Synergy and Mechanisms of Monoclonal Antibody-Chemotherapy in NSCLC

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Abstract. Lung cancer is the most prevalent and lethal malignant tumor worldwide, with non-small cell lung cancer (NSCLC) accounting for 80%-85% of cases. Most NSCLC patients are diagnosed at an advanced stage, losing curative surgical chances, making improving treatment efficacy and survival a critical clinical challenge. This study systematically reviews the research progress of monoclonal antibody (mAb) combined with chemotherapy for NSCLC, analyzes their synergistic mechanisms, and evaluates the therapy's clinical efficacy and safety. Internationally, trials like KEYNOTE-189 and ECOG 4599 confirmed the efficacy of mAb-chemotherapy, while domestically, the BEYOND trial validated bevacizumab-based combinations in Chinese patients. Representative monoclonal antibodies such as cetuximab, bevacizumab, and pembrolizumab exert their therapeutic effects through receptor blockade, anti-angiogenesis, or immune checkpoint inhibition. When combined with chemotherapy, these agents can prolong overall survival and improve response rates in patients, albeit with an increased incidence of adverse events (e.g., hemorrhage, immune-related adverse reactions). The synergistic mechanisms involve enhanced chemosensitivity, immune modulation, and co-inhibition of molecular signaling pathways, though gaps remain in mechanistic understanding and optimization of primary treatment protocols. This study provides scientific rationale for clinical decision-making and novel therapeutic strategies, advancing the field of non-small cell lung cancer treatment.

Keywords: Monoclonal antibodies; chemotherapy; synergistic mechanism.

1. Introduction

Lung cancer is the most prevalent and deadly malignant tumor worldwide, greatly endangering human health. Of all lung cancer cases, non-small cell lung cancer (NSCLC) makes up roughly 80% to 85%. Due to the fact that this disease often lacks obvious specific symptoms in its early stage, many patients are diagnosed when the disease has already progressed to an advanced stage. This not only deprives them of the best opportunity for radical surgical treatment but also adds greater difficulty to subsequent treatment efforts. In recent years, with the rapid development of medical technology, the treatment methods for NSCLC have gradually shifted from traditional radiotherapy and chemotherapy to targeted therapy, immunotherapy, and other diversified directions. However, how to further improve treatment efficacy and effectively prolong patient survival remains an important issue that urgently needs to be overcome in clinical and scientific research fields.

Foreign countries started early in targeted therapy and immunotherapy research for NSCLC. After years of exploration, a relatively complete theoretical system has been established in the field of monoclonal antibody combined chemotherapy, and rich clinical evidence has been accumulated. For example, the KEYNOTE-189 study published in the New England Journal of Medicine in 2018 clearly showed that the combination of pemetrexed and platinum-based chemotherapy with pembrolizumab can significantly prolong the median overall survival of patients with advanced non-squamous NSCLC, while significantly improving the objective response rate, providing strong support for the application of immune checkpoint inhibitors combined with chemotherapy [1]. The ECOG 4599 trial confirmed the efficacy of the combined therapy of bevacizumab and carboplatin plus paclitaxel. Relative to chemotherapy alone, this combination therapy can potently prolong the overall survival of late-stage NSCLC patients, becoming the first approved anti-angiogenic combination chemotherapy regimen for clinical use [2].

On the basis of drawing on international advanced experience, domestic research teams have conducted a series of targeted studies by combining the pathological and clinical characteristics of Chinese patients. However, compared with foreign countries, there is still a certain gap in basic mechanism research in China, such as insufficient research depth in areas such as drug resistance gene screening and tumor microenvironment regulation. At the same time, the number of clinical trials of original combination therapy regimens (such as bispecific antibody combination chemotherapy) is relatively small, and most research still focuses on "follow-up studies" of imported drugs, which limits China's independent innovation capabilities in this field.

This study aims to systematically review the research progress of monoclonal antibody combined chemotherapy in the treatment of NSCLC, deeply analyze the synergistic mechanism generated by this combined application mode, comprehensively evaluate its efficacy and safety in clinical practice, and provide a more scientific and reasonable reference basis for clinical treatment decision-making of NSCLC. An in-depth investigation into the mechanism of combined therapy is expected to offer a theoretical foundation for developing new treatment approaches, thus facilitating the enhancement of NSCLC treatment efficacy. This not only holds significant clinical application value but also carries profound implications for scientific research in relevant fields.

