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AN OVERVIEW OF OSIMERTINIB FOR EGFR-MUTATED NSCLC WITH INSIGHTS INTO MOLECULAR MECHANISMS AND RESISTANCE

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ABSTRACT

Lung cancer is the leading cause of cancer-related deaths worldwide. The high incidence, morbidity, and mortality associated with lung cancer have driven the development of novel targeted therapies. Osimertinib (AZD9291), a novel EGFR-TKI developed by AstraZeneca, was approved by the U.S. Food and Drug Administration (FDA) in November 2015. As a tyrosine kinase inhibitor (TKI), osimertinib inhibits EGFR signaling and is an effective treatment for EGFR-mutated non-small cell lung cancer (NSCLC). The drug is specific in its mechanism of action as it targets the cysteine residue at position 797 (Cys797) near the ATP-binding pocket of the EGFR tyrosine kinase domain. A comprehensive understanding of its molecular mechanisms underlying osimertinib activity and resistance is essential for optimizing its clinical efficacy. This review provides an in-depth overview of osimertinib for clinicians, pharmacists, and researchers.

KEYWORDS: Osimertinib, EGFR, TKIs, Autophosphorylation, NSCLC, Cys797.

INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide. Among all cancers, lung cancer is one of the most commonly diagnosed malignancies and is the leading cause of cancer-related deaths worldwide. Lung cancer is broadly classified as non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) of which NSCLC represents approximately 85% of all lung cancer cases.[1] Several genetic alterations play an important role in the development of NSCLC. Among these genetic alterations, mutations in the epidermal growth factor receptor (EGFR) gene are among the most extensively studied oncogenic drivers. EGFR is a transmembrane receptor tyrosine kinase that regulates cell proliferation, survival, differentiation and migration. When the EGFR gene acquires activating mutations such as exon 19 deletion or L858R mutation, the receptor becomes constitutively activated and promotes uncontrolled cell growth.[2] To treat EGFR-mutated NSCLC, first- and second-generation EGFR-TKIs such as gefitinib, erlotinib and afatinib have been developed. These drugs showed significant clinical benefits but most patients developed resistance. The most common mechanism of acquired resistance was the EGFR T790M mutation, identified in approximately 50-60% of patients with acquired resistance. This mutation increases ATP-binding affinity, thereby reducing the efficacy of first- and second-generation EGFR-TKIs.[3]

To overcome these limitations, third-generation EGFR inhibitors were developed among which osimertinib was found to be the most successful and clinically important drug. Osimertinib is an irreversible, mutant-selective EGFR-TKI that targets activating EGFR mutations along with T790M resistance. Osimertinib exhibits lower activity toward wild-type EGFR because of which its toxicity profile is improved.[4]

Clinical studies have demonstrated that osimertinib significantly improves progression-free survival, overall survival, and central nervous system (CNS) penetration compared with earlier-generation EGFR-TKIs. Consequently, osimertinib has become the standard first-line therapy for the treatment of EGFR-mutated NSCLC.

This review article provides an updated overview of osimertinib as a therapeutic agent for the treatment of lung cancer and highlights its clinical significance in overcoming resistance. It also aims to support clinicians and oncologists in making informed treatment decisions regarding the use of tyrosine kinase inhibitors (TKIs) for patients with non-small cell lung cancer (NSCLC), particularly in cases involving unknown or uncommon epidermal growth factor receptor (EGFR) mutations. A brief overview of its structural features, spectral analysis, mechanism of action, discovery and development is presented. The future perspectives and available opportunities for the development of next-generation EGFR inhibitors are highlighted.[5]

