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Clinical Management and Drug Resistance in EGFR-Mutant Lung Cancer

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Abstract. EGFR-mutant non-small cell lung cancer is more common in Asian populations. EGFR is critically involved in lung adenocarcinoma development.EGFR-targeted therapy has greatly improved patient survival. Therefore, EGFR- mutant NSCLC has become one of the models for precision oncology. Osimertinib is a third-generation EGFR tyrosine kinase inhibitor. It irreversibly binds to the cysteine residue at position 797 of the EGFR protein, selectively inhibits common EGFR activating mutations, and overcomes the classic T790M drug-resistant mutation. In addition, Osimertinib has good central nervous system permeability. Clinical trials demonstrate that osimertinib significantly prolongs progression-free survival and overall survival. These benefits are reflected in the initial and subsequent management of EGFR mutant NSCLC. The scope of application of osimertinib has been extended to adjuvant treatment and neoadjuvant therapy, which confirms its core role in disease management. However, with the wide application of osimertinib, acquired drug resistance has become a major clinical problem. Its potential mechanism is more diverse and complex than the earlier-generation EGFR-TKIs. This paper reviews the molecular activity basis of EGFR signaling pathway and osimertinib, and reviews its latest progress in clinical application. Finally, this paper discusses the mechanism of EGFR dependence and EGFR non-dependent drug resistance, aiming to provide insights into precision treatment strategies of EGFR mutant NSCLC.

Keywords: EGFR mutation, Osimertinib, Drug resistance mechanisms, Targeted therapy

1. Introduction

Lung cancer continues to pose significant challenges to healthcare systems worldwide. Non-small cell lung cancer accounts for about 85% of all lung cancer cases [1,2]. In China and other Asian countries, the incidence of lung adenocarcinoma continues to rise. Most patients are diagnosed at locally advanced or metastatic stages. Therefore, systemic therapy, especially molecularly targeted therapy, is essential for improving outcomes in NSCLC [1-3].

Among NSCLC sub-types, EGFR mutations are major oncogenic drivers.These mutations are especially common in Asian populations [1,3]. EGFR-targeted therapies have markedly improved treatment outcomes in EGFR-mutant NSCLC, making this subtype one of the most well-established models for precision oncology in lung cancer [3,4].

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Osimertinib, a third-generation, mutant-selective EGFR tyrosine kinase inhibitor, maintains high selectivity for common EGFR activating mutations while effectively overcoming classical resistance mutations such as T790M, and also has good central nervous system activity. Clinical trials confirm that osimertinib key survival outcomes and overall survival. It has changed the current clinical practice strategy for EGFR-mutant NSCLC. It is currently the standard initial management for advanced disease and is increasingly being investigated in the adjuvant and neoadjuvant settings [4-6].

Although the third-generation EGFR-TKI significantly prolongs patient survival, acquired resistance is inevitable, and its molecular mechanism is more complex and diverse than before, posing a major challenge to long-term disease control [6,7].

Based on this,this review summarizes the EGFR signaling pathway and the molecular basis of osimertinib activity, highlights its clinical application across different disease stages, and further discusses the major mechanisms of acquired resistance and potential therapeutic strategies, with the aim of providing insights into precision treatment for EGFR-mutant NSCLC.

2. The molecular mechanism of EGFR signaling pathway and the antitumor effects of osimertinib

2.1. Activation mechanism of EGFR and classical downstream signaling pathways

Binding of epidermal growth factor (EGF) or other EGFR ligands to the extracellular domain of EGFR induces receptor dimerization, leading to activation of the intracellular tyrosine kinase domain and subsequent autophosphorylation. Phosphorylated EGFR then serves as a signaling platform to recruit and activate multiple downstream signaling cascades.

Currently, EGFR regulates tumor cell behavior through several major signaling routes. One pathway involves RAS, RAF, MEK, and ERK proteins and promotes cell proliferation.Another signaling route centers on PI3K, AKT, and mTOR and supports cell survival and metabolic activity. Additional pathways, including JAK–STAT and PLCγ–PKC signaling, are involved in inflammation, migration, and invasion [8].

Persistent activation of these signaling pathways supports cell proliferation. Cell death is reduced, blood vessel formation is increased, and epithelial–mesenchymal transition can occur. Together, these changes contribute to tumor growth and spread. Consequently, highly selective and durable inhibition of EGFR kinase activity—particularly precise targeting under oncogenic mutation contexts—has become a central strategy in the therapeutic evolution of EGFR-mutant NSCLC.

