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Advanced Progress in Targeted Drugs Therapy for Non-Small Cell Lung Cancer

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Abstract: In modern society, cancer is the most therapeutic disease. Among all types of cancer, the highest mortality rate is lung cancer and 85% of lung cancer patients is non-small cell lung cancer (NSCLC). However, significant therapeutic advances—particularly in targeted therapy and immunotherapy—have revolutionized its treatment landscape. This review systematically summarizes recent progress in these two approaches of targeted therapy and immunotherapy. Regarding targeted therapy, particular emphasis is placed on three key targets: Epidermal Growth Factor Receptor (EGFR), Anaplastic Lymphoma Kinase (ALK), and ROS Proto-Oncogene 1(ROS1). EGFR mutations promote tumorigenesis by activating downstream signaling pathways. Up to the current era, the sequential development of three tyrosine kinase inhibitors (TKI) generations has enabled progressively refined targeting of EGFR-mutated tumorigenesis. ALK gene rearrangement serves as a pivotal oncogenic driver in NSCLC. It activates downstream signaling pathways to promote cancer initiation and progression, with corresponding inhibitors now advancing to the third generation. Due to its high homology with ALK, the ROS1 gene has shown significant responsiveness to some ALK inhibitors. Regarding immunotherapy, the analysis covers three approaches: cancer vaccines, cellular immunotherapy, and immune checkpoint inhibitors. For immunotherapy, we analyze three strategies. Cancer va*ccines*, which prime tumor-specific immune responses by antigen presentation; C*ellular immunotherapies* (e.g., Chimeric Antigen Receptor-Modified T Cells (CAR-T), T-Cell Receptor Engineering (TCR-T), and Tumor-Infiltrating Lymphocytes (TIL) therapies), engineered to enhance antitumor immunity. And *immune checkpoint inhibitors* (e.g., PD-1/PD-L1 blockers), which reinvigorate T-cell function by disrupting immunosuppressive signals. Despite their clinical success, challenges like drug resistance and toxicity persist. Future research should prioritize novel targets, innovative technologies, and combination strategies to further transform NSCLC treatment.

Keywords: NSCLC, targeting drug, Immune drug, treatment, progress

1. Introduction

The continuous progress in science and medicine has enabled successful treatment of numerous once-untreatable diseases. Nevertheless, cancer persists as one of the most formidable medical challenges. Notably, lung cancer exhibits the highest fatality rate among all malignancies, of which NSCLC comprises 85% [1]. The lack of discernible early clinical manifestations frequently leads to diagnosis of NSCLC at locally advanced or metastatic stages. Characterized by its highly aggressive nature and rapid disease progression, NSCLC poses significant challenges to conventional therapeutic

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approaches. Conventional surgical intervention combined with chemotherapy demonstrates favorable therapeutic outcomes in early-stage patients, yet exhibits suboptimal efficacy in advanced-stage cases. Radiotherapy, while remaining the most effective cytotoxic modality for localized solid tumors, induces substantial toxicity to adjacent healthy tissues, resulting in clinically significant adverse effects [2].

With the development of cancer treatment approaches, targeted therapies focusing on molecular targets in NSCLC have significantly altered the treatment landscape of NSCLC, which has become a key treatment method for NSCLC. Targeted therapy refers to an approach that employs small-molecule drugs or therapeutic monoclonal antibodies to inhibit specific oncogenic proteins or block related signaling pathways, thereby achieving antitumor effects. Nearly two-thirds of patients with NSCLC harbor oncogenic driver mutations, among which approximately half exhibit actionable targetable alterations. Compared to conventional therapies, targeted therapy has demonstrated improved survival rates and enhanced safety profiles for patients [3]. Targeted drugs for high-frequency driver mutations such as EGFR, ALK, and ROS1 have now been widely used in clinical treatment. However, due to factors including epigenetic modifications and tumor heterogeneity [4], the clinical application of targeted therapy still faces several challenges: patients are prone to developing secondary resistance, and those with low-frequency target mutations often lack appropriate targeted drugs. Unless addressed, these limitations will continue to impede the effective clinical adoption of targeted drug in NSCLC therapy.

