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Current Status of Research on the Relationship between Immune-Related Adverse Events and the Efficacy of Immune Checkpoint Inhibitor Therapy for Malignant Tumors

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Abstract

Although immune checkpoint inhibitors (ICIs) significantly prolong the survival of patients with certain solid tumors by blocking specific signaling pathways, the immune-related adverse events (irAEs) they induce can affect multiple organs and even be life-threatening, restricting their clinical application. Studies have shown that patients who experience irAEs have improved progression-free survival (PFS) and overall survival (OS). Mechanistically, this may be related to the highly active state of the body's immune response. This "double-edged sword" characteristic of irAEs has prompted the academic community to re-examine its clinical significance, explore its use as a potential biomarker for evaluating therapeutic efficacy, and develop new adverse event management strategies to balance efficacy and safety.

Keywords: Immune Checkpoint Inhibitor, Immune-Related Adverse Event, Progression-Free Survival, Overall Survival.

Introduction

Immunotherapy for malignant tumors represents a major breakthrough in cancer treatment. By stimulating the human immune system and remodeling the anti-tumor immune microenvironment, it has opened up a new avenue for extending the survival of patients with advanced cancer [1, 2]. Among various immunotherapeutic modalities, immune checkpoint inhibitors (ICIs) have emerged as the cornerstone of cancer immunotherapy due to their remarkable efficacy and broad applicability [3]. Immune checkpoints, typified by the CTLA-4 and PD-1/PD-L1 pathways, are key regulators of immune homeostasis, functioning to inhibit excessive T-cell activation and prevent autoimmune responses [4-6]. However, tumor cells can upregulate the expression of these checkpoints through genetic mutations and other mechanisms [7]. For instance, approximately half of patients with non-small cell lung cancer exhibit high PD-L1 expression in tumor tissues, which facilitates immune evasion. Based on this mechanism, researchers have developed CTLA-4 inhibitors (e.g., ipilimumab [8]), PD-1 inhibitors (e.g., pembrolizumab), and PD-L1 inhibitors (e.g., atezolizumab [9]). These agents block immunosuppressive signals, thereby reactivating the immune system to attack tumor cells. Clinical studies have demonstrated that ICIs, either as monotherapy or in combination regimens, significantly prolong the survival of patients with solid tumors such as melanoma and renal cell carcinoma, with some patients achieving long-term tumor-free survival [10, 11].

Despite the potent anti-tumor efficacy of immune checkpoint inhibitors (ICIs), immune-related adverse events (irAEs) induced by these agents remain a significant clinical challenge [12, 13]. These events can affect multiple organ systems, including the skin and gastrointestinal tract, with an incidence rate ranging from 60% to 80% [14]. Severe irAEs may lead to treatment discontinuation or even be life-threatening. Currently, research in

cancer immunotherapy is focused on three key areas: balancing therapeutic efficacy with safety, developing predictive biomarkers, and exploring novel combination treatment strategies.

Immune-Related Adverse Events

Immune-related adverse events (irAEs) associated with immune checkpoint inhibitor (ICIs) therapy are a hallmark phenomenon, capable of affecting multiple organ systems throughout the body. Due to their diverse clinical manifestations and potential lethality, they pose significant challenges to clinical management [15-17]. Recent epidemiological studies have shown that over 70% of patients receiving ICIs develop irAEs of varying severity, involving systems such as the skin, endocrine system, gastrointestinal tract, liver, and lungs [13, 18]. In rare cases, they may also impair the cardiovascular or central nervous system [19].

Cutaneous toxicity is the most common irAE, occurring in 30% to 50% of patients, mostly mild Grade 1-2 reactions such as maculopapular rash, pruritus, and vitiligo [20, 21]. Among these, vitiligo is associated with enhanced immune responses in the body; melanoma patients with vitiligo have a 25% to 30% higher tumor response rate than those without this symptom [22]. However, severe cutaneous toxicity of Grade 3 or higher may progress to exfoliative dermatitis, requiring immediate discontinuation of ICIs and systemic treatment.