STRUCTURE AND SPECTRAL PREDICTION

Osimertinib is a non-hygroscopic white to brown crystalline powder with the molecular formula $C_{28}H_{33}N_7O_2$. The drug is a mono-anilino-pyrimidine, the chemical name of which is *N*-(2-{2-dimethylaminoethyl-methylamino}-4-methoxy-5-{[4-(1-methylindol-3-yl) pyrimidin-2-yl]amino}phenyl)prop-2-enamide. In its crystal structure, the hydrogen atoms form weak intramolecular hydrogen bonds to the nitrogen atom of the amino group. Furthermore, two N-H---O hydrogen bonds are present between cations and anions. The drug exhibits linear pharmacokinetic properties and crosses the blood-brain barrier (BBB), which in turn contributes to its efficacy against CNS metastasis. The two-dimensional (2D) and three-dimensional (3D) molecular structures of osimertinib are represented in Fig. 1 and predicted ^{1}HNMR and ^{13}CNMR spectra of osimertinib are displayed in Fig. 2.

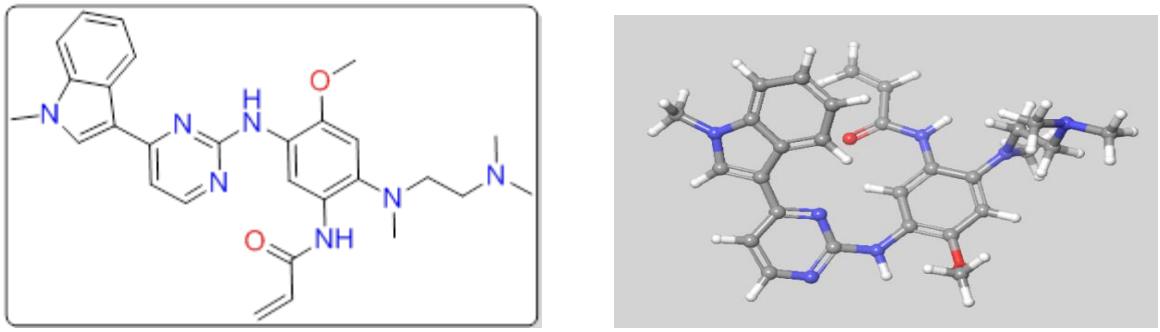

Fig. 1. The two-dimensional (2D) and three-dimensional (3D) molecular structures of osimertinib.

