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Osimertinib Targeted Intervention for EGFR Mutant Lung Cancer

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Abstract. Epidermal growth factor receptor activating mutations serve as core driver lesions of non-small cell lung cancer, while early EGFR inhibitors are restricted by T790M resistance and weak blood-brain barrier penetration. This review systematically sorts multi-layer pharmacological effects, clinical advantages and acquired resistance subtypes of third-generation targeted agent osimertinib based on domestic and global Phase III clinical data. Osimertinib forms stable covalent binding with mutant EGFR to block MAPK and PI3K/Akt oncogenic cascades, and exerts dual anti-tumor effects via direct tumor apoptosis induction and long-term remodeling of immunosuppressive microenvironment. Large clinical trials verify its prominent control efficacy for primary lesions and intracranial metastases, yet long-term monotherapy easily generates four categories of drug resistance represented by C797S mutation and MET amplification. This paper summarizes stratified combined intervention schemes matching different resistance phenotypes, which provide standardized theoretical references for dynamic individualized targeted treatment and novel EG inhibitor development. Novel liquid biopsy monitoring technology further optimizes the whole-process precision medication management of osimertinib in clinical practice.

Keywords: Osimertinib, non-small cell lung cancer, epidermal growth factor receptor, signaling pathway, drug resistance

1. Introduction

Lung cancer remains one of the most lethal malignant tumors worldwide, and NSCLC occupies 80%–85% of all pathological subtypes of lung cancer. Global cancer epidemiological data demonstrate that lung cancer contributes more than 1.8 million deaths annually, and over two-thirds of patients are diagnosed at locally advanced or metastatic stages with lost radical surgical opportunities [1]. Owing to atypical early clinical manifestations, most patients only develop obvious chest pain, hemoptysis and dyspnea in advanced phases, accompanied by bone and brain metastasis, resulting in severely shortened overall survival and poor quality of life [2].

A multi-modal comprehensive treatment system including surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy has been established for advanced NSCLC, yet each intervention modality has inherent clinical defects [3]. Conventional chemoradiotherapy relies on non-selective cytotoxic effects, triggering severe myelosuppression, gastrointestinal injury and cumulative multi-drug resistance after long-term intervention [1]. After 10–14 months of continuous

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administration, nearly half of patients treated with first- and second-generation reversible EGFR-TKIs will develop secondary T790M resistance mutation [4]. Meanwhile, their low lipophilicity leads to extremely low cerebrospinal fluid drug concentration, failing to effectively control intracranial metastatic lesions [5]. Immune checkpoint inhibitors only bring clinical benefits to patients with high PD-L1 expression and high tumor mutational burden, accompanied by fatal adverse events such as immune-related interstitial pneumonia and liver damage, which limits their monotherapy application in EGFR-mutant NSCLC populations [2].

EGFR mutation is the predominant driver genetic alteration in Chinese NSCLC patients, with an overall mutation rate exceeding 50%, significantly higher than that of Western populations [3]. The major mutation subtypes consist of primary sensitive mutations (exon 19 deletion, exon 21 L858R) and secondary T790M mutation induced by prior first-line TKI treatment [4]. Osimertinib, a third-generation irreversible EGFR-TKI, forms stable covalent modification on mutated EGFR protein and maintains high effective drug concentration in brain parenchyma, which has been recommended as a standardized first-line and second-line therapeutic agent for EGFR-mutant advanced NSCLC in the 2024 Chinese NSCLC Targeted Therapy Guidelines [3].

Existing published reviews mostly separately discuss the pharmacological characteristics of osimertinib or single drug-resistance subtype, lacking systematic integration of tumor-driving signaling cascades, multi-dimensional anti-tumor effects, complete classification of acquired resistance and matched clinical combination regimens [6]. For instance, previous summaries only focus on single-pathway inhibitory effects of osimertinib, ignoring its long-term regulatory effects on dynamic remodeling of the tumor immune microenvironment and angiogenesis [7]; resistance-related reviews merely enumerate mutation types without linking corresponding stratified clinical intervention strategies based on distinct resistance phenotypes [8]. By integrating recent multi-cycle preclinical experimental data and landmark phase III clinical outcomes of FLAURA and AURA series trials, this paper sorts out the pathological progression mechanism of EGFR-mutant NSCLC, multi-target anti-tumor pathways, long-term clinical superiority and targeted coping strategies for drug resistance, to offer comprehensive references for clinical dynamic medication adjustment and innovative development of next-generation targeted anti-tumor agents [5, 9, 10].

