilant for immune checkpoint inhibitor-related myocarditis. With many questions yet to be answered, from basic immune biology to clinical management, future research should aim to optimize the use of these drugs by identifying predictive biomarkers of either a response to therapy or the risks of myocarditis development.

Key words: immune checkpoint inhibitors, myocarditis, programmed cell death protein 1, cytotoxic T-lymphocyte antigen 4, immune-related adverse events

Introduction

To evade elimination by the host immune system, tumor cells commonly overexpress the ligands of immune checkpoint receptors, bringing T cells to a state of non-responsiveness or exhaustion (1,2). Immune checkpoint inhibitors work by blocking the inhibitory pathways of T-cell activation, facilitating an effective T-cell-mediated antitumour immune response. Targeting therapies against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and one of its ligands programmed cell death ligand 1 (PD-L1) have demonstrated significant success in cancer treatment in recent years; however, immune-related adverse events have been observed in patients treated with immune checkpoint inhibitors with a relatively high frequency (3–5). Recently, several cases of immune checkpoint inhibitor-related myocarditis were reported (6–13). Although its frequency is comparatively lower than other immune-related adverse events, myocarditis can become life-threatening.

In this review, we focus on the physiological role of CTLA-4 and PD-1-PD-L1 axes in the establishment and maintenance of immune tolerance to cardiac self-antigens and possible mechanisms of development of immune checkpoint inhibitor-related myocarditis. We also summarize the current literature on immune checkpoint inhibitor-related myocarditis, highlighting the clinical presentations, diagnosis and treatment.

Myocarditis and cardiac antigen-reactive T cells

Myocarditis is a disease characterized by the presence of inflammatory infiltrates in the myocardium, which can lead to inflammatory dilated cardiomyopathy (DCM) and ultimately to congestive heart failure (14). A variety of agents, including drugs, toxins, bacteria and viruses, are known to trigger myocarditis, and subsequent autoimmune response is thought to contribute to the disease progression (15). The contribution of autoimmunity to the pathophysiology of myocarditis is supported by the presence of cardiac-specific autoantibodies (16,17) and cardiac antigen-specific T cells (18), the genetic linkage between susceptibility to myocarditis and the major histocompatibility complex (MHC) genes (19), and the proven benefits of immunosuppressive treatment for some types of myocarditis (20).

Substantial evidence suggests that cardiac antigen-reactive T lymphocytes play a key role in autoimmune myocarditis (15). Normally, most autoreactive T cells are eliminated in the thymus through a process known as central immune tolerance. However, some cardiac antigen-reactive T cells can escape the negative selection and enter the periphery, potentially inflicting destructive autoimmune pathology against the heart (21,22). Lv et al. reported that transcripts for heart-specific myosin heavy chain α isoform (MyHC-α) were absent in both mouse and human medullary thymic epithelial cells and that MyHC-α reactive T cells were markedly more abundant in myocarditis mice and patients (18). Surprisingly, these MyHC-α reactive T cells were also found in healthy subjects, suggesting that peripheral immune tolerance is crucial to prevent these self-reactive T cells from inducing autoimmune myocarditis (21,23,24). The mechanism of peripheral immune tolerance is complicated, and immune checkpoints CTLA-4 and PD-1 are thought to play important roles in establishing peripheral tolerance to the heart (25).

Preventing cardiac autoimmunity

CTLA-4 signaling

CTLA-4 is an inhibitory co-receptor expressed on the surface of activated T cells and emerges as a key negative regulator of T-cell activation and an enforcer of peripheral tolerance to the heart, operating primarily via antagonism of CD28-mediated co-stimulation. Animal studies have revealed the importance of CTLA-4 pathway in preventing cardiac autoimmunity. In an experimental autoimmune myocarditis mouse model, anti-CTLA-4 antibody significantly increased the severity of myocardial inflammation (26). A CTLA-4-deficient murine model has demonstrated rapid development of spontaneous lymphoproliferative disease with multiorgan lymphocytic infiltration, tissue destruction, with particularly severe myocarditis and pancreatitis, and death within the first few weeks of life (27,28). Of note, loss of CTLA-4 expression in regulatory T cells (Tregs) alone also triggered fatal lymphoproliferation with severe myocardial infiltration and marked myocyte damage, although the onset of the histological changes was delayed until 7 weeks of age. These results suggest that CTLA-4 deficiency in Tregs alone suffices to cause myocarditis; however, the additional CTLA-4 deficiency in conventional T cells enhances the disease (29,30). Lv et al. reported that CTLA-4 significantly limited cytotoxic T-cell proliferation and pathogenicity in myocarditis, and CTLA-4-deficient $CD8^+$ cytotoxic T lymphocytes were more pathogenic than wild-type T cells in inducing myocarditis (31). Thus, the cardiotoxic effects induced by CTLA-4 checkpoint inhibitors could be explained by lowering the threshold for T-cell activation specific for cardiac antigens (11).