Gastrointestinal irAEs are mainly characterized by diarrhea and colitis. In severe cases, symptoms such as mucopurulent bloody stool, severe abdominal pain, and rapid weight loss may occur [23, 24]. Approximately 15% to 20% of patients develop gastrointestinal toxicity, among which the incidence of severe colitis of Grade 3 or higher is 3% to 5%. Without timely intervention, it may lead to life-threatening complications such as intestinal perforation and sepsis [25]. Among endocrine system involvements, thyroid dysfunction (hypothyroidism, hyperthyroidism, autoimmune thyroiditis) is the most common. Although hypophysitis, primary adrenal insufficiency, and insulin-dependent diabetes mellitus are rare, they can cause severe hormonal imbalances after onset, often requiring lifelong hormone replacement therapy.

Although the incidence of pulmonary toxicity is only 5% to 10%, it is highly potentially fatal. ICI-related pneumonia has an insidious onset, with early symptoms including dry cough and shortness of breath. Imaging examinations may show ground-glass opacities and other manifestations. Some patients' conditions may rapidly deteriorate to acute respiratory distress syndrome (ARDS), especially those with underlying lung diseases, who face a higher mortality rate. The incidence of cardiovascular and neurological toxicity is less than 1%, but once they occur, the risk of death or disability is extremely high: myocarditis may lead to acute heart failure and malignant arrhythmia, while neurological injuries such as immune encephalitis and myasthenia gravis can cause severe consequences including cognitive impairment and respiratory muscle paralysis.

The management of irAEs follows evidence-based medicine principles: Grade 1 adverse events require no special intervention, and ICI therapy can be continued under close monitoring [26]; Grade 2 toxicity necessitates temporary suspension of ICIs, and treatment may be resumed at a reduced dose after symptom relief, with glucocorticoids administered if necessary [26]; severe toxicity of Grade 3 or higher requires immediate discontinuation of ICIs, followed by high-dose methylprednisolone pulse therapy combined with immunosuppressants [27]. Recent studies have indicated that the pathogenesis of irAEs may be related to the imbalance of peripheral immune tolerance. ICIs break the body's immune suppression against self-antigens, promoting the production of autoantibodies [28], which in turn triggers immune attacks on multiple organs. This "double-edged sword" effect leads to a unique clinical phenomenon: multiple retrospective studies have shown that patients with irAEs have a median progression-free survival (PFS) extended by 3 to 6 months and an overall survival (OS) improved by 15% to 20%, suggesting that irAEs may serve as potential biomarkers for predicting the therapeutic benefits of ICIs. Currently, the academic community is striving to develop predictive models for accurately identifying high-risk populations of irAEs and researching novel immunomodulators, aiming to maximize efficacy while minimizing toxicity.

Pathogenesis of Immune-Related Adverse Events

The pathogenesis of immune-related adverse events (irAEs) is a research focus in the field of cancer immunotherapy, and the "antigen cross-reactivity theory" is one of the core explanatory perspectives [29]. This theory holds that the surface antigens of tumor cells are highly similar to those of normal tissue cells. During ICI therapy, activated anti-tumor T cells cannot accurately distinguish between the two types of antigens and will mistakenly attack healthy organs carrying similar antigens, leading to multi-system immune impairment.

From an immunological perspective, tumors generate neoantigens during evolution, some of which exhibit "molecular mimicry" (similar sequences or structures) with autoantigens of normal tissues. After ICIs relieve immune suppression, the awakened tumor-specific T cells may attack normal tissues due to antigen cross-reactivity while eliminating tumors, triggering autoimmune responses. Taking cutaneous toxicity as an example, in ICI-induced rash tissues, there is massive infiltration of CD3+ T lymphocytes, with CD8+ T cells accounting for over 60%. Immunohistochemistry shows that these T cells can specifically recognize the antigen peptide-MHC class I molecule complexes on the surface of keratinocytes, leading to basal cell damage and the formation of Civatte bodies, providing direct evidence for immune attack.