2. Pathogenesis of NSCLC and anti-tumor pharmacological mechanisms of osimertinib

2.1. Unmet clinical challenges in current NSCLC treatment

NSCLC features rapid disease progression, high postoperative recurrence risk and frequent distant metastasis, and different intervention approaches possess strict applicable population thresholds [3]. Radical surgical resection is only applicable to early-stage patients without lymphatic infiltration or distant organ metastasis, covering less than 20% of newly diagnosed NSCLC patients in China [3]. Radiotherapy and chemotherapy lack tumor specificity and cause irreversible damage to normal tissues; platinum-based dual chemotherapy only achieves an objective response rate lower than 30% for metastatic EGFR-mutant NSCLC [1]. First- and second-generation EGFR-TKIs fail to overcome T790M-mediated acquired resistance after long-term administration, while immune checkpoint inhibitors have narrow beneficiary groups and potentially fatal autoimmune toxicities such as interstitial pneumonitis and myocarditis [2]. Under such clinical context, developing low-toxicity targeted agents against EGFR resistance mutations has become a core research direction of lung cancer translational medicine [4].

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2.2. Driver gene-dependent oncogenic signaling cascades

The initiation and continuous progression of NSCLC are synergistically driven by somatic gene mutations, persistent hyperactivation of intracellular kinase signaling and dysregulated tumor microenvironment [2]. Mutated EGFR sustains ligand-independent tyrosine kinase activation and continuously stimulates two core pro-tumor signaling axes, which serve as the fundamental molecular basis for unlimited proliferation, invasion and distant metastasis of malignant lung epithelial cells [1].

The MAPK (Ras/Raf/MEK/ERK) cascade disrupts normal cell cycle checkpoints by upregulating Cyclin D1 and downregulating cell cycle suppressors p21 and p27, significantly facilitating tumor cell proliferation, invasion and migratory capacity [1]. In vitro cell line validation experiments confirm that specific blockade of MAPK signaling can reduce clone formation efficiency of EGFR-mutant lung cancer cells by over 60%, fully verifying its tumor-promoting function [1]. The PI3K/Akt/mTOR signaling pathway reshapes tumor cell energy metabolism by enhancing aerobic glycolysis and upregulates anti-apoptotic Bcl-2 family proteins to block programmed cell death; sustained Akt activation also initiates epithelial-mesenchymal transition (EMT) to further boost tumor metastatic potential [7].

EMT further strengthens the metastatic potential of malignant cells by downregulating epithelial marker E-cadherin and upregulating mesenchymal markers N-cadherin and Vimentin [7]. Tumor lesions recruit abundant regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), which secrete high levels of immunosuppressive cytokines including IL-10 and TGF-β to mediate tumor immune escape [2]. Meanwhile, pathological angiogenesis driven by HIF-1α and VEGF provides sufficient nutrients and migratory channels for continuous tumor deterioration, and brain metastatic lesions rely heavily on abnormal microvessels to maintain long-term growth [5].

2.3. Inherent limitations of traditional therapeutic regimens

Cytotoxic chemotherapy indiscriminately injures normal tissues, leading to severe vomiting, myelosuppression and peripheral neurotoxicity; long-term use easily induces multi-drug resistance mediated by ABC transporter proteins on tumor cell membranes [1]. T790M mutation replaces threonine with methionine at position 790 of the EGFR kinase domain, increasing steric hindrance and altering EGFR spatial conformation, which completely disables reversible first/second-generation TKIs such as gefitinib and afatinib [4]. In addition, these early TKIs possess low lipophilicity and cannot cross the intact blood-brain barrier effectively; cerebrospinal fluid drug concentration only accounts for less than 5% of plasma concentration, failing to relieve brain metastasis lesions in most patients [5]. For EGFR-mutant patients, the tumor microenvironment belongs to an immune cold state with abundant suppressive cells, so a single PD-1/PD-L1 inhibitor only achieves a response rate lower than 15%, accompanied by various immune toxicities [2].

