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Cardiotoxicity in Cancer Immunotherapy: Pathological and Future Directions

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Abstract: Cancer and its complication remain one of the most popular and serious neoplasia disease in the domain of medicine. Although more and more immunotherapies have been developed and put into use, there still exist many unknown issues waiting to be explored in the laboratory and clinical application. Cardiotoxicity is one of the complex side effect of some active immunotherapies and may bring negative treatment issues for patients have heart disease in the past times and those at risk of developing heart disease. This review analyse the pathological manifestations and specific mechanisms of cardiac side effects caused by different tumor immunotherapies are presented, along with existing drug and non drug response measures and patient education. This review find the myocarditis caused by immune inflammation could be the vital relation between immunotherapy and cardiac functions. This study can provide medical direction and patient education reference for future research on the side effects of cancer immunotherapy. However, there is insufficient medical theories of the related effects of the immune system and tumor blood vessels. Future research can focus more on the reaction between some antigen antibody cancer vaccine drugs and the immune system.

Keywords: Cancer immunotherapy, cardiotoxicity, antigen-antibody cancer vaccines.

1. Introduction

In the past several decades, numerous explorations in the field of oncology have deepen the understanding of tumor and promoted many promising therapeutic methods. The first attempt to apply the immune system in cancer treatment was attributed to William Coley in 1898 [1]. After the first immune checkpoint inhibitor (ICI) targeting cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) been approved in 2011, the care and education for patients with tumor have progressed a lot. Accompanied by significant developments occured in the field of clinical trials [1]. Nowadays, immunotherapies have proven to be an innovative approach to fight against cancers and help rise the quality of survival for Patients with this symptom to some extent. Immunotherapy can be classified into two main types: active agents like anti-tumor vaccines or adoptive T-cell(ATC) transfer and passive therapies like ICIs or programmed cell death protein 1(PD-1). Recent examples showed that nearly 36% of patients with tumor may be eligible for immunotherapy. By the end of 2019, over 3362 clinical trials were launched to evaluate the effectiveness of immunotherapy, whether as a single drug or in combination with other immunotherapies, targeted therapies, or traditional cytotoxic or radiation therapies [1].

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With the percentage of patients applying immunotherapies rising, these new therapies are also reported to pose threat on the cardiac functions of patients. The application of these particular drugs and therapies may cause various side effects on heart, from chest pain and dyspnea to myocarditis and heart failure (HF). For patients who have certainly cardiovascular risk factors and related chronic diseases, Evaluating the situation of tumors and risk of cardiac toxicity becomes an important objective for treatment teams to apply effective measures and improve prognosis. Recent findings show that recognition and developing treatment in advance can favorably alter the outcome [2].

In murine models, scientists first describe the cardiotoxic potential of ICIs. And recently several examples show this was underestimated Due to the lack of routine cardiac health monitoring in these patients, adverse cardiac events may be underreported [3]. Therefore, additional research is needed in this field to implement adequate cardiac screening and develop cardioprotective treatment strategies in such situations [4]. Also, patient education needs to be considered to improve the efficacy of drug therapy and enhance the quality of life for patients especially these elderly people with multiple chronic diseases.

This review aims to summarize different immunotherapies concerning cardiotoxicity, explain the specific functions of immunotherapies and the way they effect the heart. Finally, targeted treatment methods and patient education will be given and analyzed.

2. Immunotherapies

2.1. ICIs

ICIs are monoclonal antibodies (mAbs), that targe several inhibitory receptors on tumor cells to support the immune cells recognize and stop these evading pathways for tumor cells to escape. To be precise, CLTA-4, PD-1 and PDL-1 are main targets for ICIs. However, these therapies were found to compare with a particular spectrum of cardiotoxicity, like myocarditis, arrhythmia and acute coronary syndrome. So the therapy needs to present its cardiac evidence in particular methods. Through the method of flow cytometry, scientists found ICI therapy provoked increased myocardial lymphocytes in anti-PD1-treated mice [5]. With the development of immunotherapy testing, lack of PD-1 can easily arise spontaneous myocarditis and spontaneous dilated cardiomyopathy at a certain extent. Due to the reported mortality rate of up to 50%, myocarditis caused by ICI is one of the most serious adverse events in ICI [4].

2.2. PD-1/PD-L1

PD-1 is found to be a set of molecules that exist on the surface of T cells and was found to cause functional suppression of T cell responses to help tumor cells escape from the immune system. Therefore, blocking the PD-1 and PD-L1 can enhance the immune system to recognize the tumor cells and destroy them correctly.

Recent research shows that the PD-1/PD-L1 pathway has some positive influences on heart protection especially on keeping its homeostasis within the myocardium. It is speculated that dysregulated immune cells mislabel surface structures such as cardiac phospholipids as antigens, leading to subsequent targeting of normal myocardial cells or other cells expressing these antigens [4].