The advancement of immunotherapy has provided new momentum in the fight against lung cancer in recent years. This approach encompasses multiple modalities, such as immune checkpoint inhibitors (ICIs), cancer vaccines, and cellular immunotherapy, all of which operate by establishing or enhancing an effective immune response against tumors [5]. Compared to traditional therapies, the unique mechanism of immunotherapy lies in its modulation of the host immune system. Immunotherapy works by enhancing or activating the immune system to eliminate Pathogen., resulting in fewer and milder adverse effects compared to traditional treatments like chemotherapy and radiotherapy, which can damage healthy tissues. Moreover, immunotherapy demonstrates remarkable therapeutic efficacy, significantly prolonged patients' survival. ICI, which widely implemented in the clinical management of various malignancies, exert therapeutic effects by blocking specific molecular interactions to augment T-cell activation and proliferative capacity. This mechanism potentiates antitumor immune responses through the reprogramming of interaction networks among immune cells, and tumor cells [6]. Safe and effective, immunotherapy has become a major focus of research in the treatment of NSCLC.

In this review, we concentrate on current research advances in targeted drug therapies and immunotherapy agents for NSCLC, discuss the challenges and future directions of targeted treatment and immunotherapy in NSCLC.

2. Targeted therapy and immunotherapy for NSCLC

Not only does NSCLC have a high incidence rate, but it also has a high mortality rate. It is rooted in the obstacles to early detection and limited curability at advanced stages. Currently, multiple treatment modalities are available for NSCLC. Surgical resection remains the cornerstone of NSCLC treatment, with its historical roots dating back to the earliest therapeutic interventions. The evolution of medical technology has established chemotherapy and radiotherapy as pivotal components of the NSCLC treatment paradigm. In recent years, targeted therapy and immunotherapy have undergone rapid development and are progressively becoming central to NSCLC treatment. Despite rapid advancements in treatment modalities, clinical management of NSCLC remains challenged by short-lived therapeutic efficacy and frequent development of drug resistance. Among these approaches,

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targeted therapy and immunotherapy stand out as the most effective options with minimal toxic side effects.

2.1. Targeted therapy for NSCLC

Targeted therapy refers to a treatment approach that utilizes small-molecule drugs or therapeutic monoclonal antibodies to inhibit specific oncogenic proteins or block relevant signaling pathways, thereby achieving antitumor effects [7]. Recently, the continuous approval of targeted drugs for NSCLC has led to a profound transformation in the treatment paradigm for this disease, owing to their superior efficacy and lower toxicity compared to chemotherapy. Genetic alterations such as ALK rearrangements, EGFR mutations, inducing aberrant changes of downstream targets such as RET and ROS1 represent major drivers of NSCLC pathogenesis. Consequently, current diagnostic standards for NSCLC include testing for these molecular targets. The U.S. Food and Drug Administration (FDA) has approved numerous targeted drugs for NSCLC, with key therapeutic targets now encompassing EGFR, ALK, among others. These targeted agents act with precision on their designated molecular targets, minimizing damage to healthy tissues and organs. As a result, they have significantly improved clinical outcomes for NSCLC patients by delivering enhanced therapeutic efficacy alongside reduced toxicity compared to conventional chemotherapy or radiotherapy. The following sections will provide detailed discussions on three representative targets—EGFR, ALK, and ROS1—along with their corresponding targeted therapies.

2.1.1. EGFR

EGFR is a transmembrane protein receptor. EGFR in the cell surface respond to the intracellular tyrosine kinase receptor upon successful ligand binding. Structurally, EGFR consists of four extracellular domains, a transmembrane domain, a tyrosine kinase domain, and a carboxyl-terminal tail [8]. When it binds to the corresponding ligands, EGFR undergoes dimerization, followed by phosphorylation, which enhances its tyrosine kinase activity. This, in turn, activates downstream signaling pathways, When EGFR is mutated, it promotes cancer cell dedifferentiation, rapid proliferation, apoptosis inhibition, and ultimately tumorigenesis. The gene encoding EGFR exhibits high polymorphism and is prone to mutations, with several mutation types identified. Exon 19 deletions is the most prevalent and extensively studied mutations as well as exon 21 point mutations [9].

The first generation of TKIs, such as erlotinib and gefitinib, are primarily used for NSCLC with EGFR target mutations. Studies have shown that the 12-month survival rate for gefitinib in positive patients which were respond to the EGFR mutation was 24.9%, compared to only 6.7% with traditional chemotherapy [10], which established the first-line treatment status of EGFR-TKIs. However, first-generation TKIs were soon found to be prone to developing drug resistance. Consequently, second-generation TKIs, such as afatinib and dacomitinib, were rapidly developed.

Second-generation TKIs are irreversible inhibitors and, compared to first-generation TKIs, can also be effective against some rarer target mutations. In the preliminary clinical study, compared with the first-generation drug gefitinib, the second-generation targeted agent dacomitinib significantly improved patient survival; however, it was associated with increased side effects relative to the first-generation drug [11]. This demonstrates that second-generation EGFR-TKIs offer improved efficacy compared to first-generation TKIs but also come with more severe side effects.