PD-1-PDL1 signaling

PD-1 signaling restrains autoreactive T cells that enter the heart and recognize cardiac self-peptide, maintaining them in an anergic state (25). Nishimura and colleagues reported that PD-$1^{-/-}$ mice on BALB/c background died at an early age as a result of the impaired function of enlarged hearts, similar to human DCM (32). Interestingly, there is almost no inflammatory cell infiltration in the hearts of PD-1-deficient BALB/c mice, and subsequent analyses revealed that autoantibodies against cardiac troponin I are responsible for the disease (33). However, PD-1 deficiency in the autoimmune-prone MRL mice induced lymphocytic myocarditis with massive infiltration of $CD4^+$ and $CD8^+$ T cells, and died by 10 weeks of age (34). A similar lethal lymphocytic myocarditis occurred in PD-L1-deficient MRL mice, characterized by both $CD8^+$ and $CD4^+$ T-cell infiltrates (35). Interestingly, PD-L1 on bone marrow-derived cells also played important roles in the prevention of myocarditis in PD-L1-deficient MRL mice, confirmed by the observation that bone marrow cells from MRL-PD-$L1^{-/-}$ mice were able to induce myocarditis in wild-type mice.

The role of PD-1 in regulating pathogenic T-cell responses in the heart is clearly shown by using T-cell-mediated myocarditis models (36). Using a $CD8^+$ T-cell-mediated adoptive transfer model, Tarrio and colleagues reported that mice receiving PD-1-deficient $CD8^+$ T-cells showed enhanced pathology with severe neutrophil infiltration in the heart (36). In experimental autoimmune myocarditis, a $CD4^+$ T-cell-mediated disease, mice lacking PD-1 also developed enhanced myocarditis compared with wild-type mice (36). Together, these studies showed that PD-1 controlled not only $CD8^+$ T-cell response but also $CD4^+$ T-cell response (36).

PD-L1 is significantly unregulated on cardiac endothelial cells during myocarditis, which is dependent on T-cell-derived interferon-γ (37). Through interaction with its co-receptor PD-1, PD-L1 limits TCR-mediated activation of T cells and has been shown to reduce disease severity in $CD8^+$ T-cell myocarditis and experimental autoimmune myocarditis (36,37).

Possible mechanisms

There are at least two possible mechanisms for the development of immune checkpoint inhibitor-related myocarditis. One is the breakdown of peripheral immune tolerance to the heart (Fig. 1). CTLA-4 monoclonal antibody (mAb) interferes with CTLA-4-B7 interactions that induce anergy among cardiac antigen-reactive T cells, resulting in lowering the threshold for T-cell activation. Moreover, anti-CTLA-4 treatment may also target Tregs that constitutively express CTLA-4. CTLA-4 blockade may affect *in vivo* Treg suppressive function, leading to enhanced cardiac-reactive T-cell activation. Anti-PD-1 antibodies induce T-cell activation by preventing binding of PD-1 with its ligands. Blocking of PD-L1 on both APCs and cardiomyocytes may potentiate cardiac-reactive T-cell activity. Inhibitors of PD-1 and PD-L1 can enable the T cells to remain active and co-ordinate an attack to the heart.