The function of this cardiotoxicity has three main explanations: 1. In heart cells, ICIs could block the interaction of this target and cause Potential heart diseases, such as myocarditis or arrhythmia; 2. Another hypothesis is that both myocardial cells and tumor cells express antigens recognized by T cells; When ICIs activate T cells and attack tumors, it can also lead to autoimmune myocarditis;[6]. 3. The increase of PD-1 is owing to one mechanism that conducted by cytokine-mediated

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cardioprotective when there exists inflammation, so when the ICIs suppress the PD-1, the inflammation may not be inhibited.

2.3. CAR T-cell Therapy

CAR-T was an immunotherapy that first developed in the field of hematologic malignancies. Patients' T-cells are first separated and collected, then targeted gene segments are inserted in these T-cells to enhance their ability to recognize and kill tumor cells. Finally, these modified T-cells are reinjected into patients after large scale cultivation and amplification in vitro. Every CAT is designed differently to cater to diverse tumor characteristics and its antineoplastic activity can be maintained for several years. The patient's own T cells are modified to target CD19, an antigen that is often highly expressed in some B-cell malignancies, particularly in ALL, CLL or DLBCL [7].

A common and potentially fatal side effect of CAR T cell therapy is cytokine release syndrome (CRS), characterized by mild to high fever, severe hypotension, and hypoxia, typically occurring within a few days after treatment [8]. CRS is commonly described as an inflammatory response and it may happen in cardiac tissues and cause cardiovascular complications. Through echocardiographic and statistical analysis, the data shows that adult patients treated with CAT are at risk for MACE, mainly symptomatic HF. Also, the data shows that 16% of patients experience at least one 30 day MACE; And nearly two-thirds of the 30 day MACE is arrhythmia, which is easily controlled by standard treatment for all patients [9].

However, nowadays there are still not any useful solutions to keep screening and monitoring these patients who have negative cardiac function and treated with CAR T cell infusion.

2.4. mAbs

Commonly, scientists believe mAb is an antibody that produced by B cell clone alone and its targets can be a several of specific antigenic epitope. They have different targets according to different purposes. These antibodies targeting ErbB epitopes are related to EGFR which can induce the irregular growth of tumor cells.

The most prominent example of an AntiEGFR-antibody is the Trastuzumab, which targets Her2/neu. However, both tumor cells and cardiomyocytes involve this agent in physiological growth and survival pathways [4]. So Trastuzumab therapy can influence the myocardial function through reducing cellular energy production and support mechanisms by activating apoptotic pathways in cardiomyocytes [4]. For most patients, HF could be the main cardiac disease due to the application of Trastuzumab, but after discontinuing the medication, the symptoms of HF may be reversed to some extent.

2.5. Cytokines

Cytokines are a kind of proteins that have low weight in terms of molecular size and this protein can induced by stimulants in cells such as immunogens or mitogens. They function as a part of the non-specific humoral immunity in the body. So this therapy is widely used in cancer immunotherapy containing Interferons alpha (IFN-α) and Interleukin-2 (IL-2).

2.5.1. IFN-α

IFN-α is a type of glycoprotein that can regulate immunity and anti-tumor effects. IFN-α can adjust the inflammatory of cells in different types regardless of its various reations. It is used to promote the IL-1 and IFN-γ production of NK-cells and macrophages [4]. Through this, IFN-α can make the tumor cells more vulnerable when facing the immune cells. But this therapy also has cardiovascular side

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effects, The immune function enhanced by cytokines stimulates the T-cells or other immune cells to attack autologous, and this will also lead to the inflammatory infiltrates within the myocardium.

2.5.2. IL-2

Similarly, IL-2 therapy is also a cytokines that currently used in cancer immunotherapy. IL-2 mainly acts on T-cells by regulating their differentiation into memory, regulatory or effector T-cells [4]. T-cells actived by IL-2 can easily target tumor cells and realize immune killing. And this can also induce autoimmune reactions like ICIs or INFs.

2.6. Anti-tumor Vaccine

Anti-tumor vaccine has the fundation of applying stimulation strageties of immune system through eliciting an antitumor response in tumor antigens [10]. This therapy does not have a long period of experimental and clinical accumulation, but it also shows its function when combined with antiangiogenic therapy.

During the progress of cancer growth, tumor cells have developed different mechanisms to escape immune attacks such as tumor angiogenesis, this is an important step in tumor proliferation and metastasis. During the antiangiogenic, the factor called vascular endothelial growth factor (VEGF) not only can help tumor get more nutrient and oxygen resources, but can built barriers to inhibit immune system. In former research, a VEGF receptor pathway drug called bevacizumab can combined with anti-cancer vaccine to boost the tumor suppressive effect.

3. Clinical Manifestation

These immunotherapies have two main side effect on cardiac functions: HF and myocarditis.

3.1. HF

HF is a special stage of heart disease, and also the main cause of death of most heart disease events. Chronic HF refers to the physiological and pathological symptoms and signs of HF that gradually appear in patients on the basis of existing chronic diseases or negative immune reaction, and can stabilize, worsen or decompensate for a period of time, ultimately becoming the terminal manifestation and the main cause of death of cardiovascular disease. The ultimate outcome of cardiovascular events and the cumulative effects of various cardiac abnormalities can lead to the decompensation of chronic HF.