Osimertinib, as a third-generation EGFR-TKI, demonstrates efficacy against the T790M resistance mutation, which emerges in roughly half of patients developing acquired resistance to first-generation EGFR inhibitors. Osimertinib demonstrated a significantly longer median progression-free survival (10.1 months) in treating these patients compared to chemotherapy (4.4 months) [12]. However,

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regardless of the generation, all EGFR-TKIs inevitably lead to drug resistance, which remains an urgent issue to address.

2.1.2. ALK

ALK is a proto-oncogene that can activate signal transduction pathways through mechanisms such as have an effect on genes, thereby disrupting normal cellular physiological functions and inducing malignant transformation. Molecular profiling of NSCLC patients with aberrant ALK expression reveals that the most prevalent genetic alteration is the amplification of the fusion gene of protein and ALK. The resulting chimeric protein constitutively activates downstream signaling pathways, interferes with normal cell cycle regulation, and ultimately leads to oncogenesis [13].

Currently, the third-generation TKIs were approved for advanced ALK-positive NSCLC. The first-generation ALK inhibitor, crizotinib—a representative small-molecule competitive inhibitor targeting both ALK and ROS1—revolutionized the treatment landscape for ALK-positive NSCLC. However, similar to EGFR-TKIs, its major drawback is the tendency for patients to develop resistance after treatment.

The second-generation ALK inhibitors comprise ceritinib, alectinib, ensartinib, brigatinib, and entrectinib. In pivotal trials, the third-generation agent lorlatinib showed markedly improved outcomes, with a 12-month progression-free survival rate of 78% versus 39% for crizotinib-treated patients. The data revealed that the drug demonstrates significant blood-brain barrier penetration, with detectable drug concentrations measured in the brain, showing promising therapeutic potential for brain tumors [14]. These results highlight lorlatinib's enhanced therapeutic efficacy and its strong blood-brain barrier penetration capability.

However, However, the probability of adverse reactions such as hyperlipidemia, edema and weight gain with lorlatinib is higher than that of the first-generation TKI. While its efficacy is superior, this comes at the cost of increased toxicity.

2.1.3. ROS1

The ROS1 proto-oncogene is located on human chromosome 6 and encodes one of tyrosine kinase receptors It has three domains: an intracellular kinase structural region, a transmembrane domain, and an extracellular domain, collectively encoding a transmembrane protein with tyrosine kinase activity [15]. The ROS1 gene can undergo chromosomal translocation and fuse with other genes, leading to constitutive activation of the kinase domain and promoting cancer development.

Due to the strong homology between the kinase domains of ROS1 and ALK, many drugs used for ALK-positive patients, such as crizotinib and lorlatinib, also demonstrate significant therapeutic efficacy in ROS1-positive patients. Repotrectinib, a next-generation ROS1-TKI, has shown remarkable clinical activity in ROS1-positive NSCLC patients, primarily causing common low-grade adverse effects. Additionally, repotrectinib has demonstrated promising therapeutic effects in some patients who have developed resistance to other ROS1-TKIs.

2.2. Immunotherapy for NSCLC

Immunotherapy represents an emerging therapeutic modality. Rather than directly killing tumor cells through pharmacological agents, its mechanism involves modulating the host immune system. It functions by enhancing or activating immune system functionality, thereby boosting the body's immune capacity to combat diseases, including the elimination of cancer cells. It encompasses various methods, including immune checkpoint inhibitors (ICIs), cancer vaccines, and cellular immunotherapy. Due to its high specificity and minimal side effects, immunotherapy has become a major research focus in recent years.

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2.2.1. Immune Checkpoint Inhibitors (ICIs)

The immune checkpoint system comprises a network of interacting regulatory molecules, including both co-stimulatory and co-inhibitory molecules. These two subsets of molecules functionally coordinate to precisely modulate immune cell activation states and maintain immunological homeostasis [16]. They primarily expressed on the surface of immune cells. When corresponding ligands bind to these receptors, they transmit inhibitory signals to immune cells to prevent excessive immune responses that could cause autoimmune damage to the body. Consequently, immune checkpoint signaling reduces the functionality of immune cells, particularly T cells, inhibiting their proliferation, cytokine release, and secretion of cytotoxic granules.

As a critical component of the immune system, immune checkpoints can nevertheless be exploited by tumors as a major mechanism to evade immune surveillance, especially against tumor antigen-specific T cells. The mechanism of immune checkpoints typically involves ligand-receptor interactions. Therefore, ICIs can block these checkpoints, restoring immune cell function to eliminate tumor cells.

