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The Applications of PD1 Monoclonal Antibody in Non-small Cell Lung Cancer

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Abstract. Lung cancer is currently the most deadly type of cancer, with non-small cell lung cancer dominating, thus making it the primary focus of clinical research and treatment. Despite advances in modern medicine, traditional treatment methods still have limitations in improving patient survival rates. This is especially true in advanced cases, where the survival rate is extremely low, below 20%. Immune checkpoint inhibitors represented by PD-1 monoclonal antibodies (mAbs) have made significant progress in NSCLC treatment, which restores T cell function by blocking the PD-1/PD-L1 pathway and prolongs the patient's survival, but there are problems such as drug resistance and adverse reaction management. Currently, there is insufficient systematic integration of PD-1 mAb in NSCLC, drug resistance mechanism and combination therapy strategies. This paper analyzes the mechanism of action of PD-1 mAb, elaborates on the clinical application data of Pembrolizumab, Atezolizumab and Nivolumab in different stages of NSCLC, including efficacy, safety and adverse reaction management strategies, and discusses drug resistance mechanism and response plans. The findings demonstrate that their single-agent or combination treatment can increase patients' survival and objective response rate, but attention should be paid to immune-related adverse events (irAEs) and drug resistance issues. This study provides theoretical support for optimizing the individualized application of PD-1 mAb in NSCLC. In the future, biomarkers can be explored to accurately predict the efficacy, develop new combination treatment plans to overcome drug resistance, and promote the more efficient and safe development of NSCLC immunotherapy.

Keywords: Monoclonal antibody, non-small cell lung cancer treatment, Immunotherapy

1. Introduction

Globally, lung cancer is one of the disease types with the highest mortality rate. There are two main types of lung cancer, with non-small cell lung cancer accounting for more than 80 percent of all lung cancer cases [1]. Despite some progress in traditional chemotherapy and targeted therapy, the 5-year survival rate for patients with advanced non-small cell lung cancer (NSCLC) remains below 20%. Most patients with advanced lung cancer have missed the optimal surgical opportunity when the disease is discovered, and the efficacy of radiotherapy and chemotherapy is poor with significant toxic and side effects, while they also face severe challenges of drug resistance.

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The introduction of immune checkpoint inhibitors (ICIs) has been a landmark breakthrough in the field of tumor therapy research. In 2011, the first ICIs, Ipilimumab, was approved by the FDA to go on the market, opening a new era of tumor immunotherapy. In recent years, immunotherapy has provided new treatment options for patients with advanced NSCLC with its excellent anti-tumor function and controllable adverse reactions [2]. The main medication of ICIs, programmed death receptor 1 (PD-1) monoclonal antibody (mAb), exhibits great promise by reestablishing the immune system. However, to deeply analyze the underlying logic of the efficacy of PD-1 mAb, relevant research needs to return to the key molecule of PD-1 itself. PD-1 is an important immunosuppressive molecule. Under normal physiological conditions, the immune system needs precision regulation to maintain immune balance and avoid excessive immune responses causing damage to the body's own tissues. PD-1 plays a key role in this process. At present, anti-PD-1 drugs represented by nivolumab and pembrolizumab, as well as anti-PD-L1 drugs such as Atezolizumab and other cancer treatments have shown significant efficacy in a variety of cancer treatments, but there are still some drug resistance problems that need to be solved.

This paper systematically summarizes the mechanism of action of PD-1 mAb, its clinical application in NSCLC, efficacy prediction markers and adverse reaction management strategies, and discusses future optimization directions, which are of great significance to promoting its wide application in NSCLC treatment.