A study by the Omar Hasan Ali team explored the role of the antigen-sharing mechanism in irAEs. Their cohort study on non-small cell lung cancer (NSCLC) patients [30] found that in patients with cutaneous irAEs, rash tissues showed typical lichenoid inflammatory infiltration, and there were shared antigens such as keratin 14 and filaggrin between tumor tissues and skin cells. These antigens are expressed in both lung stem cells and keratinocytes, enabling activated T cells to "cross-recognize" different tissues and induce skin inflammation. The study also confirmed through single-cell sequencing that some T cells migrating to the skin carry tumor-specific TCRs, indicating that anti-PD-1 therapy not only activates anti-tumor immunity but also promotes the extensive migration of tumor-specific T cells, increasing the probability of irAEs.

Current research has obvious limitations: the verification of the antigen similarity hypothesis is mostly focused on a few tissues such as the skin and lungs, with fewer relevant studies on easily affected organs such as the gastrointestinal tract and endocrine system; existing evidence is mostly from retrospective analyses and small-scale cohort studies, lacking prospective verification; although antigen sharing between the lung and skin has been confirmed, the mechanism of antigen cross-reactivity between tumor cells and intestinal epithelial cells in gastrointestinal irAEs remains unclear. In addition, the antigen expression profiles of different tumor types vary significantly, posing challenges to explaining the mechanism of irAEs. In the future, it is necessary to combine high-throughput single-cell sequencing, mass spectrometry, and other technologies to systematically map the antigen overlap between tumors and normal tissues, and verify the causal relationship between antigen similarity and the occurrence of irAEs through multi-center clinical studies, providing a theoretical basis for the accurate prediction and intervention of irAEs.

Clinical Studies on Immune-Related Adverse Events and Efficacy Prediction

Gastrointestinal Immune-Related Adverse Events

Recent studies have focused on the association between immune-related adverse events (irAEs) and the efficacy of immune checkpoint inhibitors (ICIs), among which gastrointestinal toxicity has received considerable attention. A large-scale retrospective study by the Hamzah Abu-Sbeih team included 1983 melanoma patients receiving ICI therapy, of whom 173 (8.7%) developed immune-mediated diarrhea and colitis. The results showed that patients with any grade of diarrhea and colitis had significantly improved overall survival (OS) (HR=0.53, 95% CI 0.36-0.78, P<0.01), and the OS extension of patients with grade 1 mild diarrhea was more significant than that of patients with grade 2-4 moderate to severe diarrhea (P=0.04); the Kaplan-Meier survival curve also showed significant survival benefits in this patient group (P<0.001). After adjusting for confounding factors using a multivariate Cox regression model, the progression-free survival (PFS) of these patients was also significantly prolonged (HR=0.56, 95% CI 0.41-0.76, P<0.01), suggesting that gastrointestinal irAEs may serve as important indicators for predicting ICI efficacy.

Multiple studies have further confirmed the potential association between gastrointestinal toxicity and tumor response to ICI therapy: BECK et al. [31] found that among melanoma and renal cell carcinoma patients receiving ipilimumab therapy, the objective response rate (ORR) of patients with enterocolitis was significantly higher than that of those without; WANG et al. [32] pointed out that among patients with multiple cancer types receiving ICI therapy, those with diarrhea requiring intervention had significantly prolonged survival time; analysis by the ABU team [33] showed that patients with gastrointestinal adverse events not only had significantly improved OS but also statistically significant differences in PFS, implying that they may become potential biomarkers for evaluating the long-term efficacy of ICIs.

Although these studies have limitations, through multi-center and large-sample data analysis, they have initially revealed the positive relationship between gastrointestinal irAEs and ICI efficacy. In the future, prospective studies are needed to verify the causal relationship between the two and explore the underlying mechanisms, such as analyzing changes in intestinal flora and characteristics of immune cell infiltration when toxicity occurs, to provide more reliable theoretical support for clinical practice and help optimize efficacy prediction and treatment strategies.

Cutaneous Immune-Related Adverse Events

A multi-center clinical study by Alessio Cortellini et al. [34] analyzed 559 non-small cell lung cancer (NSCLC) patients and found that 231 developed irAEs of varying severity during ICI therapy, of whom 191 had involvement of only a single organ system (mainly cutaneous, gastrointestinal, or endocrine system toxicity), and 40 (17.4%) had multi-organ system adverse events, indicating a higher degree of systemic immune activation.

