Essay

Targeting Epidermal Growth Factor Receptor (EGFR) with Tyrosine Kinase Inhibitors in Lung Cancer and Role of Sensitizing and Resistance Mutations

Name

Student ID

Course

Due Date

1. Introduction

Lung cancer is considered one of the primary causes of cancer-related mortality across the globe. Among different types of lung cancer, lung adenocarcinoma or non-small-cell lung cancer (NSCLC) contains molecular alteration which promote uncontrolled tumour growth. The mutation of the epidermal growth factor receptor (EGFR) gene is one of the most clinically important molecular alterations (Grodzka et al., 2023). EGFR mutations can act as oncogenic drivers through the production of persistent activation of intracellular signalling pathways, which promote cell proliferation, survival, migration, and resistance to apoptosis. Identifying these mutations is critical for transforming these treatments from conventional chemotherapy-based interventions to molecularly targeted therapy.

EGFR tyrosine kinase inhibitors (EGFR-TKIs) are responsible for blocking the mutant EGFR activity, which can produce substantial tumour regression among patients whose cancer causes sensitization to EGFR mutations (Liu et al., 2026). However, the secondary mutations, especially T790M after the first- and second-generation EGFR-TKIs and C797S after the third-generation therapy, are critical mechanisms for resistance. Therefore, the EGFR mutation testing is critical before treatment and also in selected circumstances associated with disease progression.

2. EGFR and Signalling

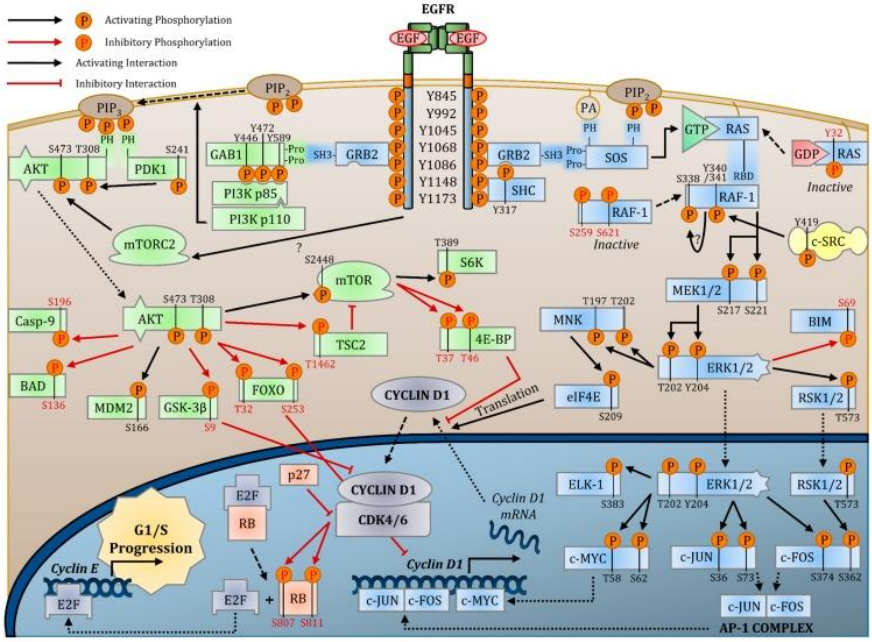

Figure 1:EGFR Signalling Pathways

(Source: Wee & Wang, 2017)

EGFR or ErbB1/HER1 is considered a transmembrane receptor tyrosine kinase that belongs to the ErbB family. The receptor includes an extracellular ligand-binding domain along with the transmembrane region and an intracellular tyrosine kinase domain. Additionally, binding the extracellular ligand, such as the epidermal growth factor (EGF), can lead to EGFR dimerization, and it activates the intracellular kinase domain. Autophosphorylation of tyrosine residues takes place in the activated receptor, which creates the docking sites for signaling proteins. The signals can activate multiple pathways, including the RAS–RAF–MEK–ERK pathway, the PI3K–AKT–mTOR pathway, and the JAK–STAT pathway (Li et al., 2022). Collectively, these pathways can regulate cell proliferation, survival, metabolism, differentiation, and migration. In the case of EGFR-mutant lung cancer, the mutations within the kinase domain are capable of stabilizing the active receptor conformation. It also produces signalling in the absence of regular ligand stimulation. Therefore, the tumor becomes dependent on EGFR signalling, which is also described as oncogene addiction. Exon 19

deletions and exon 21 L858R mutations are considered as the major sensitizing alterations and account for the clinically important EGFR mutations.

