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Research Progress of Sintilimab in Advanced Non-Small Cell Lung Cancer

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Abstract: *Lung cancer is the most frequently diagnosed cancer globally and the primary cause of cancer-related mortality. The increasing research and clinical application of immune checkpoint inhibitors (ICIs) have led to significant progress in the treatment of advanced lung cancer. This article provides a comprehensive review of the mechanism of action, therapeutic applications, and adverse reactions of sintilimab, a domestically developed PD-1 inhibitor, to offer insights for future research and clinical practices.*

Keywords: *Sintilimab, Non-Small Cell Lung Cancer, Research Progress*

1. Introduction

Lung cancer is the most common cancer in China and the leading cause of cancer-related mortality globally .According to the most recent report by the China National Cancer Center (NCC), lung cancer remained the leading cause of cancer-related morbidity and mortality in China, with incidence and mortality rates of 22.0% and 28.5%, respectively [1].Non-small cell lung cancer (NSLCL) constitutes over 85% of all lung cancer cases[2], most patients are diagnosed in advanced stages. The discovery of immune checkpoints in the immune response has transformed treatment strategy for lung cancer, leading to significant improvements in patient outcomes, including prolonged survival. Immune checkpoints are key negative regulatory mechanisms of the immune system that regulate self-tolerance, prevent autoimmunity, and protect tissues from immune-mediated damage. Tumor cells frequently exploit these mechanisms to evade immune surveillance[3].Currently, well-characterized immune checkpoints include cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed death cell 1 (PD-1), and programmed cell death-Ligand 1(PD-L1). PD-1 is expressed on T cells, B cells, and natural killer cells (NK cells). It is critical for regulating the central and peripheral immune tolerance mechanisms[4]. Immune checkpoint inhibitors effectively reverse tumor-mediated immunosuppression by targeting immune checkpoint proteins expressed on T cells, thereby restoring the immune system's capacity to engage in antitumor responses. Sintilimab, a PD-1 inhibitor developed independently in China, has demonstrated significant efficacy in blocking the PD-1/PD-L1 pathway. This article reviews the most recent research progress on the application of sintilimab in the treatment of advanced non-small cell lung cancer.

2. Sintilimab

PD-1 is a coinhibitory receptor expressed on the surface of immune cells (particularly T cells) that exerts negative regulatory effects on T cell-mediated immune responses. Tumor cells exploit this mechanism by interacting with PD-1, thereby delaying T cell activation and cytotoxicity against tumors, promoting tumor immune escape, and contributing to T cell exhaustion[5,6]. Sintilimab is a highly selective, fully human IgG4 anti-PD-1 monoclonal antibody that specifically blocks the interaction between PD-1 and its ligands (PD-L1/PD-L2), thereby inhibiting the PD-1/PD-L1 signaling pathway. This pathway is a key driver of tumor immune tolerance, and its inhibition restores T cell function, enhances T cell-mediated immune surveillance and cytotoxic activity against tumors, and generates antitumor immune responses, thereby achieving the therapeutic objective of tumor treatment[7].Sintilimab not only demonstrates comparable antitumor activity but also offers a more favorable safety profile and significantly greater cost-effectiveness compared to both nivolumab and pembrolizumab [8].

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3. Combination therapies

As a PD-1 inhibitor, sintilimab has shown significant efficacy in the treatment of lung cancer when combined with various therapeutic modalities. By synergistically utilizing agents with distinct mechanisms of action, this combination regimen aims to further enhance antitumor efficacy while effectively alleviating resistance development that often occurs with monotherapy. These combination strategies not only expand the range of treatment options available to patients but also pave the way for innovative therapeutic strategies to address tumor complexity and heterogeneity.