Predicted ^{1}H NMR and ^{13}C NMR spectra of osimertinib

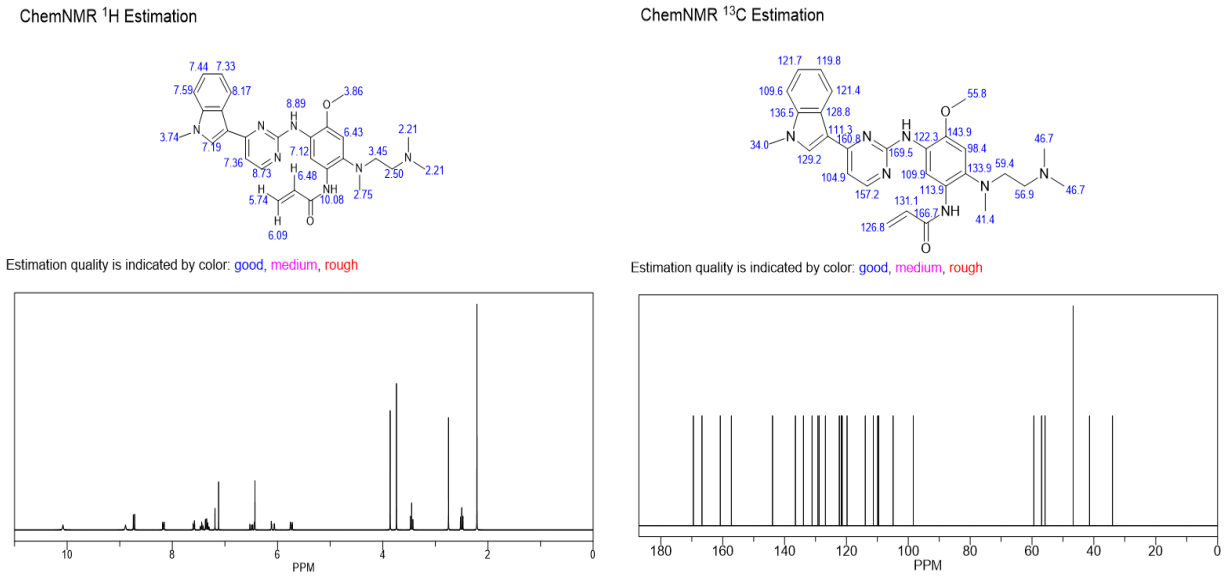

Fig. 2. Predicted ^{1}HNMR and ^{13}CNMR spectra of osimertinib.

EGFR BIOLOGY AND SIGNALING PATHWAY

EGFR is a transmembrane receptor tyrosine kinase, which is a member of the ErbB receptor family. This receptor plays an important role in regulating normal cellular processes such as cell proliferation, differentiation, survival and migration. Although EGFR is physiologically expressed in normal tissues, its overexpression or activating mutations are frequently

associated with various malignancies, promoting uncontrolled cell proliferation and tumor progression.[6]

Structurally, EGFR consists of three major domains: extracellular ligand-binding domain, transmembrane domain and intracellular tyrosine kinase domain. Ligands such as epidermal growth factor (EGF) and transforming growth factor-α (TGF-α) bind to the extracellular domain of EGFR. Receptor dimerization occurs after ligand binding due to which receptor activation takes place and autophosphorylation initiates in the intracellular tyrosine kinase domain.[7] [Fig. 3]

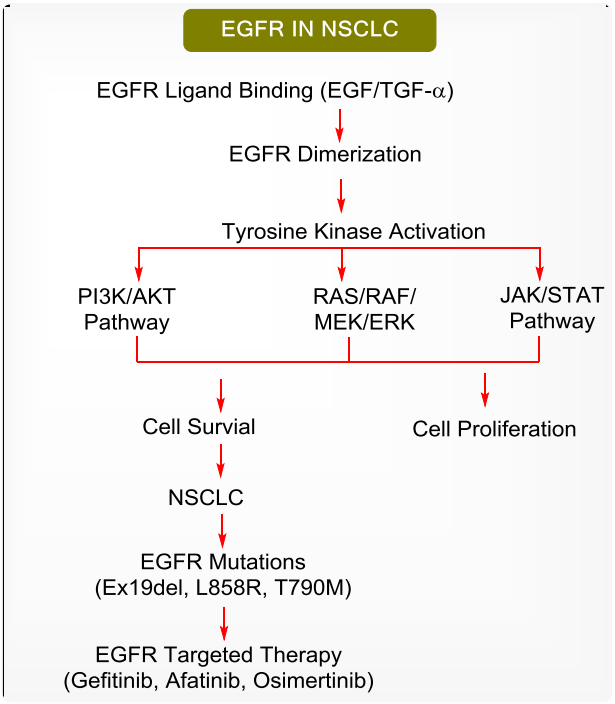

Fig. 3. Role of EGFR signaling pathways, oncogenic mutations and targeted therapy in NSCLC.

Autophosphorylation activates several downstream signaling pathways that regulate cellular growth and cell survival. The major downstream signaling pathways include the RAS/RAF/MEK/ERK, PI3K/AKT/mTOR, and JAK/STAT pathways. The RAS/RAF/MEK/ERK pathway primarily controls cell proliferation and cell differentiation whereas PI3K/AKT/mTOR pathway promotes cell survival and growth while suppressing apoptosis. Accordingly, JAK-STAT pathway is responsible for regulation of gene transcription and cellular growth.