2. Immunomodulatory mechanism of PD-1 mAb

2.1. Molecular structural characterization of PD-1/PD-L1 and its expression pattern in NSCLC

The extracellular portion of the transmembrane protein PD-1, which is a member of the immunoglobulin superfamily, has an Ig V-like domain that binds to ligands. PD-L1 is also a transmembrane protein, and its extracellular region consists of an Ig V-like domain and an Ig C-like domain, where the Ig V domain binds to the Ig V domain of PD-1 through a conserved interface, forming a "face-to-face" interaction pattern similar to antibody antigen binding. This structural feature renders the pathway a critical target for ICIs. [3]. This site is universal in the expression of NSCLC, with PD-L1 staining positive in about 43.1% of tumor cells of NSCLC patients (≥5% tumor cells), and PD-L1-positive TIL (tumor-infiltrating lymphocytes) mainly distributed in the core area of the tumor [4]. In addition to generalization, the expression of PD-1/PD-L1 in NSCLC is also associated with some pathological features, such as being strongly linked to a history of smoking, male, and vascular/lymphatic invasion [5].

2.2. The connection between tumor immune escape and the PD-1/PD-L1 immune checkpoint pathway

One of the primary pathways of tumor immune escape is the PD-1/PD-L1 immune checkpoint pathway. Throughout the body's immunological response against tumors, the expression level of the immune checkpoint receptor PD-1 on the surface of activated T lymphocytes was significantly upregulated. At the same time, tumor cells specifically bind to PD-1 on the surface of T cells by increasing the expression of the ligands PD-L1 and PD-L2 on their own surface, thereby initiating immunosuppressive signaling. This binding not only inhibits the initial activation of T cells, but also considerably reduces effector T cell production and function, including reducing cytokine secretion and reducing cytotoxic effects. This immunosuppressive effect leads to a significant decrease in T

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cells' recognition and killing ability of tumor cells, thereby inducing the occurrence of tumor immune escape and the construction of microenvironment. Studies have shown that the PIK3CA (phosphatidylinositol-4,5-diphosphate 3-kinase catalytic subunit α) gene is the most common mutation target of the PI3K subtype in cancer, and its encoded mutation of the p110α subunit can cause the continuous activation of PI3K and drive tumorigenesis. These mutations overactivate the PI3K-AKT pathway by enhancing enzyme activity or reducing the binding of negative regulatory factors. Consequently, immunosuppression is exacerbated and cancer cell invasion and proliferation are encouraged [6]. Traditionally, PD-1 is a marker for depleting CD8+ T cells and can keep these cells resting. However, However, the latest evidence shows that following T cell activation, the expression of these inhibitory receptors increases and exhibits intricate patterns across different T cell subpopulations. The effect of PD-1 is not to maintain a depleted state, but to inhibit the amplification of antigen-specific T cells during the initiation or amplification phase. Additionally, PD-1 is co-expressed in CD103+ and CD8+ tissue resident memory T cells, which mediate anti-tumor immunity. These cells can be effector T cells or stem cell-like memory T cells [7]. PD-1 inhibitors disable T cell inhibition by blocking PD-1/PD-L1 binding and reactivate anti-tumor immune responses, especially in stem-like memory T cells or effector T cell-derived immune subpopulations. This mechanism provides a theoretical basis for NSCLC immunotherapy.

3. Clinical practice and efficacy optimization of PD-1 mAb in NSCLC treatment

In recent years, with the continuous deepening of cancer immunotherapy research, the exploration of immune checkpoints in the field of NSCLC has continued to heat up. Against this background, the application of PD-1 mAb in NSCLC therapy has made significant progress and has shown significant value in patients with different stages. The following is a discussion on the three drugs: Pembrolizumab, Atezolizumab and Nivolumab from the aspects of action mechanism, clinical application and safety optimization.

