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Review

Overview of the Cardiotoxicity Induced by PD-1/PD-L1 Immune Checkpoint Inhibitor in Critical Care

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ABSTRACT

The Programmed Cell Death 1 (PD-1)/Programmed Death Ligand 1 (PD-L1) Immune Checkpoint Inhibitors (ICIs), have become a hot spot in the field of cancer research and treatment, and bring new hope to patients with advanced tumors. But, in addition to enhancing the anti-tumor effect of T cells, PD-1/PD-L1 inhibitors can also abnormally enhance the immune response, leading to the imbalance of immune tolerance. So, the adverse reactions of multiple system damage, including cardiotoxicity, which are named as immune-related adverse events, emerged one after another. PD-1/PD-L1 inhibitors-related cardiotoxicity is rare but fatal T-cell-driven drug reaction, which includes myocarditis, pericardial disease, vasculitis, Takotsubo syndrome, etc. The incidence of cardiotoxicity is not over 1%, but with high mortality. In recent years, with the popularity of PD-1/PD-L1 ICIs, increasing patients have been admitted to critical care because of severe or fatal cardiotoxicity. At present, adverse cardiac events caused by cardiotoxicity is not systematically reviewed, Intensive care physicians know little about this, and its treatment experience is even less. This review focuses on current knowledge about severe adverse cardiac events caused by PD-1/PD-L1 inhibitors. This study aimed to improve the intensive care physician's understanding and attention to cardiotoxicity induced by PD-1/PD-L1 inhibitors.

1. INTRODUCTION

The Programmed Cell Death 1 (PD-1) and Cytotoxic T-lymphocyte-associated Antigen-4 (CTLA-4) Immune Checkpoint Inhibitors (ICIs), have become a hot spot in the field of cancer research and treatment, and bring new hope to patients with advanced tumors [1]. Among them, PD-1, a member of the B7/CD28 superfamily, is the inhibitory molecules which regulate T cell survival and activation through binding to its ligands, Programmed Death Ligand 1, 2 (PD-L1, 2). The researchers found that blockade of PD-1 or PD-L1 has significantly increased the survival rate of various types of cancer, and the inhibitors of PD-1 and PD-L1 have been applied to more and more cancer patients [2,3]. But, in addition to enhancing the anti-tumor effect of T cells, PD-1/PD-L1 inhibitors can also abnormally enhance the immune response, leading to the imbalance of immune tolerance. So, the adverse reactions of multiple system damage, including cardiovascular system, which are named as Immune-related Adverse Events (irAEs), emerged one after another [4,5]. In recent years, with the popularity of PD-1/PD-L1 ICIs, increasing patients have been admitted to critical care because of severe or fatal irAEs.

The most common causes of death for PD-1/PD-L1 inhibitors were colitis and myocarditis [6,7]. In 2019, Guidelines for the management of toxicities associated with ICIs of the Chinese Society of Clinical Oncology, defined PD-1/PD-L1 inhibitor-associated cardiac adverse events as "cardiotoxicity", and the incidence is not over 1%, but with high mortality [8]. In recent years, PD-1/PD-L1 inhibitor-associated cardiotoxicity has become a new severe and fatal cardiac challenge for intensive care physicians in addition to acute myocardial infarction and cardiogenic shock. At present, adverse cardiac events caused by cardiotoxicity is not systematically reviewed, intensive care physicians know little about this, and its treatment experience is even less. This review focuses on current knowledge about severe adverse cardiac events caused by PD-1/PD-L1 inhibitors. This study aimed to improve the intensive care physician's understanding and attention to cardiotoxicity induced by PD-1/PD-L1 inhibitors.

2. CARDIOTOXICITY ASSOCIATED WITH PD-1/PD-L1 ICIs

Programmed Death Ligand 1 is highly expressed in T cells of the heart, but cardiotoxicity associated with PD-1/PD-L1 ICIs is not a common complication. It has low incidence but high mortality [8]. The cardiotoxicity of PD-1/PD-L1 ICIs have long been underestimated or even neglected. The literatures about case reports and researches describing cardiotoxicity associated with PD-1/PD-L1 ICIs is increasing in recent years [7,9]. In animal models of colon CT26 cancer with lung metastases, the researchers found that PD-1/PD-L1 pathway blockade resulted in leukocyte infiltration and accumulation in the heart [4]. Studies have reported that deletion