3.1 Sintilimab in combination with chemotherapy

In a phase 3 randomized controlled trial (ORIENT-12), sintilimab combined with platinum-based chemotherapy and gemcitabine showed a statistically significant improvement in progression-free survival (PFS) and a manageable toxicity profile in patients with advanced squamous non-small cell lung cancer[9].Yang et al.[10] demonstrated that in patients with advanced non-squamous non-small cell lung cancer, the combination of sintilimab with platinum-based chemotherapy and pemetrexed significantly prolonged PFS compared to chemotherapy alone, with median PFS of 8.9 months versus 5.0 months. The incidence rates of ≥3-grade adverse events were 61.7% and 58.8%, respectively. In addition, Liu et al.[11] further demonstrated that patients with advanced lung cancer treated with sintilimab in combination with platinum-based chemotherapy and pemetrexed showed a significant delay in time to true deterioration (TTD) across most domains of the Cancer Treatment Questionnaire (EORTC QLQ-C30) and Lung Cancer Symptom Scale (LCSS), thereby supporting the notion that the inclusion of sintilimab in chemotherapy regimens enhances or sustains health-related quality of life and reduces symptom burden.

A meta-analysis showed that sintilimab in combination with chemotherapy had significant clinical benefit for NSCLC, with significant improvement in objective response rate (ORR) and disease control rate (DCR), while reducing the risk of disease progression, with significant advantages in efficacy, cost and accessibility[12].Furthermore, a meta-analysis encompassing 3,559 patients systematically evaluated the efficacy and safety of sintilimab combined with platinum-based doublet chemotherapy versus other PD-L1 inhibitors in the treatment of advanced NSCLC. The results revealed that sintilimab in combination with platinum-based doublet chemotherapy demonstrated comparable efficacy and safety to pembrolizumab, atezolizumab, tislelizumab, camrelizumab, and nivolumab[13]. In contrast to pembrolizumab, sintilimab is uniquely designed to target the FG loop of PD-1. A pharmacodynamic study demonstrated that sintilimab exhibits stronger binding affinity for PD-1, engages a greater number of PD-1 molecules on $CD3^+$ T cells, and displays enhanced T-cell activation characteristics. Furthermore, it shows a slower dissociation rate. This enhanced binding affinity and slower dissociation likely contribute to its superior efficacy in blocking the PD-1/PD-L1 pathway, thus amplifying T-cell-mediated anti-tumor activity[14].Notably, Maggie et al.[15]further systematically evaluated the efficacy of sintilimab or pembrolizumab in combination with platinum-based chemotherapy in advanced NSCLC in a phase 2 trial. The results demonstrated an ORR of 54.5% for the sintilimab combination and 45.4% for the pembrolizumab combination, with similar progression-free survival and overall survival (OS) outcomes. Specifically, the median PFS was 7.4 months for the sintilimab group and 7.1 months for the pembrolizumab group, while median OS was 14.7 months and 17.3 months, respectively. The incidence of ≥3 treatment-related adverse events was 77.3% in the sintilimab arm and 59.1% in the pembrolizumab arm. Collectively, these findings indicate that sintilimab in combination with platinum-based chemotherapy exhibits efficacy and safety profiles comparable to pembrolizumab in patients with advanced NSCLC.

Sintilimab not only exhibits significant advantages in efficacy, but also in cost and accessibility[12]. Cost-effectiveness analysis of sintilimab in combination with chemotherapy for patients with advanced non-small cell lung cancer, conducted using a compartmental survival model, demonstrated that this regimen is a cost-effective first-line treatment in the Chinese healthcare context[16], this approach not only reduces the economic burden on patients but also enhances treatment accessibility.

3.2 Sintilimab in combination with radiotherapy

The potential synergy between PD-1/PD-L1 inhibitors and radiotherapy has been demonstrated in non-small cell lung cancer patients, particularly in stereotactic body radiation therapy (SBRT), which has been widely used as a radiotherapy method, with its advantages of precise targeting, higher dose and shorter treatment duration, showing significant efficacy in the treatment of various malignant tumors[17].