2.2. Basic pharmacological characteristics and targeted mechanism of action of osimertinib

The research and development of EGFR-TKI aims to improve the selectivity of mutant EGFR, overcome drug resistance, and enhance the central nervous system activity. Osimertinib is an oral third-generation irreversible EGFR-TKI, which has been proven to penetrate the central nervous system. Osimertinib aims to selectively inhibit common EGFR-activated mutations, including Ex19del and L858R. It can also effectively target T790M drug-resistant mutations. At the same time, it has minimal inhibitory activity of wild-type EGFR. The drug forms an irreversible covalent bond with cysteine 797 in the EGFR kinase domain. This interaction blocks EGFR kinase activity and suppresses multiple intracellular signaling processes. In vitro studies show that the inhibitory activity of osimertinib on mutant EGFR is much stronger than that on wild-type EGFR.

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Structural studies confirm that it has a higher binding affinity for mutant EGFR. In the tumor model driven by EGFR mutation, osimertinib can induce the continuous regression of the tumor with limited effect on normal tissue, which reflects its high selectivity for mutants. Clinical trials including AURA and FLAURA show that compared with the first generation of EGFR-TKI, osimertinib has better efficacy and more lasting disease control, and fewer skin and gastrointestinal side effects. These characteristics support its long-term use and application in early-stage disease [6,9].

2.3. Molecular and biological antitumor effects of osimertinib

Osimertinib inhibits the activation of mutant EGFR and blocks multiple downstream signaling pathways, including MAPK/ERK, PI3K/AKT and JAK/STAT signaling pathways. Therefore, the proliferation and survival rate of tumor cells are reduced.

By inhibiting the autophosphorylation of EGFR, osimertinib reduces the dependence of tumor cells on growth factors and promotes cell apoptosis, which leads to continuous shrinkage of tumors. Animal studies have shown that osimertinib can significantly inhibit tumor growth driven by EGFR mutation, and it is also highly active against brain metastasis. In an EGFR mutant NSCLC cell line, osimertinib reduced the phosphorylation levels of EGFR, ERK and AKT, confirming its effective inhibitory effect on these signaling pathways.

In clinical practice, osimertinib can delay the progression of the disease and maintain a high response rate, and is also effective for patients with earlier-generation EGFR-TKIs resistance. Because its inhibitory effect on wild-type EGFR is relatively weak, the treatment-related toxicity is usually relatively mild. This makes long-term treatment with good tolerance [4,5,7,9].

3. Clinical applications of osimertinib

3.1. First-line Treatment and Standard indications

Osimertinib is the first-line standard treatment for EGFR-sensitive mutations for advanced-stage NSCLC, which include Ex19del as well as L858R. Compared with earlier EGFR-TKIs, osimertinib prolongs progression-free survival. It also improves overall survival.

In the FLAURA trial, osimertinib significantly improved the median PFS and OS, and better controlled central nervous system diseases [6,9]. These results strongly support its effectiveness as a first-line treatment.

The first-line treatment of osimertinib has also changed the resistance pattern. After treatment, drug resistance is no longer mainly driven by T790M mutations, but more by other mechanisms (such as MET amplification). These changes provide the possibility for new targeted treatment strategies. Therefore, the international guidelines recommend osimertinib as the preferred first-line treatment plan [4,6,10].

3.2. Adjuvant and neoadjuvant therapy

The application of osimertinib has been extended to the early stage of the disease. Adjuvant treatment and neoadjuvant therapy are currently important research fields.

In the ADAURA trial, the auxiliary osimertinib significantly prolonged the postoperative disease-free survival and reduced the risk of brain metastasis recurrence [5,9]. These results support its role in eliminate residual disease. Osimertinib is now a standard adjuvant treatment after resection of EGFR-mutant NSCLC.

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In terms of neoadjuvant therapy, osimertinib single-agent therapy can reduce the tumor volume before surgery. However, the rate of pathological remission is limited. Osimertinib combined with chemotherapy seems to be more effective. Ongoing trials, such as the NeoADAURA trial, will further clarify its long-term efficacy [5,10].

4. Mechanisms of resistance to osimertinib

Despite the clinical success of Osimertinib, acquired drug resistance is inevitable. Its drug resistance mechanism is more complex than that of earlier-generation EGFR-TKIs. These mechanisms include genetic changes, pathway reactivation and phenotypic changes.Understanding these mechanisms is crucial for guiding follow-up treatment.

4.1. EGFR-dependent drug resistance

Some tumors still depend on the EGFR signaling pathway during the treatment of osimertinib. However, they will obtain additional EGFR mutations, thus reducing drug binding. The most common example is the C797S mutation.

In these cases, EGFR is still an effective therapeutic target. Treatment strategies include a new generation of EGFR-TKI, bispecific antibodies and combination therapy. EGFR-dependent drug resistance is still the focus of drug research and development [6,7,11].

4.2. EGFR non-dependent drug resistance

After treatment with osimertinib, EGFR non-dependent drug resistance is more common. Tumor cells will reduce their dependence on EGFR signals and activate other pathways.