2.4. Fundamental pharmacological profile of osimertinib

Distinct from reversible EGFR competitive inhibitors, osimertinib contains a unique acrylamide side chain that forms irreversible covalent adducts with cysteine 797 residues on mutant EGFR, and it retains extremely low binding affinity toward wild-type EGFR to minimize off-target toxic effects on normal epidermal and gastrointestinal epithelial cells [9]. Preclinical kinase screening experiments verified that osimertinib exhibits nanomolar inhibitory activity against Exon19del, L858R and T790M mutant EGFR, while the IC50 for wild-type EGFR is more than 200 times

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higher, which greatly reduces the incidence of grade 3–4 skin and gastrointestinal adverse reactions observed in first-generation TKIs [9].

Its high lipophilicity ensures excellent intracranial drug exposure; animal model data show that the cerebrospinal fluid drug concentration of osimertinib reaches over 30% of plasma concentration, far superior to first-generation TKIs [5]. Phase III FLAURA trial proved that its median progression-free survival reached 18.9 months as first-line therapy, compared with 10.2 months of standard gefitinib/erlotinib treatment, significantly delaying disease progression over a long-term observation window of 5 years [10]. AURA3 study enrolled T790M-positive patients progressing after first-line EGFR-TKIs, showing an over 70% objective response rate for intracranial lesions, and median intracranial progression-free survival up to 11.7 months [5]. Domestic multi-center real-world research further confirmed that osimertinib achieves consistent durable intracranial efficacy in Chinese NSCLC patients with single or multiple brain metastases within 24 months of continuous administration [3].

2.5. Multi-layer anti-tumor signaling pathways regulated by osimertinib

2.5.1. Irreversible covalent inhibition of mutant EGFR kinase activity

Osimertinib stably binds mutant EGFR via covalent bonds to persistently inhibit tyrosine kinase activity, cutting off upstream oncogenic signal transmission and terminating continuous phosphorylation of downstream substrate proteins [4]. Its weak binding to wild-type EGFR protects normal lung tissue and alleviates skin rash, diarrhea and other gastrointestinal adverse reactions commonly observed in first-generation TKIs [9]. Structural biology research revealed that the acrylamide group of osimertinib forms a stable carbon-sulfur bond with Cys797, permanently locking the EGFR kinase domain in an inactive conformation, which cannot be displaced by endogenous ATP even under high intracellular concentration conditions, maintaining long-term target inhibition efficacy during daily oral administration [4].

2.5.2. Block downstream oncogenic pathways to induce tumor apoptosis

Inactivated EGFR synchronously suppresses MAPK and PI3K/Akt cascades, arresting the cell cycle at the G0/G1 phase and weakening proliferation, invasion and clone formation of tumor cells [1]. In vitro cell experiments found that osimertinib treatment significantly reduces phosphorylated ERK and phosphorylated Akt levels within 6 hours, and inhibits mTOR downstream p70S6K activity to block tumor cell energy metabolism [7]. Osimertinib upregulates pro-apoptotic Bax and cleaved caspase-3, downregulates anti-apoptotic Bcl-2 to reverse tumor anti-apoptosis phenotype; combined flow cytometry detection showed that the apoptosis rate of H1975 (T790M mutant cell line) rises from below 5% to over 40% after 72 h osimertinib intervention, effectively shrinking solid tumors in mouse xenograft models with continuous 2-week administration [4].

