Immunotherapy Checkpoint Inhibitors for Patients with Combined Immunodeficiency

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Abstract. As a major breakthrough in the field of tumor immunotherapy, immune checkpoint inhibitors (ICIs) have shown significant efficacy in the treatment of various malignant tumors. However, the application of ICIs in patients with combined immunodeficiency diseases still faces great challenges. Immunodeficiency includes primary and secondary types. Patients have a significantly increased risk of tumors due to low immune function, such as HIV-infected patients, organ transplant recipients, and systemic lupus erythematosus patients. Although early studies have shown that HIV-infected patients did not experience an increase in viral load or a significant decrease in CD4+ T cells after ICIs treatment, and the anti-tumor effect was comparable to that of ordinary patients, long-term safety and optimal treatment strategies still need to be further explored. For patients with primary immunodeficiency, due to congenital defects in the immune system, their responsiveness to ICIs is limited, and there may be a higher risk of immune-related adverse events (irAEs). This article reviews the research progress of ICIs in immunodeficiency-related malignancies, explores key issues such as mechanism conflicts, safety and efficacy in their application, and proposes new directions for future individualized treatment and combination therapy, in order to provide more effective treatment options for this special group.

Keywords: Immunotherapy Checkpoint Inhibitor; Combined Immunodeficiency; immune-related adverse event.

1. Introduction

Immunotherapy with immune checkpoint inhibitors (ICIs), as a significant breakthrough in cancer immunology, has made remarkable progress in the treatment of various malignant tumors in recent years. By targeting immune checkpoint molecules such as programmed cell death protein-1, programmed cell death ligand-1, and cytotoxic T lymphocyte-associated antigen-4, ICIs can unblock the tumors suppression of the immune system, reactivating T-cell anti-tumor activity, thereby significantly improving patient survival outcomes. However, despite demonstrating good efficacy in patients with common cancers, the application of ICIs in patients with combined immunodeficiency diseases still faces numerous challenges. Immunodeficiency includes primary immunodeficiencies and secondary immunodeficiencies (such as HIV infection, systemic lupus erythematosus), where patients exhibit significant differences in immune status compared to healthy individuals due to congenital or acquired abnormalities in their immune systems. This presents unique safety and efficacy issues for the use of ICIs.

Since the discovery of HIV in the 1980s, about 70 million people worldwide have been infected with the virus, and nearly half of those patients have died from AIDS-related diseases [1]. Although the widespread use of antiretroviral therapy has allowed HIV-infected individuals to control their viral load and live close to normal life expectancy, their compromised immune function significantly increases the risk of malignancies. Studies have shown that HIV-infected individuals are 23 times more likely to develop non-Hodgkins lymphoma [2]. People with Kaposis sarcoma are 500 times more likely to develop the disease than the general population [3]. However, due to the continuous suppression of the immune system, such patients are greatly limited in the choice of anti-tumor therapy, and traditional radiotherapy and chemotherapy regimens are often limited in efficacy and toxic.

In recent years, preliminary studies of ICI in HIV-infected individuals have shown that its antitumor activity is similar to that in general patients, and it does not significantly increase the risk

of viral load or CD4+ T cell depletion. This has provided new hope for the treatment of HIV-related malignancies. However, due to the unique nature of the immune system in HIV-infected individuals, further exploration is needed to determine the long-term safety and optimal application strategies of ICI.