3.1. Pembrolizumab

Pembrolizumab takes PD-1 as the target and belongs to humanized IgG4 mAb. The principle of its action is that it can specifically bind to PD-1 on the surface of T cells and block the interaction between this receptor and PD-L1/PD-L2 on the surface of tumor cells or antigen-presenting cells, thereby reducing the immunosuppression of T cells by this pathway, restoring the proliferative capacity, cytokine secretion, and cytotoxicity of effector T cells, and ultimately enhancing the body's immune response to tumor cells [7, 8]. In the clinical application stage, the applicable scenarios of pembrolizumab have been fully verified. First, as a first-line treatment plan, it is suitable for patients with advanced NSCLC who are highly expressed (tumor ratio score TPS ≥50%) and are negative for epidermal growth factor receptor or anaplastic lymphoma kinase (EGFR/ALK); secondly, by combining it with chemotherapy drugs such as pemetrexed/platinum, its indication can be extended to patients with low or negative expression of PD-L1; finally, KEYNOTE-091 study conducted in 2022 further confirmed that this drug can significantly prolong the disease-free survival (DFS) of patients in postoperative adjuvant therapy, becoming a common choice for early NSCLC postoperative treatment [8].

Clinical efficacy results showed that in the KEYNOTE-024 trial, patients with high PD-L1 expression (TPS ≥50%) treated with pembrolizumab first-line monotherapy had an objective remission rate (ORR) of 44.8% and a median progression-free survival (PFS) of 10.3 months, which was significantly better than that of traditional platinum-based chemotherapy regimens (ORR

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27.8%, PFS 6.0 months); its 5-year survival rate reached 31.9%, breaking the limitations of traditional chemotherapy in terms of long-term survival. PFS 6.0 months); its 5-year survival rate reached 31.9%, breaking through the long-term survival bottleneck of traditional chemotherapy [7, 8]. In terms of combination therapy, the results of the KEYNOTE-189/407 trial showed that when pembrolizumab combined with pemetrexed/platinum was used for first-line treatment of non-squamous NSCLC, the ORR was increased to 47.6%, with a median overall survival (OS) of 22.0 months, an 8.6 month extension compared with the chemotherapy group. For patients with squamous cell carcinoma, the median survival was 3.4 months longer with the paclitaxel/platinum combination compared to chemotherapy alone [9, 10].

In terms of safety, the adverse reactions of pembrolizumab are mainly irAEs, with the incidence of grade 3-5 irAEs being about 13%. Common adverse reactions include: skin toxicity (rash, itching, incidence 15%-20%), gastrointestinal reactions (diarrhea, colitis, about 2% of grade 3 or above), endocrine disorders (hypothyroidism, incidence 8%-10%), and pulmonary toxicity (pneumonia, about 2% of incidence) [11].

Optimized management strategies for the above side effects include comprehensive evaluation of the patient's thyroid function and lung function before treatment, and review every 6-8 weeks during the treatment process to promptly detect abnormalities; graded management of adverse reactions, such as local use of glucocorticoids for grade 1-2 skin toxicity, and oral prednisone (0.5-1mg/kg/d) is required for grade 3 or above; in addition, about 10% of patients may experience pseudo-progress in the early stage of treatment, and in clinical practice, PET-CT or biopsy results should be used to avoid premature stopping of medication [8, 11].

3.2. Atezolizumab

Atezolizumab targets programmed death ligand 1 (PD-L1) and is classified as a humanized IgG1 monoclonal antibody. Its mechanism of action is to specifically bind to PD-L1 on the surface of tumor cells or immune cells, thus blocking the interaction between PD-L1 and PD-1, B7.1, while relieving T cell inhibition signals, it retains the normal immune regulatory function of PD-L2 on T cells, thereby reducing the occurrence of excessive inflammatory response [9, 12].

In the clinical application stage, the applicable scenarios of Atezolizumab include: first-line monotherapy is suitable for patients with advanced NSCLC who are highly expressed (TC3/IC3) and have a driver negative driver gene; In terms of combination therapy, when combined with carboplatin in combination with albumin paclitaxel, it can be used as a first-line treatment option for advanced squamous or non-squamous NSCLC, while when combined with bevacizumab in chemotherapy, it is indicated for non-squamous NSCLC.