2.5.3. Target T790M mutation and treat brain metastasis

T790M conformational change is the core cause of failure of early TKIs [4]. Osimertinib's dimethylindole molecular structure matches the enlarged hydrophobic pocket formed by methionine substitution, recovering kinase inhibitory effect on T790M-positive EGFR [9]. Strong blood-brain barrier penetration relies on low affinity for P-glycoprotein efflux transporter, avoiding drug outflow from brain tissue; pooled analysis of FLAURA and AURA3 trials demonstrated that osimertinib

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reduces intracranial lesion size in more than three-quarters of patients with measurable brain metastasis, and lowers the risk of intracranial disease progression by 62% compared with platinum-based chemotherapy [5]. For leptomeningeal metastasis, a severe intracranial complication with median survival shorter than 6 months without effective intervention, osimertinib still achieves durable disease control exceeding 9 months in real-world clinical cohorts with long-term maintenance monotherapy [3].

2.5.4. Remodel tumor microenvironment to suppress angiogenesis and metastasis

Osimertinib inhibits abnormal angiogenesis by downregulating HIF-1α and VEGF-A expression, cutting nutrient supply and metastatic channels for tumor lesions over long-term medication cycles [7]. Immunomics research indicated that osimertinib reduces infiltration of immunosuppressive Tregs and MDSCs within tumor tissue after 4–8 weeks of continuous administration, decreases secretion of TGF-β and IL-10, and restores anti-tumor killing function of CD8+ T lymphocytes and NK cells; this time-dependent immune normalization effect gradually transforms "cold tumor" into "hot tumor", jointly restraining tumor growth and metastasis through direct tumor cell suppression and immune activation dual pathways [2]. In vivo lung and bone metastasis mouse models verified that 8-week osimertinib intervention significantly reduces pulmonary and bone metastatic foci formation, partially through reversing EMT phenotype and upregulating epithelial marker E-cadherin expression [7].

2.6. Clinical advantages and deficiencies of osimertinib

Osimertinib has dual targeting capacity for primary sensitive mutation and T790M resistant mutation, with mild adverse reactions dominated by grade 1 and 2 diarrhea and xerosis cutis that can be relieved by symptomatic treatment without drug withdrawal [9]. Regular chest CT and electrocardiogram monitoring are needed during long-term administration to guard against rare but severe adverse events such as interstitial lung disease and QT interval prolongation, and its prominent advantage in treating brain metastasis makes it recommended as first-line medication in domestic and international lung cancer clinical guidelines [3]. However, continuous single-agent administration for 1 to 3 years will inevitably induce secondary drug resistance, and the cumulative incidence of resistance will rise with the extension of medication time, with about 25% of patients developing resistance within 12 months, 48% within 24 months and more than 60% within 36 months [6]. According to the latest translational research and large-scale sequencing data of clinical samples, the acquired resistance phenotypes of osimertinib can be divided into four major categories without clear hierarchical segmentation. The first type is new EGFR point mutations represented by C797S, together with rare G796R and L792H variants that account for nearly 30% of all resistant cases. The second type is bypass gene amplification including MET and HER2, among which MET amplification occupies about 15% of resistant populations. The third type refers to off-target driving mutations such as KRAS and PIK3CA that activate independent signal pathways without relying on upstream EGFR. The fourth category is tumor phenotypic transformation including epithelial-mesenchymal transition and histological transformation into small cell lung cancer, usually accompanied by the loss of EGFR protein expression inside tumor cells.

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3. Targeted combined therapeutic strategies for osimertinib-resistant NSCLC

To delay the emergence of osimertinib secondary resistance and elevate long-term clinical therapeutic efficacy, stratified combined intervention regimens should be adopted according to individual gene liquid biopsy detection results, which has become the core precision treatment principle stated in 2024 Chinese NSCLC targeted therapy guidelines [3]. For patients with high distant metastasis risk (multiple bilateral lung lesions, bone metastasis, asymptomatic multiple brain metastasis), osimertinib combined with anti-angiogenic agents (bevacizumab, ramucirumab) can synergistically suppress pathological neovascularization and tumor spread [2]. Preclinical data showed that dual inhibition of EGFR and VEGF pathways simultaneously reduces tumor proliferation and angiogenesis, delaying the occurrence of MET bypass amplification resistance by nearly 50% compared with osimertinib monotherapy within a 24-month observation period [7]. Phase II clinical trial results further confirmed that the combination regimen improves median progression-free survival by over 4 months in patients with high metastatic risk [6].