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of PD-1 could cause immune myocarditis with dilated cardiomyopathy in mice model [10]. In experimental autoimmune myocarditis, a disease model dependent on $CD4^+$ T cells, it was found PD-1 played an important role in limiting T cell responses in the heart. The deletion of PD-1 increased inflammation response and infiltration of inflammatory cells, enhanced myocardial damage [11]. In the clinical investigation, in a multi-center study, a large variety of cardiotoxic events caused by immune-checkpoint blocking antibodies such as heart failure, cardiomyopathy, heart block and myocarditis were reported [12]. The PD-1/PD-L1 ICI-related severe cardiological complications mainly include: myocarditis, pericardial disease, vasculitis, Takotsubo syndrome. Less commonly, it can also include other non-inflammatory left-ventricular dysfunction and arrhythmia [8].

2.1. Myocarditis

Myocarditis is the most common side effect of PD-1/PD-L1 ICIs. PD-1/PD-L1 ICI-related myocarditis usually occurs early after administration and can be fatal, accompanied by severe cardiac function decline, myocardial enzyme elevation, hemodynamic instability and even arrhythmias. In severe cases, which leads to death [13]. But so far, the predisposition factors that promote PD-1/PD-L1 inhibitor-associated myocarditis in patients treated with them are rarely known. Diabetic patients may be more prone to PD-1/PD-L1 ICI-related myocarditis, but not yet found associated with other cardiovascular risk factors [13]. In, addition, studies have shown that patients treated with PD-1 inhibitor combined other immune inhibitor therapy had higher and more severe incidence of myocarditis [13,14]. For more than half of the patients, myocarditis is the only side effect of PD-1 checkpoint immunotherapy. The duration of myocarditis varies, depending on the type of immunotherapy [13,14].

Chest tightness, shortness of breath are the most common symptoms of PD-1/PD-L1 ICI-related myocarditis, and accompanied by the rise of myocardial enzymes [14,15]. Troponin is the valid marker with a sensitivity of 94–100% for suggesting myocarditis [16]. There is also the increase in N-terminal Pro-Brain Natriuretic Peptide (NT-pro-BNP). Further signs and symptoms may include arrhythmias (atrioventricular block, atrial fibrillation, etc.), orthopnea, edema in the extremities, etc. [17]. The diagnosis of PD-1/PD-L1 inhibitor-associated myocarditis is difficult and requires extensive examination to exclude other diagnoses. Based on evidence from different diagnostic modality, PD-1/PD-L1 inhibitor-associated myocarditis was defined as definite or probable myocarditis. The American Society of Clinical Oncology recommends extensive cardiology workup, including echocardiography, chest X-ray, Electrocardiogram (ECG), endomyocardial biopsy, and Cardiac Magnetic Resonance (CMR) imaging, in addition to cardiac biomarker examinations. Among them, CMR is a better imaging and diagnosis tool for PD-1/PD-L1 inhibitor-associated myocarditis as it provides good myocardial tissue characterization [18].

2.2. Pericardial Disease

Among ICI-associated cardiotoxicity, pericardial disease was the second most common cardiac adverse event, accounting for 13.6% of all cases [19]. PD-1/PD-L1 inhibitor-associated pericardial disease can manifest as pericarditis, pericardial effusion, and cardiac tamponade [20,21]. The diagnosis of PD-1/PD-L1 inhibitor-associated pericardial disease is difficult and challenging, because its symptoms are often uncharacteristic, which may present as chest pain, shortness of breath, dyspnea, etc. When patients present with clinical symptoms, pericardial disease can be assessed by physical examination, ECG, cardiac ultrasound, chest X-ray, and myocardial enzyme test [11,17]. When pericardial disease occurs, PD-1/PD-L1 inhibitor-associated myocarditis should be evaluated. CMR can be used as an additional imaging method to assess whether the myocardium is involved [11]. There is currently no clinical study on the morbidity and mortality of ICI-related pericardial disease, which is only reported in cases, and no systematic review was conducted.