2. Overview of NSCLC

2.1. Epidemiological Characteristics

The incidence of NSCLC has obvious geographical differences, with a higher incidence in areas with developed industry and severe air pollution. The age of onset is mostly over 50 years old, and men have a higher incidence rate than women, but the incidence rate in women has shown an upward trend in recent years. The main risk element for NSCLC is smoking. In addition, air pollution, occupational exposure, genetic factors, etc., are also closely related to the occurrence of NSCLC. The prognosis of NSCLC is poor, and the 5-year survival rate of advanced patients is low, which seriously threatens human health.

2.2. Limitations of Traditional Treatment Methods

The traditional treatment methods for NSCLC mainly include surgical treatment, radiotherapy and chemotherapy. Surgical treatment is only appropriate for patients with early-stage NSCLC, and has limited effect on patients with advanced disease. Although radiotherapy can control tumor growth to a certain extent, it causes great damage to normal tissues and is prone to a series of complications. Chemotherapy is one of the main treatment methods for advanced NSCLC, but traditional chemotherapy drugs have problems such as poor selectivity and large side effects. Many patients interrupt treatment due to intolerance to side effects, and the treatment effect is often unsatisfactory.

3. Progress of Monoclonal Antibodies in the Treatment of NSCLC

3.1. Classification of Mechanisms of Action

Monoclonal antibodies exert therapeutic effects by accurately identifying and binding to specific molecules in tumor cells or tumor microenvironments. Their mechanisms of action are diverse, and there are cross-synergistic effects between different mechanisms, which together form the basis of their anti-tumor effects. Among them, receptor tyrosine kinase signal blockade is one of the important mechanisms. Monoclonal antibodies can bind to the extracellular domain of receptor tyrosine kinase overexpressed on the surface of tumor cells with high affinity. This binding effect can block the interaction between the receptor and its natural ligand, and inhibit the subsequent receptor dimerization process, thereby effectively preventing the continuous activation of downstream signaling pathways such as RAS-RAF-MEK-ERK and PI3K-AKT-mTOR, and ultimately causing tumor cells to enter a cell cycle arrest state and undergo apoptosis [3].

Another important mechanism by which monoclonal antibodies exert their effects is the inhibition of the vascular endothelial growth factor (VEGF) pathway. These antibodies can neutralize VEGF in the circulation or bind to its matrix, thereby blocking the binding of VEGF to VEGFR-1/2 receptors on the surface of vascular endothelial cells. This process can inhibit angiogenic signaling mediated by PI3K-AKT and PLCγ-MAPK, reducing the microvascular density and blood perfusion in tumor tissues. As a result, tumor cells cannot obtain sufficient nutrients, and their growth and metastasis are effectively suppressed [4]. The immune checkpoint inhibition mechanism is achieved by binding monoclonal antibodies to programmed death receptor-1 (PD-1) on the surface of T cells or programmed death ligand-1 (PD-L1) on the surface of tumor cells. This binding blocks the interaction between PD-1 and PD-L1, relieving tumor cells from inhibiting T cell activation, proliferation, and cytotoxicity, allowing the body's immune system to restart immune surveillance and killing of tumor cells [5].

In addition, receptor degradation and antibody drug conjugates are also important mechanisms in monoclonal antibody therapy. Receptor degrading antibodies can induce target proteins (such as c-MET) to enter lysosomes for degradation, rapidly clearing these oncogenic proteins at the post-translational level, thereby persistently inhibiting their mediated oncogenic signaling. Antibody drug conjugates are engulfed by cells after specific binding of antibodies to tumor cell surface antigens, and then release cytotoxic payloads through enzymatic hydrolysis in lysosomes. These payloads can cause DNA damage or inhibit microtubule function in cells, achieving selective killing of tumor cells and reducing their impact on normal cells [6].

3.2. Clinically Commonly Used Monoclonal Antibody Drugs

At present, there are many types of monoclonal antibody drugs applied to the clinical treatment of NSCLC. Among them, the representative drug of anti EGFR monoclonal antibody, cetuximab, can bind to EGFR, thereby blocking its binding to ligands and downstream signaling pathways such as RAS/RAF/MEK/ERK, effectively inhibiting the proliferation and metastasis of tumor cells. The anti VEGF monoclonal antibody bevacizumab binds to VEGF, preventing its interaction with VEGFR, suppressing the proliferation of endothelial cells and the generation of new blood vessels, cutting off the nutritional supply of tumors, and achieving the goal of inhibiting tumor growth. The immune checkpoint inhibitor pembrolizumab binds to PD-1 on the surface of T cells, blocking the interaction between PD-1 and tumor cell PD-L1, relieving immune suppression, and restoring T cell killing ability against tumor cells. It has shown significant efficacy in clinical treatment. The table 1 lists the representative drugs of these three categories with different mechanisms of action.