Clinical efficacy data showed that in the IMpower110 study, for patients with high PD-L1 expression, the median overall survival reached 20.2 months, significantly better than the chemotherapy group (13.1 months), with an ORR of 38.3% [12]. In terms of combined chemotherapy, the IMpower130 study showed that when Atezolizumab combined with carboplatin + albumin paclitaxel was treated with advanced non-squamous NSCLC, the median PFS reached 7.0 months (5.5 months in the chemotherapy group) and OS reached 18.6 months, especially in patients with liver metastasis (immunosuppressive microenvironment) (ORR 34%) [9].

In terms of safety, Atezolizumab is generally well tolerated, with the incidence of grade 3-5 irAEs at about 15%. The main adverse reactions include: fatigue (invasion 24%), rash (15%), pulmonary toxicity (pneumonia, about 2.6% above grade 3), and liver toxicity (elevated aminotransferase, 5%) [11].

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Optimized management strategies for side effects include patients with hepatotoxicity and baseline liver insufficiency should be used with caution, monitor ALT/AST every 2 weeks during the treatment process, and treatment should be suspended and glucocorticoids should be given; when combined with bevacizumab, blood pressure and proteinuria should be closely monitored to avoid severe bleeding (incidentally <1%) [11, 12].

3.3. Nivolumab

Nivolumab also targets PD-1 and is a fully human IgG4 mAb. Its mechanism of action is dual: on the one hand, it relieves immunosuppression by preventing them from binding to each other; on the other hand, regulatory T cells in the tumor microenvironment can be eliminated through antibody-dependent cell-mediated cytotoxic effects, further enhancing the anti-tumor activity of effector T cells [6].

In clinical practice, the primary indications for nivolumab can be categorized into two main scenarios: In first-line therapy, the drug is combined with another immune checkpoint inhibitor to form a “dual immunotherapy regimen,” This regimen is suitable for patients with advanced NSCLC who have no mutations in specific genes and whose tumor cells have a high number of genetic mutations (reaching a certain burden level). In second-line therapy, the drug can be used alone for patients with advanced NSCLC whose condition continues to worsen after receiving platinum-based chemotherapy, and its use is not restricted by the expression levels of relevant immune molecules in the body.

From a clinical treatment efficacy perspective, the CheckMate-227 study confirmed the advantages of the dual-immunotherapy regimen combining two immunotherapy drugs in first-line treatment: for patients with high tumor mutational burden, the median OS in the dual-free regimen did not reach (11.3 months in the chemotherapy group), and the 1-year progression-free survival rate reached 42.6%; even in PD-L1-negative patients, the median OS in the dual-free regimen was still extended by 4.9 months (17.1 months vs 12.2 months) than the chemotherapy group [13]. In second-line monotherapy, the results of the CheckMate-017/057 study showed that patients treated with this immunotherapy had a median overall survival of 9.2 months, compared to 6.0 months in the chemotherapy control group. For patients with non-squamous cell carcinoma, the median overall survival was 12.2 months with immunotherapy, compared to 9.4 months in the chemotherapy control group. The 2-year survival rates for these two groups of patients were 23% and 29%, respectively [6].

Regarding side effects, the incidence of grade 3-5 irAEs in nivolumab monotherapy was about 10%, while this rate rose to 35% when combined with ipilimumab. The main adverse reactions include: gastrointestinal toxicity (colitis, incidence 12%, about 5% above grade 3), pulmonary toxicity (pneumonia, incidence 9%, about 3% above grade 3), and liver toxicity (elevated aminotransferase, incidence 6%) [13].