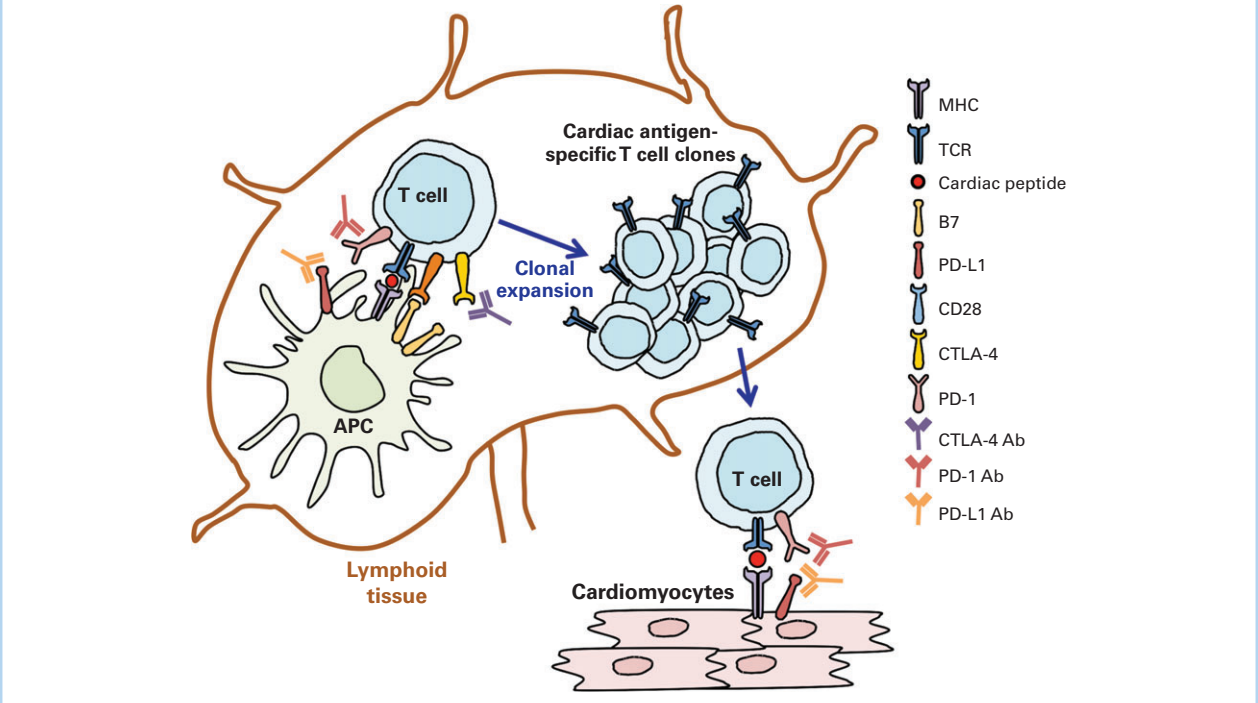

Figure 1. Immune checkpoint inhibitor-induced breakdown of peripheral immune tolerance to the heart. Targeting CTLA-4 and PD-1 signaling could activate cardiac antigen-specific T cells that escape central tolerance in the lymphoid tissue. Those T cells clonally expand and enter the heart. Anti-PD-1 antibodies induce T-cell activation by preventing binding of PD-1 with its ligands. Blocking of PD-L1 on cardiac cells and PD-1 on heart-reactive T cells can enable the T cells to remain active and co-ordinate an attack to the heart.

Another potential mechanism is the expansion of T cells targeting an antigen shared by the tumor and the heart (Fig. 2). Johnson and colleagues recently reported two cases of lethal myocarditis accompanied by myositis in patients treated with a combination of nivolumab and ipilimumab (9). They found that selective clonal T-cell populations infiltrating the myocardium were identical to those present in tumors and skeletal muscle, suggesting that these T cells may be responding to a common antigen. In support of this hypothesis, they further observed high levels of muscle-specific antigens (desmin and troponin) in tumors from these patients. Taken together, these observations suggest that T cells targeting an antigen shared by the tumor and the heart may exist, and the immune checkpoint inhibitors can enhance the T-cell effector function, resulting in the development of lethal autoimmune myocarditis.

Clinical aspects

To date, four immune checkpoint inhibitors have been approved by the FDA: ipilimumab, a CTLA-4-blocking mAb; pembrolizumab and nivolumab, PD-1-blocking mAbs; and atezolizumab, a PD-L1-targeted mAb. A pharmacovigilance analysis revealed that the incidence of myocarditis was 0.09% in patients treated with nivolumab or a combination of nivolumab and ipilimumab (9). Patients treated with a combination of ipilimumab and nivolumab appeared to have more frequent and severe myocarditis compared with patients receiving nivolumab alone (0.27% vs 0.06%, $P < 0.001$, five fatal cases vs one case). However, since cardiac monitoring has not been routinely performed, the true incidence is unknown.