2.3. Takotsubo Syndrome

The incidence of Takotsubo Syndrome (TTS) in ICI-associated cardiac adverse events is less, but recently, increasing literatures have reported the occurrence of TTS-like cardiac adverse events induced by PD-1/PD-L1 inhibitor [22,23]. TTS has also been increasingly reported in patients undergoing chemotherapy for cancer, with up to 29% of TTS patients eventually diagnosed with cancer [20]. In contrast to PD-1/PD-L1 inhibitor-associated myocarditis, the pathogenesis of TTS is unclear and may be non-inflammatory, either as a direct PD-1/PD-L1 inhibitor-related effect or indirectly induced by adrenergic stress during early PD-1/PD-L1 inhibitor treatment [24]. As with the assessment of pericardial disease, evaluating TTS should include physical examination, ECG, echocardiography, myocardial enzyme, NT-proBNP, etc. According to ESC and AHA guidelines, Acute Coronary Syndrome (ACS) should be excluded.

2.4. Acute Coronary Syndrome

Immune checkpoint inhibitor-associated vasculitis can affect vessels throughout the body, including coronary arteries, but the role of PD-1/PD-L1 ICIs in the pathogenesis of atherosclerosis remains unclear. Bu et al. [25] found that PD-L1 deficiency leads to increased atherosclerotic lesion inflammation and an increase in the number of infiltrating T cells. This suggested that PD-1 inhibitor treatment may lead to atherosclerosis. Recently, a review provided a hypothetical explanation of the mechanism by which PD-1/PD-L1 inhibitor caused atherosclerosis. The authors hypothesize that ICIs may activate the inflammatory response in atherosclerotic coronary plaques, trigger fibrous cap rupture, lead to coronary thrombosis, and induce acute myocardial infarction [17]. According to AHA myocardial infarction guidelines, in addition to symptoms of chest pain, coronary angiography, coronary CT, echocardiography, and elevated myocardial enzymes, especially troponin, may promote further diagnosis of ACS.

3. MANAGEMENT OF CARDIOTOXICITY ASSOCIATED WITH PD-1/PD-L1 ICIs

Treatment of PD-1/PD-L1 ICI-related cardiac adverse events varies depending on the severity of cardiotoxicity, ranging from

asymptomatic, only abnormal laboratory biomarkers or minor ECG changes to fatal fulminant myocarditis, cardiogenic shock, tamponade, severe arrhythmias, or even cardiac arrest [17]. In general, the treatment of PD-1/PD-L1 ICI-related cardiotoxicity requires three complementary approaches. For asymptomatic patients, with only laboratory abnormal (e.g., cardiac biomarker elevation or ECG changes), the approach is to consider discontinuing PD-1/PD-L1 inhibitor treatment. Although discontinuation of PD-1/PD-L1 ICIs treatment does not reverse its immunosuppressive effects, because they have the long half-life. However, patient's safety is important, and PD-1/PD-L1 ICIs treatment should be discontinued until no ICI-associated cardiotoxicity is established [17]. For the patients with moderately abnormal testing or symptoms with mild activity, the approach is to recommend the use of conventional cardiac therapy in addition to discontinuation of PD-1/PD-L1 inhibitor to reduce complications, such as β-blockers and angiotensin converting enzyme inhibitors for the treatment of heart failure, amiodarone for arrhythmia, diuretics for pulmonary edema, etc. [11,17]. For confirmed or strongly suspected cardiotoxicity, symptomatic heart failure, or severe arrhythmias, the recommended treatment in addition to the above approaches is immunosuppressive therapy. Corticosteroid immunosuppressive therapy is recommended as initial treatment for confirmed myocarditis, symptomatic heart failure, pericarditis, or severe arrhythmias [11,17]. In life-threatening atrioventricular block and cardiogenic shock, it may be considered to implant a permanent pacemaker or use veno-arterial extra corporeal membrane oxygenation. However, all the treatment recommendations are based on case series, case report and anecdotal evidence, there are no available prospective data.

4. DISCUSSION

Malignant tumor can suppress these immune responses by activating negative regulatory immune checkpoints, including PD-1/PD-L1 and CTLA-4 pathway. Tumor's ICIs therapy could induce the antitumor immune response by promoting T cell activation. Different from traditional chemotherapy and targeted therapy, Checkpoint inhibitors therapy is a new concept and method of anti-tumor therapy by changing the in-patients' immune suppression and reactivating the immune cells to eliminate the tumor, which has greatly advanced in recent years. Especially, PD-1/PD-L1 inhibitors have become a major immunotherapy regimen [26,27]. Although survival of cancer patients has improved, irAEs induced by PD-1/PD-L1 ICIs remains a critical issue, and the number of fatal events at the department of Critical Care Medicine is increasing. But its mechanism has not been fully elucidated, it is generally believed that PD-1/PD-L1 inhibitors block T cells' negative resistance control signal, remove immunosuppression, and enhance antitumor effect of T cells at the same time. But it also can enhance their abnormal immune response, leading to imbalance of immune tolerance, and show the autoimmune inflammatory reaction. The main toxicity on immune organs are hepatic, dermatologic, gastrointestinal, endocrine, respiratory, and cardiovascular systems [28–30].