3. EGFR Mutation Testing, Capillary Sequencing, and NGS

The traditional capillary sequencing or Sanger sequencing is capable of identifying EGFR mutations in exons 18, 19, 20, and 21. DNA extraction is done from the tumour specimen, and it is amplified by PCR before being sequenced. The resulting sequence is compared with the reference sequence for identifying nucleotide substitutions, deletions, and insertions. Capillary sequencing is useful as it offers information about direct sequence, and it can identify unexpected variants. However, capillary sequencing has limited sensitivity if the mutation is observed in a small proportion of tumour DNA. Modern molecular testing is done using sensitive PCR-based assays or NGS in case when the tumour cellularity is low. The CAP/IASLC/AMP guideline permits the validated EGFR method with analytical performance (Penault-Llorca et al., 2022). NGS is capable of simultaneous analysis of different genes and different types of genomic alterations. The NGS Panel for lung cancer can examine EGFR along with the genes such as ALK, BRAF, ERBB2/HER2, KRAS, MET, RET and ROS1. It is especially useful as a patient who is EGFR negative can have another actionable driver mutation. For example, Mayo Clinic Laboratories typically offer a lung-cancer NGS panel which examines different genes associated with lung cancer and treatment response. EGFR mutation testing is also done by Labcorp which covers exons 18–21 and has PCR-based EGFR assays.

Formalin-fixed paraffin-embedded (FFPE) tumour tissue is used for performing the testing. When the tissue is inadequate and difficult for obtaining, circulating cell-free DNA (cfDNA) from blood can be utilised. Additionally, a negative plasma result does not exclude the EGFR

mutation as the tumor cannot to release adequate DNA into the bloodstream. The tissue testing is recommended in situations when it is clinically appropriate.

4. Major EGFR Mutations in Lung Cancer

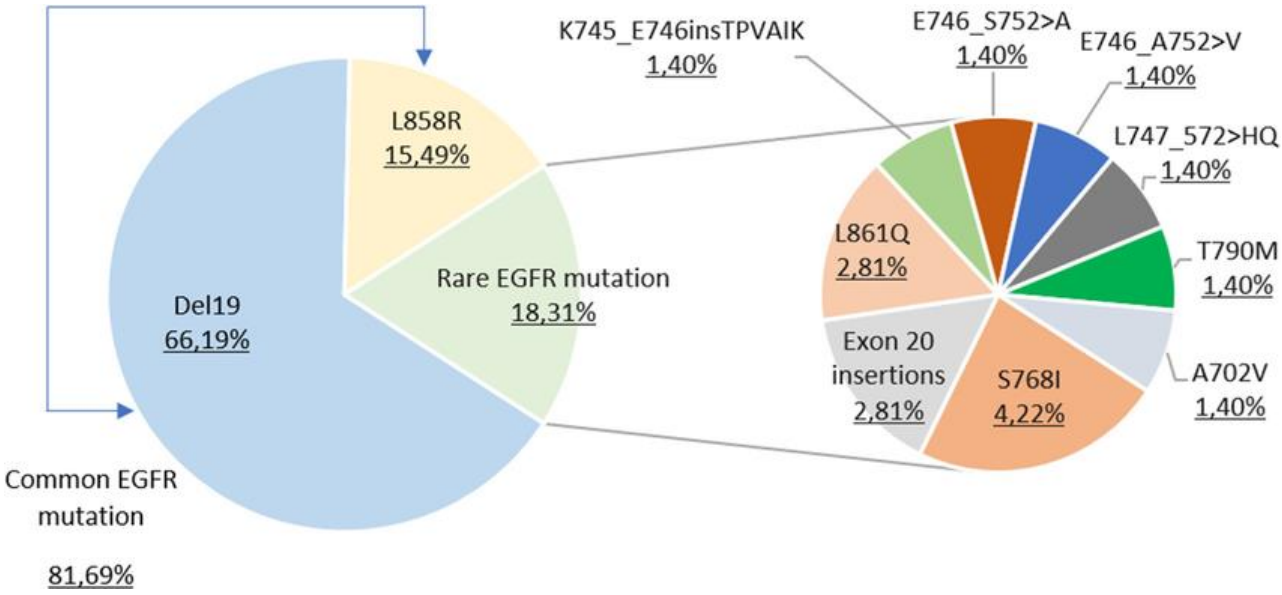

Figure 2: Distribution of EGFR Mutations

(Source: Boukansa et al., 2024)