For patients with an immune-active tumor microenvironment (high PD-L1 expression, low MDSC infiltration before treatment), combination with immune checkpoint inhibitors (PD-1/PD-L1 monoclonal antibodies) can reverse tumor immune escape and amplify anti-tumor cytotoxicity [2]. Osimertinib-mediated immune remodeling increases tumor-infiltrating CD8+ T cells after 2–3 months of administration, laying a foundation for synergistic immunotherapy; however, clinicians need to closely monitor the increased risk of interstitial lung disease caused by combined long-term application [3].

For MET-amplified resistant populations confirmed by ctDNA or tissue sequencing, dual-target therapy consisting of osimertinib and selective MET inhibitors (savolitinib, capmatinib) is the standard clinical scheme [6]. The SAVANNAH trial proved that osimertinib plus savolitinib achieves an objective response rate over 30% in MET-amplified osimertinib-resistant patients, effectively blocking bypass oncogenic signaling activated by MET overexpression [6]. For C797S-mutant resistant patients, dual EGFR inhibitors targeting both C797S and mutant EGFR are under phase I/II clinical development, and long-term preclinical xenograft models have obtained satisfying durable anti-tumor activity [8].

In routine clinical management, liquid biopsy should be applied dynamically every 3–6 months to monitor gene variation, predict drug resistance risk in advance and adjust therapeutic schemes in a timely. Circulating tumor DNA (ctDNA) detection can identify emerging resistance mutations 2–4 months earlier than imaging examination, realizing early intervention before imaging disease progression [1]. For pharmaceutical R&D, new-generation EGFR inhibitors targeting the C797S mutation and brain-targeted sustained-release formulations should be developed to elevate intratumoral drug concentration and reduce systemic toxicity [9]. Multi-center randomized controlled trials need to be carried out to establish a fully individualized stratified treatment system based on genetic testing results, providing high-level long-term cohort evidence for clinical medication optimization [10].

4. Conclusion

This paper centers on osimertinib, the mainstream third-generation EGFR-TKI, systematically analyzing the complex molecular mechanism of EGFR-mutant NSCLC and the multi-path anti-tumor effects of osimertinib, as well as its clinical strengths and secondary resistance subtypes, with sufficient domestic and international clinical trial and multi-cycle preclinical research literature support throughout the full text. EGFR-driven persistent activation of MAPK and PI3K/Akt

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pathways, T790M acquired resistance and refractory brain metastasis are major therapeutic bottlenecks limiting early first/second-generation targeted drugs. Depending on irreversible covalent binding to mutant EGFR, osimertinib blocks oncogenic signaling transduction, induces tumor cell apoptosis, penetrates the blood-brain barrier efficiently and remodels immunosuppressive anti-tumor microenvironment over long-term administration cycles, breaking the core therapeutic limitations of early EGFR-TKIs and greatly improving long-term survival outcomes of advanced NSCLC patients with EGFR mutations, especially those complicated with brain metastasis.

However, long-term single-agent monotherapy inevitably produces various secondary resistance variants with time-dependent cumulative incidence, which cannot be solved by a single targeted drug alone. This study clarifies the complete time-dependent action network of osimertinib and sorts out classified combined long-term intervention strategies for different resistance phenotypes, providing practical reference for clinical individualized dynamic medication and subsequent translational targeted drug research.

Limitations of this paper: the upstream and downstream multi-omics regulatory network of various drug resistance mutations is not fully explored due to limited access to original multi-center long-term trial raw data; the synergistic toxicities and long-term safety of multiple combined regimens lack 5-year real-world cohort data support. Future research can further explore the upstream and downstream interaction pathways of resistance mutations, develop novel small-molecule targeted agents specifically against the C797S mutation, and perfect the whole-process precise diagnosis and treatment system of EGFR-mutant NSCLC combined with dynamic liquid biopsy ctDNA long-term monitoring technology.

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