Consequently, activating mutations of EGFR gene are frequently observed in NSCLC. The exon 19 deletions and exon 21 L858R mutations are the most common activating mutations. These mutations provide the receptor the capacity for ligand-independent activation due to which the receptor remains constitutively activated and stimulates uncontrolled signaling pathways. This ultimately results in uncontrolled cell proliferation, angiogenesis, metastasis, and tumor progression. Given the central role of EGFR, TKIs have been developed to target the ATP-binding pocket and stop receptor activation. Osimertinib is a third-generation, mutant-selective and irreversible EGFR-TKI that effectively inhibits both EGFR mutations as well as T790M mutations. Osimertinib forms an irreversible covalent bond with the Cys797 residue of the kinase domain due to which downstream signaling pathways are suppressed and cancer cell proliferation is inhibited.[8]

EGFR MUTATIONS IN NSCLC

EGFR regulates cellular growth and survival in normal cells. However, when the EGFR gene is mutated, the receptor remains constitutively activated even without ligand. As a result, downstream signaling pathways, including RAS/RAF/MEK/ERK and PI3K/AKT/mTOR, remain constitutively activated, leading to uncontrolled cell proliferation, angiogenesis, and metastasis. Consequently, EGFR mutations are recognized as major oncogenic drivers and constitute the molecular basis for targeted therapy in NSCLC.[9] [Fig. 4]

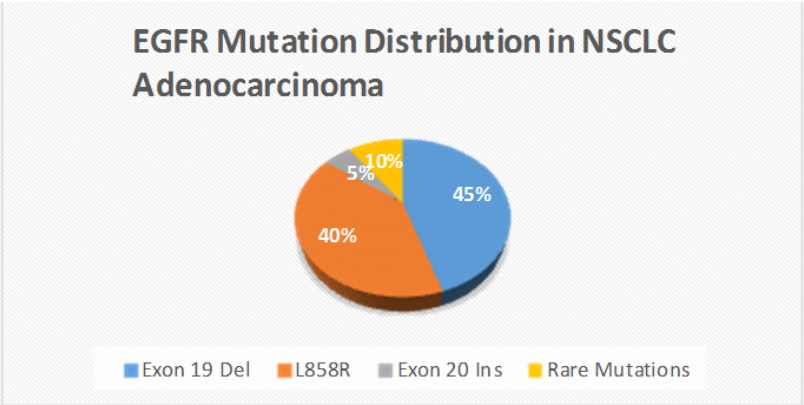

Fig. 4. Prevalence of clinically relevant EGFR mutations in NSCLC.

EGFR mutations can be broadly classified into two categories: activating (sensitizing) mutations and resistance mutations.

1. Activating (sensitizing) mutations

These mutations improve the response of EGFR-TKIs. The most common activating mutations include.

Exon 19 deletions (Del19): This mutation is observed in approximately 45–50% of EGFR-mutant NSCLC cases. In this mutation, some amino acids of exon 19 are deleted due to which kinase domain remains constitutively activated. Generally, patients with del19 mutation show a favourable response for EGFR-TKIs.[10]

L858R Mutation (Exon 21): In this mutation, leucine (L) amino acid is replaced with arginine (R). This mutation accounts for approximately 40–45% of EGFR-mutant NSCLC cases. Together, exon 19 deletions and the L858R mutation account for approximately 85–90% of EGFR-mutant NSCLC cases and are collectively referred to as the classical EGFR mutations.[11]

2. Resistance mutations

Initially, patients respond to gefitinib, erlotinib, afatinib or osimertinib but eventually develop acquired resistance. The major mechanisms of acquired resistance involve secondary and tertiary EGFR mutations.