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In a prospective phase I study of 29 patients with stage IV NSCLC who received stereotactic body radiation therapy for small lesions and low-dose radiation therapy (LDRT) for large lesions, followed by immunotherapy with sintilimab, the ORR was 60.7% and the median PFS was 8.6 months, this finding supports the feasibility and safety of a combination strategy involving stereotactic body radiation therapy, low-dose radiation therapy, and immunotherapy with sintilimab in this patient population[18].Another recent study found that granulocyte-macrophage colony-stimulating factor (GM-CSF) plays a key role in the differentiation, maturation, and expansion of dendritic cells (DCs),and that it potentiates anti-tumor immune responses by enhancing tumor antigen presentation to T cells[19]. NiJ et al.[20]systematically evaluated the safety and efficacy of a triple therapy regimen comprising sintilimab, stereotactic radiation therapy, and GM-CSF in patients with metastatic NSCLC (NCT04106180). The results showed that 18 out of 49 patients achieved an objective response, with the PFS and the OS durations of 5.9 and 18.4 months, respectively. Notably, the treatment was well-tolerated, as no grade 3 adverse events were detected during the treatment period. These findings suggest that the triple therapy regimen exhibits favorable efficacy and tolerability in patients with metastatic NSCLC.

3.3 Sintilimab in combination with angiogenic drugs

Anlotinib is a novel oral, small-molecule, multi-target tyrosine kinase inhibitor (TKI), primarily targeting vascular endothelial growth factor receptor (VEGFR). It exerts antitumor effects by inhibiting receptor tyrosine kinases involved in tumor proliferation and angiogenesis. In 2018, it was approved in China for third-line treatment of advanced non-small cell lung cancer[21]. Several preclinical studies have shown that anlotinib enhances the infiltration of innate immune cells, such as natural killer cells (NK cells) and antigen-presenting cells (APCs), which enhances antitumor efficacy, and may exhibit synergistic effects when used in combination with immune checkpoint inhibitors[22].A phase II clinical trial to investigate the efficacy and safety of sintilimab combined with anlotinib in patients with metastatic NSCLC. This trial enrolled 99 patients with metastatic NSCLC lacking EGFR, ALK, or ROS1 mutations. The ORR and PFS in the sintilimab plus anlotinib group were significantly higher than those in the chemotherapy group (44.9% vs. 18.0%; 14.4 months vs. 5.6 months), with a lower incidence of ≥ grade 3 treatment-related adverse events (28.0% vs. 49.0%). These findings demonstrate a significant therapeutic benefit alongside a more favorable safety profile compared to standard platinum-based chemotherapy[23].

3.4 Sintilimab in combination with autologous NK cells

In recent years, the combination of tumor immunotherapy and NK cell therapy has been increasingly explored. Compared with ICI monotherapy, ICIs combined with NK cells can improve ORR and extend PFS and OS in NSCLC patients (6.5 months vs. 4.3 months for PFS;15.5 months vs 13.3 months for OS)[24].A study demonstrated that the combination of sintilimab and autologous NK cells exhibited significant antitumor activity and a favorable tolerability profile in patients with advanced NSCLC who had failed first-line treatment[25].This finding may be explained by the PD-1 inhibitor's capacity to enhance NK cell immune function, which subsequently amplifies their antitumor effects. Notably, updated overall survival data revealed a median OS of 27.3 months for this combination therapy, with no new adverse events reported. These results underscore the potential of this regimen to effectively extend long-term survival in NSCLC patients[26].These findings establish a foundation for future research on immune checkpoint inhibitor and NK cell combination therapies. However, additional studies with larger sample sizes and more comprehensive clinical trials are necessary to validate these results and fully elucidate their clinical implications.