Optimization strategies for side effects include strict screening before treatment, excluding uncontrolled autoimmune diseases (such as ulcerative colitis); liver function (ALT/AST) and myozyme spectrum are tested before treatment, and follow-up is performed every 4 weeks during the treatment; for patients with grade 3 colitis, intravenous infusion of methylprednisolone (1-2mg/kg/d), and infliximab is added if the efficacy is not good [6, 13]

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4. Safety assessment, drug resistance mechanism and response strategies of PD-1 mAb

4.1. Safety assessment and IrAEs management

There are some common features of immune-related side effects among the three such immune checkpoint-associated immune medications, although the chance of occurrence and severity will vary with the different medications and co-administration regimens. Overall, the management of immune-related adverse reactions must follow the principle of grading treatment. Skin toxicity is the most common irAEs (occupation rate 15%-25%). Local rashes in grade 1 can be treated with topical glucocorticoid ointment; extensive rashes in grade 2 require oral antihistamine combined with prednisone (0.5mg/kg/d); immunotherapy is required for grade 3 if blisters or epidermal necrosis occurs, and intravenous infusion of methylprednisolone (1mg/kg/d)[11]. Gastrointestinal toxicity is more common in nivolumab combined regimen. Loperamide can be taken orally for grade 1-2 diarrhea (avoid opioids); Grade 3 colitis requires prednisone (1-2 mg/kg/d) after colonoscopy is eliminated, and infliximab is added if the efficacy is not good [13]. Although the incidence of lung toxicity is low, it has a high risk of fatality. For patients with suspected symptoms of pneumonia such as cough and dyspnea, chest CT should be performed immediately. Patients with level 3 or above need to be hospitalized for treatment, and methylprednisolone (2mg/kg/d) is given, combined with immunoglobulin if necessary [8, 11]. Endocrine toxicity occurs, such as hypothyroidism can be controlled by supplementing levothyroxine without the need for pause of immunotherapy; while rare pituitary inflammation (incidentally <1%) requires hydrocortisone replacement therapy and permanent discontinuation of immunotherapy [11].

4.2. Drug resistance mechanism and response strategies

The drug resistance problem faced by PD-1/PD-L1 mAb in clinical applications is a key factor restricting its efficacy. The drug resistance mechanisms of the three drugs are common. The first is the immunosuppressive state of the tumor microenvironment. Certain cytokines secreted by tumor-associated macrophages (e.g., IL-10 and TGF-β) are capable of inhibiting T-cell infiltration. The coping strategy was combined with anti-TGF-β mAb (e.g. pembrolizumab + M7824), and the Phase II trial showed that this regimen could increase ORR to 32% [14].

The second mechanism is reduced expression or abnormal secretion of the molecule, whereby tumor cells can competitively bind another class of related molecules by reducing the expression of the molecule, or releasing soluble versions of the molecule, thereby rendering the drug inactive. Combination of chemotherapy (such as paclitaxel) can revert resistance by inducing immunogenic cell death, increasing ORR from 10% to 28% [14]. Then there is pathway cross-activation: hyperactivation of PI3K-AKT pathway in patients with EGFR mutations can lead to immune escape, and combined with EGFR-TKI (such as Osimertinib + Nivolumab) can result in ORR up to 41% in patients with EGFR T790M mutations [6].

5. Conclusion

The main body of this paper revolves around the application of PD-1 mAbs in NSCLC. It not only explains the structure, expression characteristics and relationship with tumor immune escape, but also introduces the mechanism of action, clinical application, efficacy, safety and adverse reaction management strategies of the three drugs: Pembrolizumab, Atezolizumab and Nivolumab, and analyzes the management of irAEs, drug resistance mechanism and coping strategies. The above

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findings lay a theoretical basis for optimizing the application of this class of immune drugs in the treatment of relevant lung cancers, elucidate their application value at different stages, and also provide a specific reference for clinical treatment. However, this article has certain limitations, that is, the specific impact of individual differences in different patients on the efficacy of PD-1 mAb is not discussed in depth, and some drug resistance mechanisms are still superficial. Based on this, biomarkers can be studied in depth in the future to accurately predict therapeutic efficacy and develop more combination treatment plans to overcome drug resistance, thereby promoting the further development of individualized immunotherapy for NSCLC.

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