Efficacy evaluation showed that the objective response rate (ORR) of patients with irAEs reached 46.5%, which was significantly higher than the 25.7% of patients without irAEs (the difference was highly statistically significant), indicating that irAEs may be a marker of activated immune response in the body. Stratified analysis showed that there was no significant difference in ORR between patients with grade 3/4 severe irAEs and those without severe toxicity, but irAEs of the endocrine and cutaneous systems were strongly associated with higher ORR. This is the first confirmation in NSCLC patients, providing a new direction for the accurate clinical screening of potential beneficiaries of ICIs.

A retrospective cohort study by SAN et al. [35] included 83 melanoma and lung cancer patients receiving pembrolizumab therapy. The results showed that regardless of the dose, patients with cutaneous toxicity had significantly better PFS than those without; especially in melanoma patients, the median PFS of patients with hypopigmentation was 4.2 months longer than that of patients without cutaneous toxicity, suggesting that cutaneous irAEs can serve as a marker of immune activity, and different tumors have differences in response to immunotherapy.

The above studies suggest that clinically, monitoring irAEs (especially toxicity of the endocrine and cutaneous systems) can assist in evaluating patients' responsiveness to ICIs, but further exploration of the mechanism of irAEs is needed to clarify the causal relationship between irAEs and anti-tumor immunity. In the future, combined with technologies such as single-cell sequencing and proteomics, the dynamic changes of immune cells when irAEs occur can be analyzed to achieve balanced regulation of immune responses, reduce toxicity risks, and maximize efficacy.

Endocrine System-Related Adverse Events

The association between endocrine system toxicity induced by ICIs (especially thyroid dysfunction) and patients' clinical prognosis has received widespread attention. A clinical study by the J.C. Osorio team [36] analyzed 51 advanced NSCLC patients receiving pembrolizumab therapy. Among them, 3 had pre-existing hypothyroidism, and 21% of the remaining 48 patients with normal thyroid function developed thyroid dysfunction (including hypothyroidism and thyroiditis) during treatment, of which 50% were subclinical hypothyroidism (mild), 40% were grade 2 (accompanied by symptoms such as fatigue and chills), and 10% were grade 3 (requiring emergency intervention). Surviv-

al analysis showed that the median OS of patients with thyroid dysfunction was 40 months, which was significantly better than the 14 months of patients without abnormalities (HR=0.29, 95% CI 0.09-0.94, P=0.029), suggesting that thyroid dysfunction is associated with long-term survival benefits.

A prospective study by the OSORIO team [37] observed 48 advanced NSCLC patients receiving pembrolizumab therapy. Ten patients developed thyroid insufficiency, and their OS was significantly longer than that of 38 patients without abnormalities. This prospective evidence fills the gap in retrospective studies and provides a more reliable basis for thyroid dysfunction as a predictive indicator of ICI efficacy.

Thyroid dysfunction may be a key biomarker for evaluating ICI efficacy, because immune attack on the thyroid may indicate a highly activated immune system in the body, and this enhanced systemic immune response may trigger both endocrine irAEs and anti-tumor immune responses. However, current studies have limitations such as small sample size and lack of multi-center verification. In the future, large-scale cohort studies are needed, combined with dynamic monitoring of thyroid autoantibodies and analysis of immune cell subsets, to clarify the causal relationship between the two, helping to accurately screen ICI-benefiting patients and optimize treatment strategies clinically.

Respiratory System-Related Adverse Events

ICIs therapy for NSCLC may induce pulmonary toxicity. Although the incidence is low, its potential lethality and clinical prognosis have attracted attention. A multi-center retrospective study by the Daichi team [38] included 613 NSCLC patients receiving nivolumab therapy. 10.1% developed pneumonia of various grades during treatment, and immune-related pneumonia mostly occurred in the early stage of treatment: nearly half of the patients had disease progression within 8 weeks of medication, and 18% of the patients developed symptoms only after 24 weeks of medication, indicating significant differences in the onset time. Clinically, it is necessary to be vigilant and monitor patients' lung conditions in a timely manner.