In addition to HIV infection, patients with other secondary immunodeficiency diseases (such as organ transplant recipients with immune suppression, autoimmune diseases, etc.) and primary immunodeficiency diseases also face unique challenges in ICI therapy. Primary immunodeficiency diseases are a category of disorders caused by genetic mutations leading to abnormalities in the development or function of the immune system. Patients often exhibit recurrent infections, increased risk of autoimmune diseases, and malignant tumors. Since the mechanism of action of ICI relies on the normal functioning of the immune system, its application in PID patients is still in the exploratory stage, with very limited research available. Moreover, due to underlying conditions or long-term immunosuppressive therapy, the immune systems of patients with secondary immunodeficiency diseases are often more vulnerable, potentially increasing the risk of immune-related adverse reactions when using ICI. Despite the numerous challenges in applying ICI in immunodeficiency patients, its potential clinical value cannot be overlooked. In recent years, several small-scale clinical studies and case reports have shown that ICI can still exert antitumor effects in some immunodeficiency patients, and through individualized treatment strategies and close monitoring of adverse reactions, its safety can be effectively managed. Furthermore, with deeper research into the mechanisms of immune checkpoint molecules, new types of ICI and their combination therapies (such as with ART, targeted therapy, or chemotherapy) are emerging. Development is expected to further broaden its application prospects in patients with immunodeficiency diseases. In view of this, this paper reviews the research progress of ICIs in cancer patients with combined immunodeficiency diseases, in order to provide new ideas for the treatment of such patients.

2. The Relationship between Immunodeficiency Disease and Cancer

2.1. Types and Mechanisms of PID Related to Malignant Tumors

Primary immunodeficiency diseases are a group of diseases with abnormal immune system function caused by genetic defects. Some PID patients have significantly increased risk of malignancy due to impaired immune surveillance function or accumulation of gene mutations.

2.1.1 X-linked agammaglobulinemia (XLA)

XLA is caused by a mutation in the Bruton tyrosine kinase (BTK) gene, characterized by B cell developmental arrest and complete absence of antibodies. The mechanisms include: Immune surveillance defect: The absence of B cells leads to the failure of humoral immunity against carcinogenic pathogens such as EB virus (EBV), abnormal proliferation of EBV-infected B cells, ultimately leading to lymphoma.

Chronic infection stimulation: Chronic inflammation caused by repeated infection may promote cancer through NF-κB and other pathways.

2.1.2 Wiskott-aldrich syndrome (WAS)

WAS is caused by mutations in the WAS protein gene and is characterized by thrombocytopenia, eczema and immunodeficiency. The article reports "WAS 441 cases" with a malignancy incidence of about 20-30%, mainly non-Hodgkins lymphoma and leukemia. The mechanism involves:

T cell dysfunction: WAS protein is involved in cytoskeletal reorganization, and its defect leads to impaired T cell migration and killing function, which cannot eliminate cancerous cells.

Autoimmunity and inflammation: chronic inflammatory microenvironment promotes genomic instability and increases the risk of solid tumors [4].

2.1.3 X-linked lymphoproliferative syndrome (XLP)

XLP is categorized into two subtypes: XLP1, resulting from SAP gene mutations, and XLP2, caused by XIAP gene mutations. This article primarily focuses on XLP1 and its association with Epstein-Barr virus (EBV) infection, which often manifests as explosive infectious mononucleosis and progresses to lymphoma. The underlying mechanism involves SAP protein deficiency, which impairs the ability of NK cells and $CD8^+$ T cells to recognize and eliminate EBV-infected B cells, leading to their uncontrolled proliferation. Moreover, EBV contributes to immune evasion by upregulating anti-apoptotic proteins through its latent membrane protein (LMP), and in the context of SAP deficiency, this further promotes lymphoma development. In parallel, chronic granulomatous disease (CGD), another primary immunodeficiency (PID) affecting approximately 1 in 16 PID patients, is characterized by a deficiency in NADPH oxidase, resulting in impaired bactericidal function of phagocytes. CGD is associated with an increased risk of malignancies, particularly solid tumors in the gastrointestinal and reproductive systems. This elevated risk is attributed to chronic inflammation and oxidative stress due to persistent infections, which generate excessive reactive oxygen species (ROS) that damage DNA and activate oncogenes. Additionally, microbial dysbiosis in the intestinal tract may contribute to tumorigenesis through activation of Toll-like receptor (TLR) signaling pathways [5,6].