Common EGFR mutations constitute cooking for double as a reaching round 81.69% of the mutations (Boukansa et al., 2024). Exon 19 deletions (Del19) are the most frequent, representing 66.19% of the total mutations (Boukansa et al., 2024). L858R mutation is another major category of mutation; it accounts for 15.49% (Boukansa et al., 2024). These two mutations are clinically important as they are considered major sensitizing categories. It indicates that tumors that carry them typically respond to EGFR tyrosine kinase inhibitors (TKIs). In contrast, the rare EGFR mutations account for 18.31% of the mutations (Boukansa et al., 2024). These types include S768I (4.22%), L861Q (2.81%), exon 20 insertions (2.81%), and multiple other place frequent alterations such as T790M, A702V, and other exon 18–21 variants (Boukansa et al., 2024). Each of the mutations accounts for approximately 1.40% (Boukansa et al., 2024). The presence of different EGFR mutations can impact the treatment

response, as not all the mutations have the same sensitivity to EGFR-TKIs. For instance, T790M is significant as the acquired resistance mutation. Del19 and L858R are strongly associated with TKI sensitivity. Importantly, the presence of EGFR mutations can impact the treatment response, as all the mutations demonstrate the same sensitivity to EGFR-TKIs. For instance, T790M is particularly significant as the acquired resistance mutation. Del19 and L858R are closely associated with TKI sensitivity. Therefore, the molecular heterogeneity of EGFR-mutant lung cancer is important to consider while selecting suitable targeted therapy.

5. Resistance Mutations After EGFR-TKI Therapy

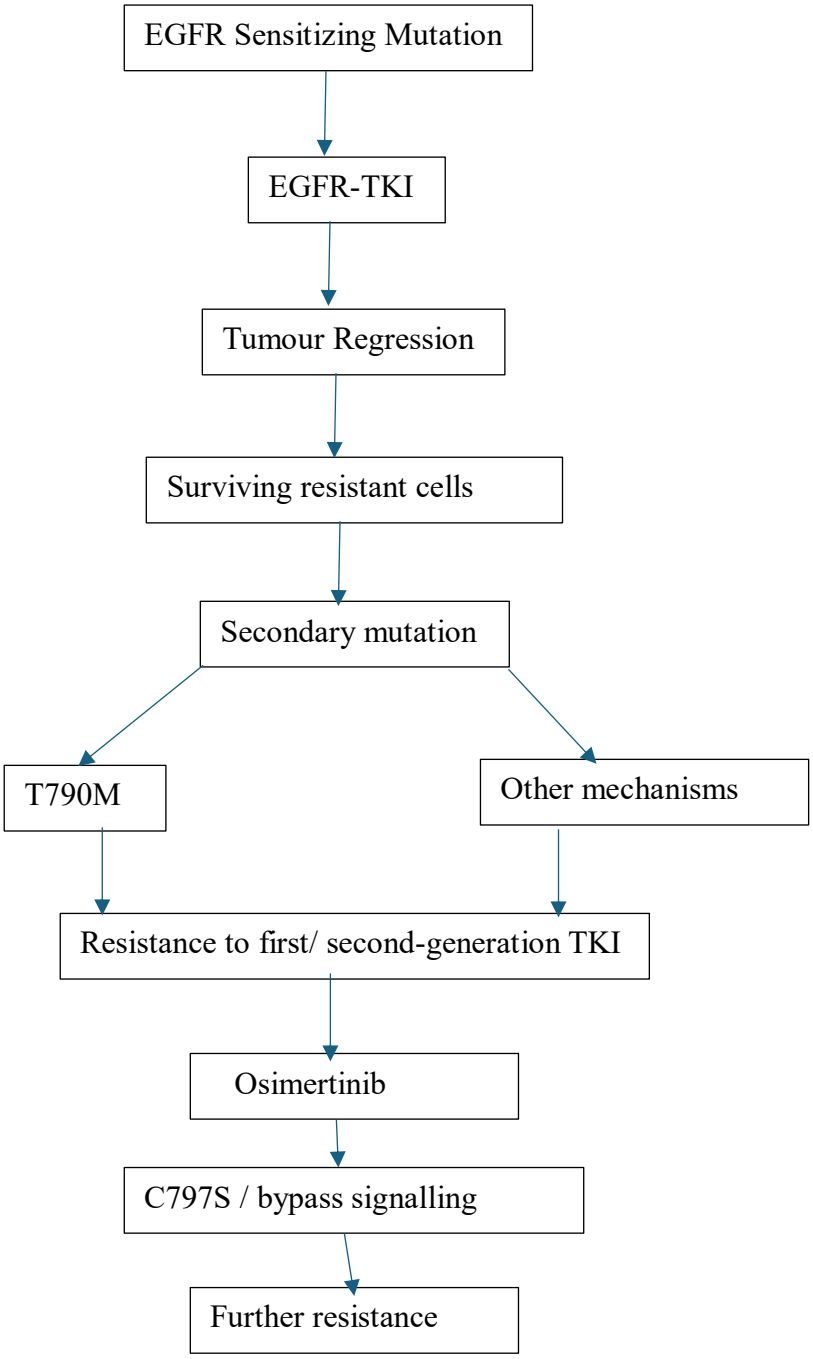
EGFR Sensitizing Mutation
EGFR-TKI
Tumour Regression
Surviving resistant cells
Secondary mutation
T790M
Other mechanisms
Resistance to first/ second-generation TKI
Osimertinib
C797S / bypass signalling
Further resistance