3.2. Myocarditis

The typical symptom of myocarditis may manifest as arrhythmias with serious side effects, this can expressed as advanced atrioventricular block or ventricular tachycardia. In addition, common cardiac inflammations like recurrent pericardial and pleural effusions may also induced by ICIs [11]. The mechanisms of myocardial toxicity has numerous unclear explanations, Some T cells may target an antigen shared by cancer cells and myocardial cells, resulting in viral myocarditis characterized by T cell infiltration into the myocardium. Also, scientists found a kind of protein called immunoglobulin G antibody, which can deposit on the cardiomyocytes and its autoantibodies were specific to cardiac structures [11].

Almost all the myocarditis caused by immunotherapies are irMyocarditis. Autoimmune myocarditis is an inflammatory disease caused by the immune system attacking myocardial tissue. This inflammation may be influenced by multiple factors, including certain viral infections, autoimmune diseases, or drug reactions. For patients have both immune problems and myocarditis,

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recent research shows that immune related myocarditis occurs with infiltration of CD4/CD8+T cells and inflammatory macrophages in the heart. For myocarditis induced by trastuzumab, existing examples suggect that in cardiac myocytes structures, ErbB2 inhibition plays a key component [12]. And immunotherapies focus on HER2 antagonists will become a important point.

4. Suggestions

4.1. Pharmacological Therapy Measures

For cardiac toxicity induced by immunotherapy, The most commonly used treatment is drug therapy.

4.1.1. Medicine for Myocarditis

Cardiotoxicity has a significantly higher mortality rate than other irAEs, and it is recommended that ICIs are discontinued if cardiotoxicity is suspected [12]. Also, it is not allowed to reenable ICIs therapy. Systemic steroids like Prednisolone and Dexamethasone can serve as emergency response to immune reactions and act as first-line medications when cardiac symptoms appear. When faced with steroid refractory myocarditis, abatacept (CTLA-4 agonist), and alemtuzumab (anti-CD52 Ab) have been used to inhibition of immunoglobulin induced immune inflammation [12].

4.1.2. Medicine for HF

The occurrence of heart failure can be caused by various internal and external factors. The major goals of treatment in heart failure are: 1) To improve prognosis and reduce mortality; 2) To alleviate symptoms and reduce morbidity by reversing or slowing the cardiac and peripheral dysfunction [13]. For HF caused by the use of mAbs, β-adrenalinecan be applied to assist patients in improving arrhythmia and controlling ventricular rate. Thiazides and loop diuretics can used as diuretics to improve capacity and alleviate edema symptoms.

4.2. Nonpharmacological Treatment Measures

In addition to medication, proper monitoring measures and appropriate life guidance can effectively improve patients' survival rates in the hospital and enhance their quality of life upon discharge.

4.2.1. Nonpharmacological Treatment for Myocarditis

For irMyocarditis, patients need to closely monitored about their electrocardiogram status and myocardial enzyme levels after discovering the condition. In addition, if there exists acute and severe blood disorders or impaired heart function, IVIG or plasmapheresis for unstable patients can also be used as a temporary alternative therapy [12].

4.2.2. Non Pharmacological Treatment for HF

For refractory HF, ultrafiltration therapy is used for fluid reduction for patients that are not responsive to medical therapy [13]. Recently, invasive hemodynamic monitoring gradually become an effective method to guide cardiac therapy and improve outcomes.

4.3. Patient Education

The discharge plan for patients with cardiac dysfunctions should address several key issues to ensure effective management and recovery. For patients with myocarditis, the plan should include medication reconciliation, written plans for dietary sodium restriction, and recommendations for

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appropriate activity levels. Follow-up by phone or clinic visits soon after discharge is crucial to reassess volume status. Emphasis should be placed on medication and dietary adherence, moderation of alcohol intake, and cessation of smoking. Patients should monitor their body weight, electrolytes, and renal function regularly, with consideration given to referrals for formal disease management when necessary. For HF patients, the discharge plan should encompass comprehensive education and counseling tailored to their specific disease, socio-economic background, and educational level. Education should promote self-care, including self-adjustment of diuretic therapy in suitable patients with the assistance of family members or caregivers. Early recognition and attention to signs and symptoms of fluid overload are essential, as are behavioral strategies to enhance adherence. Optimization of medical therapy and vigilant follow-up after hospital discharge or periods of instability are also critical components of the management plan [13].

5. Conclusion

In this review, the first part summerizes several widely used immunetherapies nowadays, then the second demonstrates the principles and mechanisms of these therapies, and elaborate on their potential cardiac toxicity. ICIs, CAR-T and Cytokines can induce myocarditis by inflammatory reaction, while the combination of mAbs and monoclonal antibody can lead to both myocarditis and recoverable heart failure. The third part concentrates on the manifestations of these side effects and the last part gives related strategies and clinial suggestions. Although anti-cnacer immunotherapies may induce such cardiac issues, there still exist drug and non drug therapies. With the continuous deepening and refinement of research on the side effects of immunotherapy, improvements and response measures related to cardiac function will also continue to advance.

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