Common mechanisms include MET amplification, HER2 or HER3 activation, and KRAS, NRAS or BRAF gene mutations. ALK, RET or ROS1 gene fusion may also occur. In some cases, histological transformation to a small cell phenotype occurs.

The treatment depends on specific drug resistance mechanisms. Combined treatment is usually required. Due to its heterogeneity, EGFR non-dependent drug resistance remains the biggest challenge to long-term disease control [6,7,10,11].

5. Conclusion

Osimertinib changed the management pattern in EGFR-mutant non-small cell lung cancer. It is highly selective for EGFR-activated mutations and T790M. It binds to EGFR irreversibly and has strong central nervous system activity. These characteristics improve the efficacy of advanced, first-line and adjuvant therapy. However, acquired drug resistance still limits the long-term efficacy. Drug resistance involves EGFR-related changes and activation of alternative pathways. A better understanding of these mechanisms will help formulate more accurate and effective treatment strategies. Despite potent and durable pathway inhibition, prolonged osimertinib exposure inevitably leads to acquired resistance via diverse molecular mechanisms. EGFR-dependent resistance is primarily mediated by secondary mutations such as C797S that disrupt covalent drug binding. In contrast, EGFR-independent resistance involves pathway bypass and oncogenic rewiring, including MET amplification, HER2/HER3 activation, RAS–RAF pathway mutations, oncogenic gene fusions, and lineage plasticity such as small-cell-like phenotype transformation. These results highlight adaptive nature EGFR-driven signaling networks and underscore the need for

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combinatorial and next-generation strategies to achieve sustained suppression of oncogenic signaling in EGFR-mutant NSCLC.

References

[1] Rodak, O., Peris-Diaz, M. D., Olbromski, M., Podhorska-Okołów, M., & Dzięgiel, P. (2021).Current landscape of non-small cell lung cancer: epidemiology, histological classification, targeted therapies, and immunotherapy.Cancers, 13(18), 4705. https: //doi.org/10.3390/cancers13184705

[2] Alduais, Y., Zhang, H., Fan, F., Chen, J., & Chen, B. (2023).Non-small cell lung cancer (NSCLC): A review of risk factors, diagnosis, and treatment.Medicine, 102(8), e32899. https: //doi.org/10.1097/MD.0000000000032899

[3] Cheng, Y., Zhang, T., & Xu, Q. (2021).Therapeutic advances in non-small cell lung cancer: Focus on clinical development of targeted therapy and immunotherapy.MedComm, 2(4), 692–729.https: //doi.org/10.1002/mco2.105

[4] Fu, K., Xie, F., Wang, F. et al. Therapeutic strategies for EGFR-mutated non-small cell lung cancer patients with osimertinib resistance. J Hematol Oncol 15, 173 (2022). https: //doi.org/10.1186/s13045-022-01391-4

[5] Su, PL., Furuya, N., Asrar, A. et al. Recent advances in therapeutic strategies for non-small cell lung cancer. J Hematol Oncol 18, 35 (2025). https: //doi.org/10.1186/s13045-025-01679-1

[6] Chmielecki, J., Mok, T., Wu, YL. et al. Analysis of acquired resistance mechanisms to osimertinib in patients with EGFR-mutated advanced non-small cell lung cancer from the AURA3 trial. Nat Commun 14, 1071 (2023). https: //doi.org/10.1038/s41467-023-35962-x

[7] Ríos-Hoyo, A., Moliner, L., & Arriola, E. (2022).Acquired mechanisms of resistance to osimertinib—the next challenge.Cancers, 14(8), 1931.https: //doi.org/10.3390/cancers14081931

[8] Cheng, W. L., Feng, P. H., Lee, K. Y., Chen, K. Y., Sun, W. L., Van Hiep, N., … Wu, S. M. (2021).The role of EREG/EGFR pathway in tumor progression.International Journal of Molecular Sciences, 22(23), 12828.https: //doi.org/10.3390/ijms222312828

[9] Frampton, J. E. (2022).Osimertinib: A review in completely resected, early-stage, EGFR mutation-positive NSCLC.Targeted Oncology, 17(3), 369–376. https: //doi.org/10.1007/s11523-022-00883-0

[10] Borgeaud, M., Olivier, T., Bar, J., Saw, S. P. L., Parikh, K., Banna, G. L., De Vito, C., Feldman, J., Le, X., & Addeo, A. (2025).Personalized care for patients with EGFR-mutant non-small cell lung cancer: Navigating early to advanced disease management.CA: A Cancer Journal for Clinicians, 75(5), 387–409.https: //doi.org/10.3322/caac.70024

[11] He, J., Huang, Z., Han, L., Gong, Y., & Xie, C. (2021).Mechanisms and management of 3rd-generation EGFR-TKI resistance in advanced non-small cell lung cancer (Review).International Journal of Oncology, 59(5), 90. https: //doi.org/10.3892/ijo.2021.5270