Table 1. Classification and mechanism of action of representative monoclonal antibody drugs for clinical treatment of NSCLC [3-5]

Drug Category	Representative Drug	Mechanism of Action
Anti-EGFR monoclonal antibody	Cetuximab	Binds to EGFR, blocks its binding to ligands and downstream signaling pathways (such as RAS/RAF/MEK/ERK), and inhibits tumor cell proliferation and metastasis
Anti-VEGF monoclonal antibody	Bevacizumab	Binds to VEGF, prevents its binding to VEGFR, inhibits the proliferation of VE cells and the formation of new blood vessels, and cuts off the nutrient supply of tumors
Immune checkpoint inhibitor	Pembrolizumab	Binds to PD-1 on the surface of T cells, blocks the interaction between PD-1 and PD-L1 of tumor cells, relieves immune suppression, and restores the killing effect of T cells on tumors

3.3. Clinical Efficacy and Application Status

The effect of monoclonal antibodies in the treatment of NSCLC has been confirmed by multiple phase III clinical trials, and their application scenarios are constantly expanding. Taking immune checkpoint inhibitors as an example, the KEYNOTE-024 test results showed that for advanced NSCLC patients with PD-L1 expression levels ≥ 50%, the median overall survival of patients treated with pembrolizumab monotherapy reached 30.0 months, significantly better than the 14.2 months of traditional chemotherapy. For patients with low PD-L1 expression (1%-49%), combination chemotherapy can still bring significant benefits [7]. For example, in the KEYNOTE-189 trial, the objective response rate of pembrolizumab combined with chemotherapy reached 48%, and the median overall survival was extended by nearly 11 months compared to chemotherapy alone [1]. The combination of anti angiogenic antibodies has also achieved good results. In the JO25567 trial, the treatment regimen of bevacizumab combined with erlotinib (A+T regimen) was used for EGFR mutant lung cancer patients, and its progression free survival was 16.0 months, significantly longer than the 9.7 months of erlotinib monotherapy [8]. The NEJ026 trial 4 years later also reached a consistent conclusion, further confirming the effectiveness of this combination regimen [9].

4. Classic Chemotherapy Regimens

The classic chemotherapy regimen for NSCLC is mainly based on platinum based combination chemotherapy, which blocks the growth and division of tumor cells through the synergistic effect of different drugs, and has been widely used in clinical treatment. For patients with non-squamous NSCLC, the combination of cisplatin and pemetrexed is applicable. This regimen not only has an ideal therapeutic effect but also has relatively good tolerance in patients, which can control tumor progression while reducing the incidence of severe adverse reactions. The combination of cisplatin and gemcitabine has certain therapeutic effects on patients with squamous NSCLC. These two drugs kill tumor cells through different mechanisms of action, which helps to enhance the therapeutic efficacy. In the treatment of NSCLC, the combination of carboplatin and paclitaxel is widely used, which can effectively control tumor progression, alleviate patient symptoms and improve their quality of life. However, it should be noted that these chemotherapy regimens may cause damage to normal cells during the treatment process, triggering a series of side effects, thereby affecting the tolerance and treatment compliance of patients.

Chemotherapy faces many limitations and challenges in the treatment of NSCLC. On the one hand, chemotherapy drugs have poor selectivity. While killing tumor cells, they also damage normal tissues such as bone marrow and gastrointestinal tract, leading to side effects including myelosuppression, nausea and vomiting, and alopecia in patients, which seriously affect the quality of life and treatment compliance of patients. On the other hand, tumor cells are prone to developing resistance to chemotherapy drugs, which gradually reduces the chemotherapy effect and leads to treatment failure. In addition, the difference in sensitivity to chemotherapy drugs among different patients is also one of the challenges.

5. Clinical Study of Monoclonal Antibody Combined with Chemotherapy in the Treatment of NSCLC

The combination of monoclonal antibodies and platinum-based dual drug chemotherapy is the core first-line treatment model for driver gene-negative advanced NSCLC, based on complementary mechanisms to exert synergistic effects. According to the antibody mechanism, it can be divided into three categories: anti-angiogenic antibodies combined with platinum-based chemotherapy, immune checkpoint inhibitors combined with platinum-based chemotherapy, and exploratory schemes of novel ADCs combined with chemotherapy. The theoretical basis is chemotherapy-induced immunogenic death of tumors, downregulation of the immunosuppressive microenvironment, and enhancement of antibody action; Antibodies reverse chemotherapy resistance.

Multiple clinical researches have confirmed the effectiveness of the combination therapy. In the ECOG-4599 trial, better median PFS and OS were observed in bevacizumab combined with chemotherapy than in chemotherapy alone [2]. The Keynote-189 trial showed significant efficacy of pembrolizumab combined with chemotherapy in non squamous cell carcinoma patients[1]. The Keynote-407 trial confirmed that this combination therapy is equally effective for squamous cell carcinoma, with median OS and ORR superior to chemotherapy [10].