The first ICI antiboby therapy is for the target of cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) approved by the FDA [17]. Subsequently, other ICIs such as programmed cell death protein 1 (PD-1) antibody have been developed. Currently, the most extensively studied ICIs are focus on these targets,such as PD-1, PD-L1 and CTLA-4

The PD-1/PD-L1 signaling pathway plays a critical role in regulating CD8+ T cell immune function. It induces CD8+ T cell exhaustion, thereby suppressing the immune system's ability to eliminate tumor cells and facilitating tumor immune escape. It is precisely for this reason that PD-1/PD-L1 inhibitors have emerged as the most promising therapeutic targets among immune checkpoint inhibitors (ICIs) [18]. Currently, several PD-1 or PD-L1 blocking antibodies have been successfully developed and approved for treating various advanced cancers, including NSCLC. In previous clinical trials utilizing ICIs for NSCLC treatment, the pembrolizumab treatment arm demonstrated a median progression-free survival (PFS) of 10.3 months, significantly outperforming the chemotherapy arm's 6.0 months. Subsequent 6-month overall survival rate analysis revealed superior outcomes for the ICI treatment group compared to the chemotherapy group [19]. Pembrolizumab demonstrates better therapeutic efficacy and lower toxicity in NSCLC treatment, making it a first-line treatment option.

ICIs have also made new advances in recent years. For example, combining pembrolizumab with chemotherapy can significantly improve treatment outcomes. Meanwhile, new resistance mechanisms have been discovered. PD-1/CTLA-4 bispecific antibodies have been developed and shown good results in clinical trials. The development of ICIs is expected to transform the current landscape of NSCLC treatment

2.2.2. Cancer vaccines

Vaccines represent a monumental achievement in human disease prevention, with limited application in cancer therapy. Cancer vaccine therapy, analogous to conventional vaccines, does not directly delivery drugs to the tumor site., It stimulates the host's immune response to generate or enhance anti-tumor immunity by introducing tumor antigens in various forms (cells, peptides, viruses, or nucleic acids). This approach activates immune cells and cytokines to mount a more robust immune response for targeted tumor cell elimination [20]. Cancer vaccine therapy is regarded as a groundbreaking advancement in oncology, offering multiple advantages including low toxicity, precise targeting, and the ability to induce long-lasting immune memory, thereby effectively addressing tumor heterogeneity and reversing immunosuppressive microenvironments. Currently, various cancer vaccines have entered clinical trials for malignancies such as melanoma and lung cancer. However,

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this approach still faces several technical challenges, including limited antigen selection, suboptimal immunogenicity, and inadequate host immune responses, which collectively hinder its clinical translation [21].

Significant progress has been made in cancer vaccine research. The mRNA-4157/V940 vaccine has become the first personalized neoantigen vaccine to enter Phase III clinical trials with promising clinical outcomes. Breakthroughs have also been achieved in DNA vaccine technology. The clinical application of cancer vaccines is imminent.

2.2.3. Cellular immunotherapy

Cellular immunotherapy represents an innovative strategy in cancer treatment. Rather than directly targeting cancer cells, this approach involves isolating a patient's own T cells, modify them in vitro to specifically recognize tumor-associated antigens, expanding the cells ex vivo, and ultimately reinfusing the amplified cell products back into the patient. The therapy induces a more rapid and potent immune reaction against cancer. Currently, the main cellular immunotherapies being applied to NSCLC. The main cell therapies for non-solid tumors are currently CAR-T and TCR-T treatments. In recent years, researchers have gradually adapted these technologies for solid tumors through technical improvements. Common solid tumor therapies include NK (natural killer) cell and TIL therapies. Among these, NK cells primarily play an adjunctive role, demonstrating limited efficacy as a standalone treatment, all of which have demonstrated significant clinical potential

2.2.3.1. CAR-T

CAR-T therapy currently represents the most rapidly advancing cellular immunotherapy. Its core principle involves genetically engineering immune cells through artificial modification—introducing designed chimeric antigen receptors (CARs) into T cells to enable targeted recognition of specific tumor-associated antigens on cancer cell surfaces. This approach facilitates highly efficient immune attacks against malignant cells and induces significantly enhanced immune clearance effects compared to natural immune responses [22]. A CAR consists of three domains: the extracellular domain determines antigen affinity, while the transmembrane and intracellular domains function to achieve stable binding to tumor cell antigens and mediate downstream signaling, respectively. However, CAR-T therapy still faces challenges, including severe toxicity, antigen escape, limited tumor infiltration, and functional impairment due to the immunosuppressive tumor microenvironment.