Clinical presentation and diagnosis

The clinical presentation and diagnostic tests of immune checkpoint inhibitor-related myocarditis are summarized in Table 1. In immune checkpoint inhibitor-related myocarditis, cardiac signs and symptoms were reported to be heterogeneous and lacking specificity, and some affected patients were even asymptomatic (6–13). Signs and symptoms varied from atypical chest pain to cardiogenic shock, depending on the degree of myocardial inflammation and ventricular dysfunction. The time to onset was variable, but fatal myocarditis cases have been reported after a single treatment with nivolumab (7) and the combination of nivolumab and ipilimumab (9). Myocarditis occurred alone or with other immune-related adverse events. In many cases, the serum levels of cardiac biomarkers (creatine kinase [CK], troponin I/T) were elevated, likely due to myocardial injury.

The majority of patients with immune checkpoint inhibitor-related myocarditis showed abnormal electrocardiogram (ECG) patterns, with a variety of findings (8–13), including nonspecific ST- segment and T-wave abnormalities, conduction abnormalities such as bundle-branch blocks and atrioventricular conduction delays, and all types of atrial and ventricular tachy and bradyarrhythmias. PR-segment depression and ST-segment elevation without reciprocal changes were observed with pericardial inflammation.

Echocardiography is one of the most useful clinical tools for diagnostic evaluation and management. Temporal changes in ventricular function, cardiac chamber size, and thickness may occur very quickly in myocarditis in parallel to disease progression, requiring repeat-echocardiographic examinations (38). Typically in fulminant myocarditis, the left ventricle was non-dilated, thickened