2.1.4 Severe combined immunodeficiency

In patients with severe combined immunodeficiency (SCID), the loss of both T and B cell function results in a near-complete breakdown of immune surveillance, significantly increasing the risk of malignancy. Approximately 1 in 10 SCID patients develop malignant tumors, primarily T-cell leukemia and lymphoma. This heightened risk is driven by multiple mechanisms. First, abnormalities in the thymic microenvironment, stemming from defects in thymic stromal cells, impair T cell development and create conditions conducive to the malignant transformation of immature T cells. Second, gene therapy, particularly when using retroviral vectors to correct IL2RG gene mutations, carries oncogenic risks. These vectors may integrate near proto-oncogenes such as LMO2, inadvertently activating them and leading to leukemia. Collectively, primary immunodeficiencies (PIDs), including XLP, CGD, and SCID, increase malignancy risk through various pathways, such as immune surveillance defects, chronic inflammation, genetic mutations, and the unintended consequences of therapeutic interventions [7].

2.2. The Relationship between HIV and Malignant Tumors

Current research indicates that 30% to 40% of AIDS patients develop various types of malignant tumors, which are one of the leading causes of death in these patients. The increased risk of cancer in AIDS patients is attributed to their unique immune status and social factors, with immune status (such as reduced immune surveillance function and enhanced susceptibility to tumor viruses) playing a primary role [6]. AIDS-related malignant tumors are divided into AIDS definite malignant tumors and AIDS uncertain malignant tumors. The former refers to the determination of malignant tumors related to AIDS, while the latter refers to the occurrence of malignant tumors is not necessarily related to AIDS [5]. The occurrence of AIDS-related definitive malignant tumors is often associated with opportunistic viral infections during the course of AIDS patients illness. Common tumors include: Kaposis sarcoma caused by the herpes virus, anal, penile, vulvar, and cervical cancers related to human papillomavirus, and nasopharyngeal cancer and non-Hodgkin lymphoma associated with EB virus. The occurrence of AIDS-related uncertain malignant tumors is mainly related to the extended survival time of patients due to the use of antiretroviral drugs [8,9].

2.3. Organ Transplant Recipients and Malignant Tumors

Long-term immunosuppressive therapy after organ transplantation significantly improves the survival rate of recipients, but the incidence of malignant tumors is 3 to 5 times higher than in the general population, becoming a critical factor affecting the long-term prognosis of transplant

recipients. Taking kidney transplant recipients as an example, according to statistics, among 1,132 kidney transplant recipients, 19 developed malignant tumors, with an incidence rate of 1.67%, which is significantly lower than the reported rates of 4% to 18% (average 6%) abroad [10]. In another study, the incidence of new malignancies in 3150 recipients of kidney transplants was 1.9% (59/3150) with urological malignancies being the most common [11]. In 119 patients with hepatocellular carcinoma (HCC) liver transplantation, the median follow-up was 27 months (15-43 months). Tumor recurrence or metastasis occurred in 27 cases (22.7%), and 11 cases (9.2%) died of tumor recurrence [12]. The pathogenesis can be divided into immunosuppression and other factors. Immunosuppression is mainly the decreased ability of the immune system to clear mutant cancer cells and the direct carcinogenic effect of immunosuppressants (such as azathioprine causing chromosomal breakage and increased risk of skin cancer) [10].

3. Basic Principles of ICIs

The essence of immune checkpoints lies in the co-stimulatory/inhibitory receptors on the surface of T cells, which transmit regulatory signals through ligand binding. The PD-1/PD-L1 pathway is the core inhibitory mechanism: tumor cells overexpress PD-L1, which binds to T cell PD-1 and triggers a SHP-2 phosphatase cascade reaction, suppressing TCR signaling and leading to T cell exhaustion. CTLA-4 competitively binds to B7 molecules with CD28, blocking co-stimulation signals and inhibiting T cell activation. Inhibitors block these binding interfaces using monoclonal antibodies, restoring the cytotoxic function of CD8+ T cells. ICIs significantly improve cancer patient outcomes by targeting CTLA-4, PD-1/PD-L1, and other pathways, but they also trigger irAEs in multiple systems. IrAEs are common in cancer patients with autoimmune diseases, though severe irAEs are relatively rare [13]. Severe cases can be life-threatening. Understanding the mechanisms and management of irAEs is critical to optimizing ICI treatment strategies, improving patient survival rates, and improving quality of life.