4. Therapeutic application of sintilimab in patients with driver gene - positive non - small cell lung cancer

With the progressive advancement of mechanistic understanding and evidence-based insights into targeted therapies, immunotherapy has gradually emerged as a viable treatment option for patients with driver gene-positive non-small cell lung cancer. Liu et al.[27] evaluated the efficacy of sintilimab combined with either the anti-angiogenic agent IBI305 and pemetrexed plus cisplatin in patients with advanced EGFR-mutated NSCLC who had disease progression after EGFR-TKIs, compared to chemotherapy alone. The interim results indicated that the PFS in both the sintilimab plus IBI305 and chemotherapy group (6.9 vs. 4.3 months) and the sintilimab plus chemotherapy group (5.5 vs. 4.3 months) was significantly prolonged, with acceptable tolerability. These findings suggest that the integration of

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ICIs with anti-angiogenic agents and chemotherapy holds promise, providing an alternative therapeutic strategy for patients who develop resistance to EGFR-TKIs. However, further research is required to validate these results and refine the treatment regimen.

5. Safety management and adverse reactions

In recent years, tumor immunotherapy has achieved breakthrough advancements, not only promoting the innovation of cancer treatment paradigm, but also significantly improving the survival rate of cancer patients. However, with the widespread use of immunosuppressants, the incidence of immune-related adverse events (irAEs) has increased significantly. Although immunotherapy has many advantages in terms of efficacy, its adverse effects on patients should not be overlooked . IrAEs may involve any organ or system and present with diverse clinical manifestations. The National Cancer Institute (NCI) has developed a standardized grading system for irAEs, which categorizes them into mild or asymptomatic (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4), and fatal (Grade 5)[28].The exact pathophysiological mechanisms of irAEs remain not yet fully understood. Current evidence suggests that these adverse events are primarily associated with the dysregulation of the autoimmune system, which involves either the loss of autoimmune tolerance or an exaggerated immune response to self-antigens, ultimately resulting in autoreactive attacks on healthy tissues. Several mechanisms have been proposed to explain the development of irAEs, including the production of autoantibodies, T-cell infiltration, and the involvement of inflammatory cytokines such as IL-6 [3]. These events often present with a range of clinical manifestations, such as skin rash and pruritus, gastrointestinal reactions, endocrine dysfunction (e.g. pituitary, thyroid, and adrenal disorders)[29],pneumonitis, hepatitis, neurological toxicities, myocarditis, and myelosuppression.

As a fully humanized monoclonal antibody, sintilimab exhibits low immunogenicity and is expected to reduce the risk of immune-related adverse effects[14]. A meta-analysis showed that sintilimab was associated with an increased risk of hypothyroidism, particularly in younger women[30]. In another meta-analysis involving 1,162 patients, indicating that sintilimab was well tolerated and had a manageable safety profile due to overall low discontinuation rates and mortality rates associated with chemotherapy[31]. Although multiple Phase 3 clinical trials have shown that the use of ICIs can significantly prolong the overall survival of patients, exhibit controllable toxicity, and most patients can tolerate adverse reactions with active symptomatic treatment. However, further clinical trials and studies are needed to reduce the occurrence of immune-related adverse events. Therefore, it is crucial for clinicians to enhance their understanding of immune-related adverse events associated with PD-1 inhibitors, to ensure precise identification, accurate diagnosis, and timely intervention.

6. Conclusion

In conclusion, sintilimab, a PD-1 inhibitor independently developed in China, has great potential in combination therapy. Its application in patients with driver gene mutations in advanced NSCLC is well worth attention. During the use of this inhibitor, the occurrence of adverse events can be controlled. It is also quite good in terms of cost-effectiveness, which makes it more attractive in clinical practice. The results of the ongoing trials are still very encouraging. However, regarding strategies for reducing treatment-related adverse events and addressing drug resistance in immunotherapy, we still need to conduct in-depth research. Subsequent research should prioritize large-scale clinical trials guided by precision and personalized treatment paradigms, focusing on optimizing combination therapy regimens, defining ideal drug synergies and treatment sequencing, to ultimately improve the survival outcomes of patients and enhance their quality of life.

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