T790M Mutation (Exon 20): In this mutation, threonine (T) is replaced with methionine (M) at 790 position of amino acid. Due to this, ATP-binding affinity increases and first-generation EGFR inhibitors cannot effectively bind at the receptor site. T790M is considered as the most common mechanism for acquired resistance. To target such resistance, third-generation inhibitors such as osimertinib were developed.[12]

C797S Mutation: This mutation is considered as the major cause for osimertinib resistance. Normally, osimertinib forms the covalent bond with Cys797 residue. When cysteine (C) is replaced with serine (S) then covalent bond formation is not possible and the drug loses its inhibitory activity. Due to this, C797S mutation is considered as the major target for fourth-generation EGFR inhibitor development.[13]

Other Emerging Resistance Mutations

Recent studies have identified G724S, L718Q, L792H mutations and some other rare mutations that contribute to osimertinib resistance. Novel fourth-generation EGFR inhibitors and allosteric inhibitors are developed against these mutations.

OSIMERTINIB: DISCOVERY AND DEVELOPMENT

Osimertinib is a third-generation EGFR-TKI that was specifically developed for the treatment of EGFR-mutated NSCLC. The first and second-generation EGFR inhibitors such as gefitinib, erlotinib and afatinib show good initial responses but over time patients develop acquired resistance. The most common mechanism of acquired resistance was the EGFR T790M mutation, which was identified in approximately 50-60% of patients.[14,15]

To overcome this problem, researchers developed osimertinib. This drug selectively binds mutant EGFR receptors and effectively inhibits T790M mutation. One of the key characteristics of this drug is its relatively lower inhibitory activity against wild-type EGFR, which contributes to a reduced incidence of adverse effects.

According to its mechanism of action, osimertinib forms an irreversible covalent bond with the Cys797 amino acid residue in the ATP-binding pocket. This binding permanently blocks tyrosine kinase activity, thereby suppressing downstream signaling pathways, including the RAS/RAF/MEK/ERK and PI3K/AKT/mTOR pathways. The inhibition of these pathways suppresses cancer cell proliferation, survival, angiogenesis and metastasis.[16]

A key characteristic of osimertinib is its efficient penetration across the blood–brain barrier. This property provides significant therapeutic benefit for patients with NSCLC and brain metastases. The clinical studies have demonstrated that osimertinib can improve progression-free survival and overall survival; therefore, it is currently considered the first-line treatment option in EGFR-mutated NSCLC patients. However, resistance mutations can develop against osimertinib with time among which C797S mutation is considered one of the most important resistance mutations. In addition, current research is focusing on the development of fourth-generation EGFR inhibitors and novel combination therapies.[17]

BIOCHEMICAL MECHANISM OF ACTION OF OSIMERTINIB

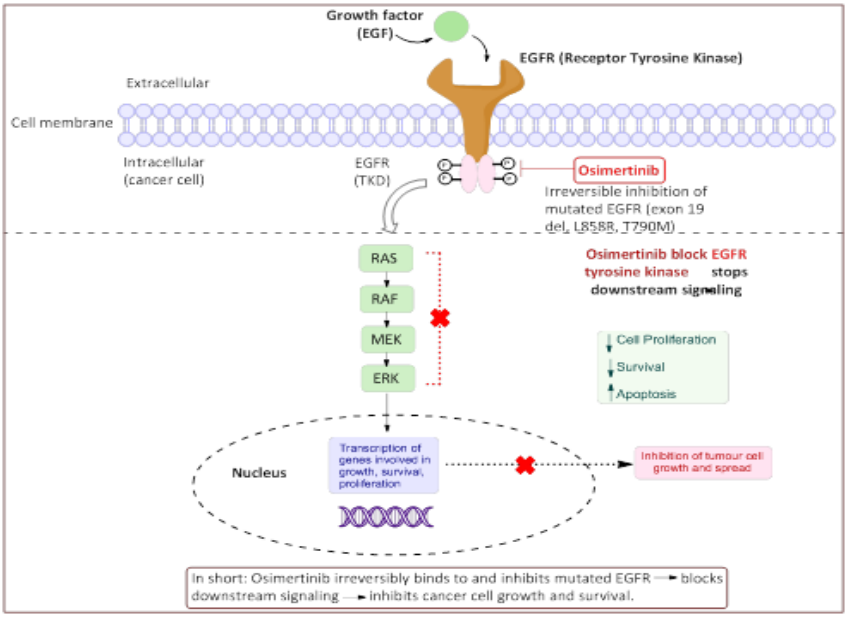

Fig. 5. Schematic representation of the mechanism of action of osimertinib.