Efficacy evaluation and safety analysis showed that immunotherapy significantly prolonged mOS and mPFS, and the lower the PD-L1 expression, the more significant the benefit. The combination of anti-angiogenesis and chemotherapy improves mPFS, with OS benefits mainly in non-squamous subtypes. In terms of safety, about 70% of patients with grade≥3 adverse events in the anti-angiogenic combination group, and those with squamous cell carcinoma, should be cautious of fatal hemoptysis; immune combination group≥grade 3 AE 60-70%, immune-related AE can be controlled through early intervention.

6. The Synergistic Mechanism of Monoclonal Antibody Combined with Chemotherapy in the Treatment of NSCLC

Monoclonal antibodies enhance the sensitivity of tumor cells to chemotherapy drugs through various pathways. Partial antibodies inhibit the expression of resistance-related proteins, reduce the efflux of chemotherapy drugs, and increase intracellular drug concentration. They can also disrupt the tumor microenvironment, break down the barrier for drugs to reach tumor tissue, make chemotherapy drugs more effective, and enhance the killing effect. The combined application has significant immunomodulatory effects. Chemotherapy releases tumor-associated antigens and activates the immune system when killing tumor cells; Programmed death receptor 1 inhibitors and other antibodies relieve tumor immune suppression, enhance immune cell recognition and killing ability, synergistically improve anti-tumor immune response, and suppress tumor growth and metastasis. At the molecular biology level, the two produce synergistic effects by affecting different signaling pathways. Chemotherapy induces DNA damage in tumor cells, and antibodies inhibit their DNA repair mechanism, increasing the sensitivity of tumor cells to chemotherapy; They also jointly regulate the expression of cell cycle-related proteins, prevent tumor cell proliferation, promote apoptosis-related gene expression, accelerate tumor cell death, and achieve synergistic anti-tumor effects.

7. Conclusion

This study systematically found that the combination of monoclonal antibodies and chemotherapy has a significant synergistic effect in the treatment of NSCLC, which can improve efficacy, prolong survival, and improve quality of life. Its synergistic mechanism includes enhancing the sensitivity of tumor cells to chemotherapy, exerting immune regulatory effects, and synergistically inhibiting tumors by affecting signaling pathways at the molecular level. However, combination therapy has problems and increases the risk of adverse reactions, such as the risk of bleeding from anti-angiogenic combined chemotherapy and immune-related adverse events from immune combined chemotherapy, which may affect patient tolerance or lead to treatment interruption; Some patients may develop drug resistance, leading to reduced efficacy and complex resistance mechanisms. Future research should optimize joint protocols, explore biomarkers for predicting efficacy and drug resistance, achieve personalized treatment, improve NSCLC treatment levels, and bring greater benefits to patients.

References

[1] Garassino, M. C., et al. Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non-Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study. Journal of Clinical Oncology, 2023, 41(11), 1992–1998.

[2] Tyagi P. Bevacizumab, when added to paclitaxel/carboplatin, prolongs survival in previously untreated patients with advanced non-small-cell lung cancer: preliminary results from the ECOG 4599 trial. Clinical lung cancer, 2005, 6(5), 276–278.

[3] Wheeler, D. L., et al. Understanding resistance to EGFR inhibitors—impact on future treatment strategies. Nature Reviews Clinical Oncology, 2010, 7(9), 493-507.

[4] Ferrara, N., et al. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. Nature Reviews Drug Discovery, 2004, 3(5), 391-400.

[5] Brahmer JR, Tykodi SS, Chow LQM, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012, 366(26):2455-2465.

[6] Beck, A., et al. Strategies and challenges for the next generation of antibody–drug conjugates. Nature Reviews Drug Discovery, 2017, 16(5), 315-337.

[7] Reck, M., et al. Pembrolizumab versus chemotherapy for PD–L1–positive–small-cell lung cancer. New England Journal of Medicine, 2016, 375(19), 1823–1833.

[8] Seto, T., et al. Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): An open-label, randomised, multicentre, phase 2 study. The Lancet Oncology, 2014, 15(11), 1236–1244.

[9] Saito, H., et al. Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ026): Interim analysis of an open-label, randomised, multicentre, phase 3 trial. The Lancet Oncology, 2019, 20(5), 625–635.

[10] Novello, S., et al. Pembrolizumab Plus Chemotherapy in Squamous Non-Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study. Journal of Clinical Oncology, 2023, 41(11), 1999–2006.