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Research Article

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Pembrolizumab induced cardiotoxicity

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Abstract

Background: *Pembrolizumab is a monoclonal antibody-based chemotherapy infusion, recently approved for unresectable or metastatic solid tumors with certain genetic anomalies.*

Discussion: *Pembrolizumab is an IV infusion therapy for treating non-surgical or metastatic melanoma and non-small cell lung cancer. Multiple cardiac complications have been related to this drug, the mechanism is not precise, but a possibility is immune events involving the cytotoxic T-cell resulting in fibrosis of the cardiac cells.*

Conclusion: *New oncologic medications have emerged with a potential reversible or irreversible cytotoxicity, including inflammation, dysfunction, or apoptosis that could represent a life-threatening condition. There is not enough data to establish proper therapy to avoid cardiotoxicity on monoclonal therapies, but an early approach and immunosuppressive therapy are thought to improve the outcome.*

Keywords: Pembrolizumab, Cardiotoxic, Chemotherapy-Induced Cardiotoxicity.

Introduction

Pembrolizumab is a humanized monoclonal antibody used as an immunotherapy agent to treat melanoma, lung cancer, head & neck cancer, Hodgkin's lymphoma, and stomach cancer [1]. This therapy was approved for medical use in the USA in 2014 for unresectable or metastatic solid tumors with certain genetic anomalies in 2017 [2].

Pharmacology Mechanism of Pembrolizumab

The mechanism of Keytruda, the brand name for pembrolizumab, is a therapeutic is based on the Programmed Cell Death Protein (PD) -1 bind to bind molecules on the surface of the T cells. These molecules are located on the surface of B and T cells, promoting self-tolerance via downregulation of the immune system, and preventing the immune system from attacking its tissues, known as an immune checkpoint [3-5].

Pembrolizumab occupies the PD-1 precisely; steric hindrance effects can hinder the combination between PD-1 and its ligands, PD-L1 or PD-L2, to restore the normal anti-tumor immune response suppressed by the PD-1 pathway [6]. The PD-1 receptor on activated T-cells normally binds to ligands PD-L1 or PD-L2 on other cells, thus deactivating a potential T-cell-mediated immune response against normal cells in the body [7].

Some cancers make PD-L1 that bind to PD-1, resulting in shutting down the ability of the body to kill cancer [8]. When PD-1 is inhibited on the lymphocytes, it prevents binding to ligands that deactivate an immune response, allowing the immune system to target and destroy cancer cells. This exact mechanism allows the immune system to attack the body itself, and the checkpoint inhibitors like pembrolizumab, which results in immune dysfunction, could result in a paradoxical side effect.

Medical Uses of Pembrolizumab

Pembrolizumab is an IV infusion therapy for treating non-surgical or metastatic melanoma and non-small cell lung cancer [9]. It is also a first-line treatment for metastatic bladder cancer for patients who are not candidates for cisplatin-based chemotherapy and have high levels of PD-1. It could also be used for head and neck

squamous cell carcinoma, Hodgkin's lymphoma, and advanced or metastatic esophageal squamous cell carcinoma [10]. Recently, in 2020 it is approved by FDA for first-line treatment for people with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer.

Cardiotoxicity of Mechanism

Severe side effects have been reported regarding pembrolizumab, including inflammation of lung, liver, kidney, and endocrine organs, including the pituitary gland, thyroid, and pancreas[11]. Isolated cardiac adverse effects have been reported under treatment with ipilimumab, a PD-1 inhibitor, but pembrolizumab has exceedingly rare cardiac adverse effects.

This agent has been related to new-onset hypertension, stable angina (Resolved after discontinuation of the therapy), new-onset tachycardia related to induced thyroiditis; besides the mechanism is not well established, there is a hypothesis for cardiotoxicity relates the myocyte immune tolerance with the cytotoxic T-cells and macrophages resulting in fibrosis [12,13]. There is one case of acute heart failure in the literature review due to autoimmune myocarditis under pembrolizumab, cases of arrhythmias including sinus tachycardia, atrial flutter, ventricular arrhythmia, and atrioventricular block [14,15].

The atrial flutter and left ventricular systolic dysfunction with an ejection fraction of 15-25% showed worse outcome; these patients have been getting a systemic treatment of prednisolone (1.0 mg/kg body weight p.o.) with a stop of treatment with pembrolizumab, but the patient died due to ventricular arrhythmia, and the autopsy showed myocarditis with cardiomyopathy [16].

Management of Cardiotoxicity Caused by Pembrolizumab

There are no diagnostic guidelines for newly rising cardiotoxicity related to PD-1/PDL-1 inhibitors. The clinical diagnosis can be based on history & physical exam combined with investigational tools, including cardiac biomarkers, electrocardiogram, and imaging.

High-risk patients such as the history of cardiac disease, lung cancer, combined immunotherapy, or cardiotoxic chemotherapy should be evaluated by a cardiologist or cardio-oncologist before treatment [17]. Pembrolizumab-induced cardiac adverse effects consist of various heart diseases (0-4%), Myocarditis (0.5%), Myocardial Infarction (2%), Pericarditis (2%), Arrhythmia (4%), and Takotsubo syndrome [18].

The early initiation of high-dose steroids as immunosuppression therapy is the usual therapeutic approach to Pembrolizumab-induced cardiac adverse effects, but benefits are not established [20]. A recent study showed that higher initial steroid dose (i.e., intravenous methylprednisolone 1,000 mg/d) and earlier initiation (within 24 hours of admission) were associated with improved cardiac outcomes [19]. However, steroids may reduce the efficacy of PD-L1 blockade [20]. Plasma exchange has been used and proven effective in Pembrolizumab-induced myocarditis, which is resistant to immunosuppressive agents.

In a review of pembrolizumab-associated myocarditis, only 3 out of 42 case reports from 2015–2018 described the use of plasma exchange[21]. Nevertheless, a definite myocarditis diagnosis is possible without biopsy when characteristic clinical syndrome, elevated myonecrosis markers, electrocardiographic, echocardiographic, and CMR changes are present [22,23].Another reported side effect is the pembrolizumab-induced atrioventricular, it can be treated with pacemaker implantation with the addition of high-dose steroids [24].

Conclusion

New medications for cancer have been emerging in recent years; the potential reversible or irreversible cytotoxicity, including inflammation, dysfunction, or apoptosis, could represent a life-threatening condition. On monoclonal therapies, the standard therapy to avoid this potential side effect is to achieve proper immunosuppression to avoid self-damage, but this does not necessarily guarantee better outcomes. There is not enough data to establish proper therapy to avoid cardiotoxicity in these patients, but an early approach and immunosuppressive therapy are thought to improve the outcome. In the limited data obtained during our review, patients who developed cardiac arrhythmia had poor outcomes despite steroid use, but there is insufficient literature to establish a definitive therapy and outcome. Prospective studies with genetic and race diversity would be needed to establish these concerning side effects and its treatment for pembrolizumab, a novel agent showing positive results in our patients with non-surgical and metastatic malignancy

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