Cardiotoxicity after treatment with PD-1/PD-L1 ICIs has historically been a major problem. There are many forms of cardiotoxicity such as cardiomyopathy, heart failure, pericardial effusion, arrhythmia, ACS, valvular disease, and etc. It has low incidence but high lethality. The mortality of myocarditis is as high as 39.7–50%, which is rapidly aggravated within several days or 1–2 weeks, and even develops to cardiogenic shock or cardiac arrest [12,31], but its pathogenesis is not clear. First, the tumor itself activates clonal expansion of the T cell population, and the T cell response of tumor also leads to target cardiotoxicity. Second, studies suggests that this may be related to the fact that PD-1/PD-LI inhibitors further enhance T cell activity throughout the whole body, thus promoting an autoimmune response [12,17]. Significantly, PD-1/PD-L1 ICIs-related cardiotoxicity exist inflammatory cascades which play an important role in the progression of disease. Hyperactive inflammatory response not only directly damages cardiomyocytes, leading to myocardial edema, necrosis and apoptosis, but also affects the stability of coronary plaques and increases the risk of potential cardiac events. Although the internal mechanism of PD-1 monoclonal antibody causing inflammatory storm still needs to be further improved. During the recent years several cases of fulminant myocarditis and fatal heart failure induced by PD-1/PD-L1 ICIs have been reported [13,32]. Severe cardiovascular adverse events introduce important issues for intensive care physicians.

PD-1/PD-L1 ICI-related cardiotoxicity is life-threatening and not easily detected early. Its diagnosis should exclude viral and autoimmune cardiomyopathy, ACS, and acute pulmonary embolism, and etc., which was supported with progressively change of cardiac biomarker, and findings of ECG, echocardiography and CMR. Cardiac enzymes, especially troponin to detect myocardial injury is sensitive, but specificity of cardiac enzymes except for troponin is currently inadequate. Troponin is a specific marker of myocardial injury, indicating the damaged or necrotic cardiomyocytes [33]. At the same time it is necessary to pay attention to the changes of ECG and cardiac ultrasound in patients. CMR is a better imaging and diagnosis tool for PD-1/PD-L1 inhibitor-associated cardiotoxicity as it provides good myocardial tissue characterization [18], but sensitivity is currently inadequate. Endomyocardial biopsy could be considered for tissue proof in clinical practice. Guidelines recommend that patients with PD-1/PD-L1 ICI-related myocarditis, symptomatic heart failure, pericarditis, or severe arrhythmias receive a large dose of glucocorticoid as soon as possible after diagnosis [34]. In the case of life-threatening arrhythmias and cardiogenic shock, higher levels of life support are recommended. It can be considered that when the diagnosis of immune-related cardiotoxicity is clear, the occurrence of severe heart failure, ventricular tachycardia, ventricular fibrillation, atrioventricular block and other malignant arrhythmias often indicate extremely dangerous conditions. High enough dose of glucocorticoid shock and further advanced life support have become the key to maintain vital signs and successful treatment in the acute phase in critical care [33].

5. CONCLUSION

The use of PD-1 and PD-L1 blockade could cause fulminant and fatal cardiotoxicity. Immune-related myocarditis and cardiotoxicity exist hyperactive inflammatory response, curbing the inflammatory storm is key to treatment. In the case of life-threatening

arrhythmias and cardiogenic shock, higher levels of life support are recommended.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

AUTHORS' CONTRIBUTION

Ruiting Li and You Shang devised the project. Ruiting Li wrote the manuscript with the support from Xiaojing Zou and Huaqing Shu. You Shang revised the manuscript.

ABBREVIATIONS

PD-1, programmed cell death 1; PD-L1, programmed death ligand 1; CTLA-4, cytotoxic T-lymphocyte associated antigen-4; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; ECG; electrocardiogram; CMR, cardiac magnetic resonance imaging; TTS, Takotsubo syndrome; ACS, acute coronary syndrome.

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