Figure 3: Resistance Mutations

Source: Created by Author

The patients with sensitizing EGFR mutations can respond dramatically to EGFR-TKIs. However, resistance can develop eventually. It can be considered an important example of tumour evolution. The treatment eliminates sensitive cancer cells. The pre-existing resistant clones and the newly selected resistance cells survive and expand. EGFR T790M is the best-known acquired resistance mutation (Sun, 2023). It is a substitution of threonine by methionine at codon 790 in exon 20. After receiving treatment with first-generation EGFR-TKIs, such as gefitinib or erlotinib, T790M accounts for a large proportion of acquired cases of resistance. The mutation alters the ATP binding pocket of EGFR. It increases the affinity of the receptor for ATP. It reduces the effectiveness of reversible inhibitors.

This discovery has led to the development of third-generation EGFR-TKIs such as osimertinib. It can inhibit sensitization of EGFR mutations and T790M and it spares most of the wild-type EGFR. However, resistance can be developed against osimertinib also. C797S involves an important mechanism. It eliminates the binding site and reduces the drug's effectiveness. Other EGFR-dependent resistance mechanisms can include changes in L718Q and L792H. The EGFR-independent mechanisms can include MET amplification, HER2 alterations, activation of signal in Pathways and epithelial–mesenchymal transition. The resistance should not be considered as the failure of the drug, but it represents the evolutionary adaptation of the tumour.

6. Sensitizing Mutations in EGFR Exons 18–21

Sensitizing mutations can make the tumour cells especially vulnerable to EGFR-TKIs. Exon 19 deletions and exon 21 L858R are the most important mutations.

Exon 19 deletions

Exon 19 deletions remove the amino acids around the LREA motif of EGFR. The structural changes support an active kinase configuration. They also enhance EGFR signalling. Importantly, they alter the kinase domain in a way that makes the receptors more susceptible to inhibition by EGFR-TKIs. Exon 19 deletions are considered classic sensitizing mutations.

Exon 21 L858R

In the case of L858R mutation, leucine is replaced with arginine at codon 858. It these stabilizers the inactive conformation of EGFR (Imam et al., 2025). It also favours kinase activation. The cancer cells become dependent on the abnormal EGFR signalling. It inhibits the receptor which can produce substantial tumour cell death and growth suppression.

Other sensitizing mutations

The less common mutations also confer sensitivity. G719X occurs in exon 18. L861Q takes place in exon 21. S768I takes place in exon 20 (Pang et al., 2022). The sensitivity to individual EGFR-TKIs is variable compared to that of the exon 19 deletions and L858R. For example, Afatinib showed activity against multiple uncommon EGFR mutations such as G719X, L861Q and S768I.

7. Conclusion

The discovery of EGFR mutations established an important paradigm of precision medicine in lung cancer. EGFR plays an important role as a central signalling receptor. It also activates mutations in the kinase domain, which can drive tumour growth using multiple pathways. EGFR-TKIs exploit the molecular dependency and it can produce impressive responses among the patients with sensitizing mutations, especially in the case of exon 19 deletions and exon 21 L858R. However, the evolutionary capacity of Cancer cells indicates that treatment resistance is developed frequently. T790M is considered a classic acquired resistance mutation, which is

followed by first- or second-generation EGFR-TKI therapy. C797S represents the mechanism of resistance to the third-generation inhibitors. The resistance can take place by activating bypass Pathways and changing the tumour phenotype. Hence, EGFR testing is critical not only to identify the patients who can benefit from targeted therapy but also to understand the reasons behind treatment failure.

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