2.2.3.2. TCR-T

Compared to CAR-T therapy, TCR-T therapy offers several advantages. First, it targets a broader range of antigens, as TCR-T cells can recognize both membrane-bound and intracellular targets, whereas CAR-T cells are restricted to extracellular targets. Second, TCR-T cells require lower target antigen density for activation than CAR-T cells [23], enabling them to detect and eliminate tumor cells with minimal antigen expression. However, TCR-T therapy is associated with stronger toxicity and the development of resistance, which remain significant hurdles.

2.2.3.3. TIL

TILs naturally recognize tumor cells, though tumors often evade this immune response. TILs contain a diverse repertoire of tumor antigen-specific T-cell clones, which can be isolated from a patient's tumor, expanded out of the body, and reinfused to promote TIL proliferation, activation, and tumor cell killing.

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Breakthroughs have been achieved in cellular immunotherapy, yet critical challenges remain regarding target selection, toxicity reduction, and overcoming microenvironment-induced functional alterations. However, research progress continues to advance rapidly. Notably, the allogeneic CAR-T therapy UCART19 received FDA approval in January 2024 for relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL), while novel techniques like IL-21 substitution for IL-2 have significantly shortened TIL production cycles from weeks to days. The widespread clinical implementation of cellular immunotherapies still requires further development of innovative technologies and therapeutic agents.

3. Challenges and future perspectives

Although both targeted therapy and immunotherapy currently demonstrate favorable efficacy and widespread utilization, they still face several challenges.

Despite the initial effectiveness of EGFR-TKIs, ALK-TKIs, and ROS1-TKIs, targeted therapy continues to struggle with significant resistance issues. For instance, Patients typically experience reduced drug efficacy within 8-16 months after treatment initiation, ultimately leading to drug resistance and disease progression [24]. Additionally, some patients exhibit resistance to osimertinib due to the amplification of wild-type EGFR alleles [25]. Furthermore, tumor heterogeneity poses a major obstacle. Spatial heterogeneity results in varying drug responses across different targets, while temporal heterogeneity accelerates the evolution of resistant clones [26], thereby diminishing therapeutic efficacy.

Moreover, the effectiveness of immunotherapy is often hampered by the immunosuppressive tumor microenvironment. Consequently, even PD-L1-high patients show suboptimal response rates to immunotherapy [27]. Moreover, a small subset of patients experience hyperprogressive disease (HPD) upon PD-1 inhibitor treatment [28].

Moving forward, targeted therapy urgently requires the development of novel targets, with fourth-generation EGFR-TKIs expected to address existing resistance mutations. Breakthroughs have also been made in drugs targeting rare mutations. In immunotherapy, antibody inhibitors target PD-1, /PD-L1, and CTLA-4have become widely used ICIs for NSCLC treatment. In recent years, T-cell immunoglobulin and ITIM domain (TIGIT) has emerged as a novel immunoregulatory molecule of significant research interest. This protein is selectively expressed on activated T cells where it delivers immunosuppressive signals upon ligand binding to inhibit immune cell function. Studies demonstrate that using PD-1 ICI together with the inhibitors that target TIGIT pathways can effectively counteract this immunosuppression, markedly enhancing $CD8^+$ T cell proliferation in vitro and potentiating the body's antitumor immunity. Currently, TIGIT-targeting ICIs are under development, with tiragolumab (Roche) in Phase III clinical trials. If approved, it could provide a paradigm for next-generation NSCLC immunotherapies.

The continued progress in both targeted and immune therapies promises to revolutionize NSCLC treatment, offering renewed hope for patients.

4. Conclusion

Targeted therapies and immunotherapies have fundamentally transformed the treatment landscape for NSCLC. Both targeted agents against key molecular drivers (EGFR/ALK/ROS1) and immunotherapeutic approaches including cancer vaccines, cellular therapies, and immune checkpoint inhibitors, have demonstrated significant clinical value. While challenges such as drug resistance, tumor heterogeneity, and immune-related adverse events remain, these therapeutic advancements have provided timely and effective treatment options for numerous NSCLC patients.

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Looking ahead, we can address current limitations by developing next-generation TKIs to overcome resistance mechanisms and investigating combination strategies with novel immunomodulators (e.g., TIGIT inhibitors). Furthermore, we should explore more advanced therapeutic modalities, such as rationally designed multimodal combination therapies to enhance efficacy, and even develop gene-editing treatments capable of eliminating oncogenic mutations. Continued progress in these areas will elevate NSCLC treatment to new heights, ultimately delivering better outcomes and renewed hope for patients worldwide.

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