4. Advances in the Investigation of ICI Therapy for Immunodeficient Patients

4.1. Research Background and Core Contradiction

Immunotherapy checkpoint inhibitors (ICIs) work by blocking pathways such as PD-1/PD-L1 and CTLA-4 to activate T cell function. However, in immunodeficient patients, inherent defects like T cell depletion and reduced proliferation may weaken their efficacy. For example, HIV-infected individuals often have a CD4+ T cell count below 200/μLCD4 +T lymphocytes (CD4), which plays a crucial role in generating an immune response. A decrease in CD4 is a significant characteristic of HIV infection. Additionally, organ transplant recipients require long-term use of immunosuppressants, all of which fundamentally conflict with the mechanism of action of ICIs.

4.2. Safety and Effectiveness

4.2.1 HIV patients

Patients with AIDS generally have a high risk of cancer. Currently, it is believed that ICIs are effective in cancer patients co-infected with HIV, with a lower incidence of toxic side effects. Under effective antiviral therapy, cancer patients co-infected with HIV can use ICIs for anti-tumor treatment. The antiviral activity of ICIs remains controversial, but existing evidence confirms that they at least do not lead to an increase in HIV viral load in patients. In 21 HIV-infected individuals, 16 received monotherapy with PD-(L)1 (such as nivolumab or pembrolizumab), and 5 received ICI combined with chemotherapy (carboplatin/pemetrexed/pembrolizumab regimen). The overall incidence of immune-related adverse events was 24% (5/21), with severe events (≥3 grade) accounting for 14% (3/21), including hepatitis (1 case) and pneumonia (2 cases). It has been effectively proven that the incidence of irAEs is comparable to that in general tumor populations, and low CD4+ status does not affect the anti-tumor response; patients with high PD-L1 expression show excellent remission rates,

achieving breakthroughs in efficacy. However, the sample size is small, and PD-L1 testing only covers 43% of cases, requiring further improvement in biomarker analysis [14].

4.2.2 Organ transplant recipients

Clinical data show that patients with HIV infection who are well-controlled use of pembrolizumab have an incidence of grade 3-4 immune-related adverse events (irAEs) similar to that of the general population, but there may be baseline immunosuppression or chronic inflammation [9]. According to a retrospective study, among 31 patients with malignant tumors who received ICIs after kidney transplantation, the overall rejection rate was 32.26%. Among these, PD-1 inhibitors (nivolumab, pembrolizumab, etc.) had the highest rejection rate (52.94%), while CTLA-4 inhibitors (ipilimumab) had the lowest rejection rate (12.50%) [15]. The JMS review points out that its rejection mechanism involves the PD-1/PD-L1 signaling axis by regulating Treg function, which destroys transplant tolerance and leads to T cell-mediated acute rejection.

5. Conclusion

With the widespread application of ICIs in the field of tumor treatment, their potential in immunodeficient patients has gradually attracted attention. Although there is a natural conflict between the immunodeficiency state and the immune activation mechanism of ICIs, such as T cell number or function defects, long-term immunosuppressive therapy, etc., there are still studies showing that ICIs can play a good anti-tumor effect in some immunodeficient people without significantly increasing HIV viral load or immune-related toxicity. Especially in HIV-infected patients, ICIs treatment shows acceptable safety and a certain remission rate. For organ transplant patients, although there is a risk of rejection, the incidence of immune rejection is expected to be reduced by selecting the appropriate type of ICIs and immune monitoring methods. Due to the complex disease mechanism, the current research on primary immunodeficiency patients is relatively scarce. In the future, it is necessary to strengthen large-sample clinical research, develop more accurate immune phenotype assessment and predictive biomarkers, and explore the combination strategy of ICIs with antiviral, targeted therapy and chemotherapy to improve its safety and efficacy in immunodeficient patients and achieve the goal of personalized treatment.

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