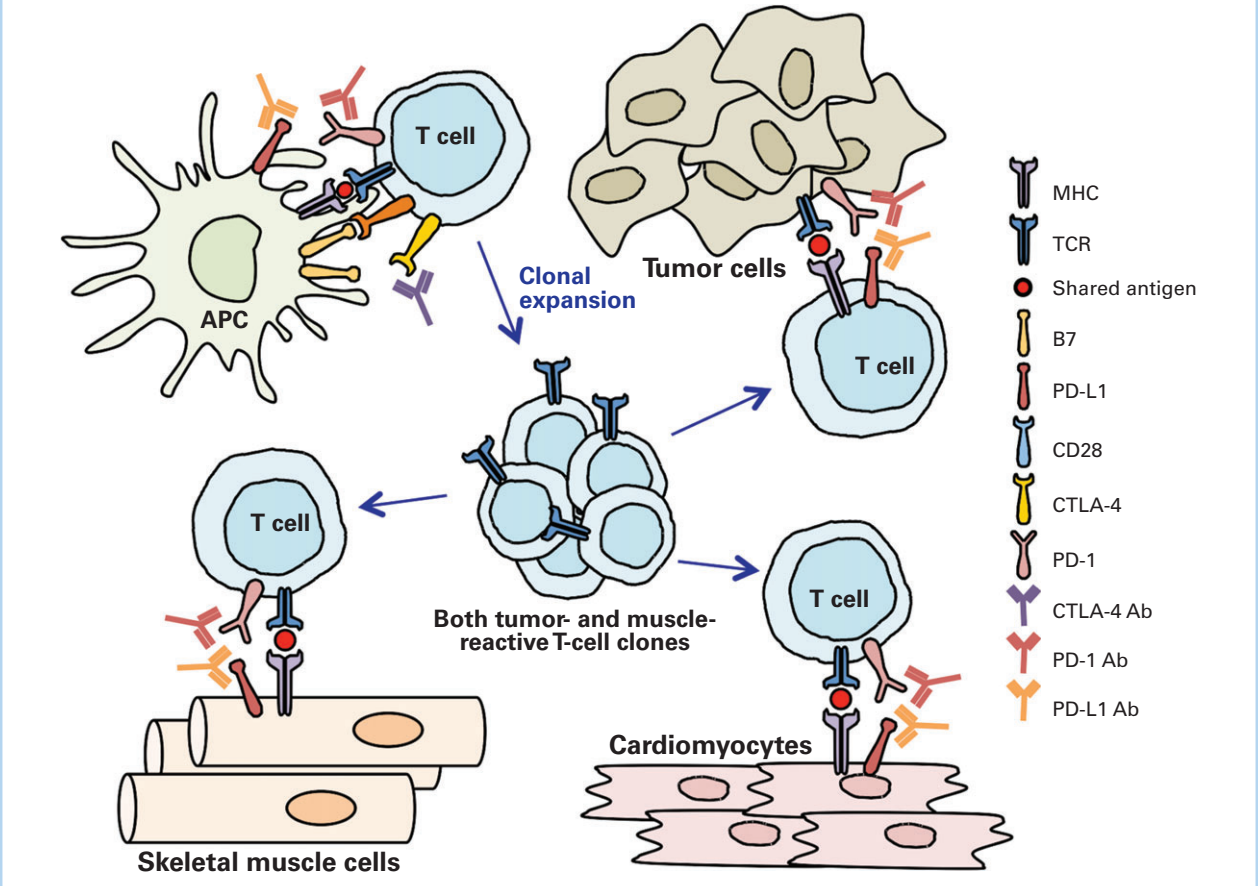

Figure 2. Immune checkpoint inhibitor-induced expansion of T cells targeting an antigen shared by the tumor, skeletal muscle and the heart. As a consequence of immune checkpoint blockade, T cells targeting an antigen shared by the tumor, skeletal muscle and the heart expand clonally. These T cells are highly activated by the immune checkpoint inhibitors and attack not only the tumor but also skeletal muscle and the heart.

Table 1. Symptoms, signs, and clinical tests of immune checkpoint inhibitor-related myocarditis

Signs and symptoms
- Vary from chest discomfort, peripheral edema, dyspnea, fatigue and palpitation to cardiogenic shock and collapse with cardiac arrest
- Variable time to onset, from a few weeks to a few months
- Accompanied with/without other immune-related adverse events

Biomarkers
- Troponin I/T and creatine kinase MB
- B-type natriuretic peptide (BNP)/N-terminal prohormone of BNP (NT-pro BNP)

Electrocardiogram
- ST/T-wave change (ST elevation or non-ST elevation, T-wave inversion): PR-segment depression and ST-segment elevation without reciprocal changes
- Atrioventricular block, bundle-branch block, intraventricular conduction delay
- Atrial and ventricular tachyarrhythmia
- Sinus arrest, asystole, bradyarrhythmia

Echocardiography
- Transient wall thickening, Temporal changes of ventricular function, cardiac chamber size with/without pericardial effusion

Cardiovascular magnetic resonance imaging
- Regional or global myocardial signal intensity increase in T2-weighted images
- Increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images
- Nonischemic regional distribution of late gadolinium enhancement in inversion recovery-prepared gadolinium-enhanced T1-weighted images

Endomyocardial biopsy
- T-cell (with a predominance of $CD8^+$) and macrophage infiltrates in the myocardium with/without the conduction system

and globally hypocontractile, but regional wall-motion abnormalities were also present in some cases (8–12).

The endomyocardial biopsy remains the gold standard for the diagnosis of myocarditis (39,40). Due to the nature of the disease, inflammatory infiltrates can be focal and transient, and sometimes inaccessible to the bioptome. Hence, sampling error contributes appreciably to false-negative diagnosis in biopsy sample from patients with myocarditis (39). In the histopathological examination, T-cell (with a predominance of $CD8^+$) and macrophage infiltration were typically observed in the myocardium of immune checkpoint inhibitor-related myocarditis (6,8–11). It sometimes involved the cardiac conduction system, leading to conduction block. To optimize diagnostic accuracy and reduce sampling error in focal myocarditis, endomyocardial biopsy should be performed early in the course of the disease and multiple specimens should be collected (39). Endomyocardial biopsy should be repeated if necessary to monitor response to etiology-directed therapy, or if a sampling error is suspected in a patient with unexplained progression of heart failure (40).