Survival analysis showed that the median PFS of patients with pneumonia was 5.8 months, which was significantly longer than the 2.1 months of patients without pneumonia (P=0.002), suggesting that pulmonary irAEs may predict a stronger immune response. A multi-center retrospective study by the FUJIMOTO team [39] compared 552 advanced NSCLC patients without pneumonia and 61 patients with pneumonia. The ORR of the pneumonia group (42%) was significantly higher than that of the non-pneumonia group (28%), and the median PFS was extended to 3.5 months, further confirming that although immune-related pneumonia has potential risks, patients with pneumonia may achieve better tumor control effects.

In clinical management, it is necessary to identify high-risk populations of immune-related pneumonia early and establish a close monitoring system (especially strengthening imaging and symptom assessment within the first 8 weeks of medication). At the same time, the clinical significance of pulmonary irAEs needs to be re-examined—severe pneumonia may be fatal, but mild toxicity may serve as a biomarker for efficacy prediction. In the future, combined with technologies such as dynamic monitoring of plasma inflammatory factors and analysis of immune cells in bronchoalveolar lavage fluid, methods to distinguish between "beneficial inflammation" and "fatal toxicity" can be explored to maximize ICI efficacy while ensuring patient safety.

Summary

Since the application of immune checkpoint inhibitors (ICIs) in the treatment of malignant tumors, biomarkers for predicting their efficacy have been a research focus in the field of tumor immunology. Clinical data show that patients with immune-related adverse events (irAEs) have significantly better progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) than those without [40]. A meta-analysis covering 12 clinical centers worldwide showed that among melanoma patients, those with irAEs had a median PFS extended by 4.2 months and an overall survival rate increased by 28%; among NSCLC patients, the ORR of those with irAEs was 19% higher than that of the group without irAEs. This indicates that irAEs may serve as a "dynamic indicator" reflecting the intensity of the body's immune response, but current research still faces many obstacles to be overcome.

Existing studies show that there is an obvious tumor type imbalance in irAEs research: over 70% of studies are focused on melanoma and NSCLC, while research in fields such as gastrointestinal tumors and gynecological tumors is significantly lagging behind. Taking gastric cancer as an example, due to the complexity of the tumor microenvironment and patient heterogeneity, there is no consensus on the incidence, clinical manifestations, and association with prognosis of irAEs, and large-sample cohort studies are urgently needed to fill the gap.

In terms of research methods, retrospective studies rely on electronic medical record data, which have problems such as information bias, confounding factors (such as patient age, comorbidities, and treatment history affecting the risk of irAEs and treatment outcomes), and missed diagnosis of subclinical irAEs (leading to underestimation of the true incidence), resulting in insufficient generalizability of conclusions; although prospective studies can avoid these problems, they face challenges such as long enrollment cycles, high sample attrition rates, and ethical constraints, and high-quality research evidence is relatively scarce.

With the expansion of the application scope of ICIs, the timely identification and intervention of irAEs have become an urgent clinical need. The latest guidelines point out that establishing a multi-dimensional monitoring system (such as dynamic detection of peripheral blood inflammatory factors and autoantibody profiles) is crucial for early warning of toxic and side effects; combining radiomics (such as CT texture analysis) and liquid biopsy technologies (circulating tumor DNA, exosome biomarkers) may accurately predict the occurrence of irAEs. In addition, artificial intelligence-assisted diagnostic systems have shown initial results in identifying high-risk irAEs patients, but the clinical application of these new technologies still requires large-scale retrospective verification. It is urgent to establish a cross-regional cooperation network to verify the clinical significance of new biomarkers through multi-center, randomized controlled studies and incorporate them into standardized diagnosis

and treatment processes. In the future, it is necessary to combine innovative technologies with traditional medical practices to help improve the level of identification and intervention of irAEs.

Declarations

Conflict of Interest

The authors have no relevant financial or nonfinancial interests to disclose.

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Author Contributions

Sijie Yang and Zidong Zhao wrote the manuscript.

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