Osimertinib exhibits a unique mechanism of action characterized by high potency and selectivity toward mutant EGFR. [Fig. 5] Activating mutations in EGFR, such as exon 19 deletions and the L858R substitution, along with the T790M resistance mutation, are key targets of osimertinib, a third-generation EGFR-TKI. These mutations are commonly observed in patients who initially respond to first- and second-generation EGFR-TKIs.[18,19]

Osimertinib demonstrates greater selectivity for mutant EGFR while sparing the wild-type receptor, resulting in improved therapeutic efficacy and a more favourable safety profile compared to earlier EGFR-targeted therapies.[18,20]

The antitumor activity of osimertinib is mediated through irreversible inhibition of EGFR kinase signaling. Specifically, osimertinib forms a covalent bond with the cysteine residue at position 797 (C797) within the ATP-binding site of the EGFR tyrosine kinase domain.[14] This covalent interaction prevents ATP from binding, thereby inhibiting receptor autophosphorylation and subsequent activation of downstream signaling pathways. As a result, EGFR-driven oncogenic signaling is effectively suppressed.

Inhibition of EGFR activation leads to the disruption of several critical signaling pathways involved in tumor growth and survival. These include the PI3K/AKT/mTOR pathway, which promotes cell survival and inhibits apoptosis; the RAS/RAF/MEK/ERK pathway, which controls cellular proliferation; and the JAK/STAT pathway, which contributes to tumor progression.[19,21] By blocking these pathways, osimertinib reduces tumor cell proliferation, induces apoptosis, and ultimately inhibits tumor growth.[22,23]

Osimertinib provides significant clinical benefit in overcoming resistance mediated by the EGFR T790M mutation. This mutation increases the affinity of EGFR for ATP, thereby reducing the effectiveness of earlier reversible TKIs such as gefitinib and erlotinib. Through its irreversible binding mechanism, osimertinib retains activity against T790M-mutant EGFR and continues to inhibit downstream signaling.[18]

In addition, osimertinib exhibits favourable pharmacokinetic properties, including effective penetration of the blood–brain barrier. This enables clinically meaningful activity against central nervous system (CNS) metastases in patients with EGFR-mutant NSCLC. However, acquired resistance remains a major clinical challenge. The EGFR C797S mutation is a well-established resistance mechanism, as it prevents the covalent binding of osimertinib to the kinase domain. Consequently, ongoing research is focused on developing fourth-generation EGFR inhibitors capable of overcoming C797S-mediated resistance.[24,25]

Overall, the therapeutic efficacy of osimertinib is attributed to its selective and irreversible inhibition of mutant EGFR, leading to disruption of oncogenic signaling pathways, suppression of tumor growth, and induction of apoptosis. These properties make osimertinib a cornerstone treatment for patients with EGFR-mutated NSCLC, with demonstrated activity against both systemic and CNS disease.

CONCLUSION

The therapeutic potential of osimertinib is reflected in its significant contribution to the advancement of targeted

therapy for EGFR-mutated NSCLC. This review provides clinicians with valuable insights into emerging therapeutic strategies for the future management of patients. Research on osimertinib will pave the way for its broader clinical application and the development of improved therapeutic strategies for patients with EGFR-mutated NSCLC.

FUTURE PERSPECTIVES

Future research and development of osimertinib are focused on overcoming acquired resistance and exploring combination strategies with other anticancer therapies to enhance its therapeutic potential. A comprehensive understanding of the molecular mechanisms underlying osimertinib activity and resistance will facilitate the optimization of the clinical efficacy of osimertinib. Moreover, identifying mechanisms of osimertinib resistance will help prolong patient survival.

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