Cardiovascular magnetic resonance (CMR) imaging enables non-invasive tissue characterization of the myocardium and can support the diagnosis of myocarditis. CMR assessment of right and left ventricular function is very reproducible and allows for identifying, quantifying, and following even mild functional abnormalities, if present (41). Owing to its ability to provide detailed information about myocardial inflammation, CMR has become the primary tool for non-invasive assessment of myocardial inflammation in patients with suspected myocarditis. Semper and colleagues reported an immune checkpoint inhibitor-related myocarditis case confirmed by CMR techniques, which showed signs of active myocardial inflammation, i.e. globally elevated T2 times in T2 mapping and increased early enhancement after gadolinium administration (12). CMR methodology is evolving at a rapid pace. Novel approaches for characterizing tissue such as time-resolved assessment of gadolinium wash-out, T1 mapping, T2 mapping, parametric imaging, and combination of imaging criteria with cardiac injury biomarkers likely will further increase the utility of CMR for diagnosis (41).

Patients affected by immune checkpoint inhibitor-related myocarditis often experienced rapid onset of profound hemodynamic compromise progressing to cardiogenic shock. Early diagnosis is mandatory to address specific therapy and correct the timing of circulatory support (42). However, the diagnosis of myocarditis is challenging owing to the heterogeneity of clinical presentations. There currently are no standardized monitoring protocols for the development of immune checkpoint inhibitor-related myocarditis. For early detection of subclinical myocarditis, serial ECG and troponin testing would be useful in all patients before and during the treatment. If there is a suspicion of drug-induced myocarditis, urgent diagnostic procedures should be performed to exclude other reasons of heart affection like myocardial infarction or infectious myocarditis. Patients presenting with ST elevations, elevated cardiac markers, and ischemic symptoms should undergo prompt coronary angiography to rule out acute coronary syndromes.

Clinical management

In general myocarditis, about half of the cases resolves in the first 2–4 weeks, about 25% will develop persistent cardiac dysfunction, and 12–25% may acutely deteriorate and either die or progress to end-stage DCM with a need for heart transplantation (40). However, a pharmacovigilance analysis revealed that the mortality of immune checkpoint inhibitor-related myocarditis exceeded 60% in patients receiving the combination of nivolumab plus ipilimumab (9). In patients taking nivolumab alone, the mortality was still 10% (9). Clinicians should be aware that the immune checkpoint blockade-related myocarditis may have worse prognosis than general myocarditis; therefore, rapid and appropriate management is necessary.

Highdose steroids have been used to treat immune checkpoint blockade-related myocarditis (7,9–12). In patients without an immediate response to highdose steroids, the administration of other immunosuppressive drugs, high-dose intravenous immunoglobulin, or immunoadsorption therapy should be considered according to the treatment strategy for general myocarditis (40). Restriction of physical activity, heart failure therapy and antiarrhythmic management according to current guidelines are fundamental treatment options.

In surviving patients, ventricular function was partial or fully recovered at discharge; however, some might proceed to develop DCM in the future. In general myocarditis, up to 30% of biopsy-proven myocarditis progressed to DCM and a poor prognosis (40). Long-term follow-up of patients diagnosed with immune checkpoint-related myocarditis will be necessary. Moreover, all patients treated with immune checkpoint inhibitors should be made aware of the high risk for cardiac dysfunction, because undiagnosed subclinical myocarditis may exist.

Conclusions

With early onset, nonspecific symptomatology, and fulminant progression, especially when these drugs are used in combination, oncologists should be vigilant for immune checkpoint inhibitor-related myocarditis. With many questions yet to be explored, from basic immune biology to clinical management, future research should aim to optimize the use of these drugs by identifying predictive biomarkers of either a response to therapy or the risks of myocarditis development. In addition, more work is needed to establish the true incidence of immune checkpoint inhibitor-related myocarditis. The denominator of patients treated with immune checkpoint inhibitors should be carefully evaluated so that the frequency of manifestations can be understood and the risk of these events can be appropriately presented to patients. Currently, a numbers of cancer drugs targeting novel immunomodulatory targets have been explored, and some of them are studied in clinical trials (43). We strongly recommend careful and close cardiac monitoring in using these drugs that may affect immune tolerance to the heart.

Recently, a wide variety of cardiovascular toxicities have been observed in patients treated with targeted drugs and have become a critically important topic of discussion for the practicing oncologist and cardiologists (44,45). Awareness of the potential side effects, recognition of signs and symptoms, and the establishment of therapeutic strategies are all crucial to providing quality patient care.

Conflict of interest statement

The authors declare no conflicts of interest.

Funding

This work was supported by a grant from Daiwa Securities Health Foundation.

Acknowledgments

We would like to thank Editage (www.editage.jp) for English language editing.

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