EGFR Mutation and Tyrosine-Kinase Inhibitors (TKI) in Non Small Cell Lung Cancer: An Overview

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ABSTRACT- Lung cancer is the most common cause of cancer related mortality worldwide. The epidermal–growth-factor receptor (EGFR) cascades the signaling pathway that regulates tumor-cell proliferation, invasion, angiogenesis, metastasis, and apoptosis. Since EGFR is often over-expressed in NSCLC and the level of EGFR expression correlates with poor prognosis. EGFR inhibitors have been developed as a novel therapy for non-small-cell lung cancer (NSCLC). Gefitinib is the first molecular targeted agent approved for the treatment of advanced NSCLC. It is a highly effective EGFR TK inhibitor (TKI) selectively blocks the signal transduction pathways implicated in cancer growth.

Key-words- Lung Cancer, EGFR, NSCLC, Tyrosine Kinase Inhibitor (TKI)

INTRODUCTION

Lung cancer is the most common cause of cancer related mortality worldwide. Lung cancer is defined as the uncontrolled cell growth of lung tissues which may lead to metastasis, invasion of adjacent tissue and infiltration beyond the lungs. Majority of lung cancers are carcinoma of the lung and are derived from epithelial cells [1]. After breast cancer, the second most common cancer present in women is lung cancer. It also constitutes the second leading cause of cancer-related deaths in women [2]. Despite recent advances in the management of advanced non-small-cell lung cancer (NSCLC), the cure rate remains still low [3-4]. Hence further molecular investigation of lung cancer is required for the development of the new treatment strategies to improve the prognosis of lung cancer patients. It has been found that the activation and proliferation of NSCLC is regulated by growth factors and receptors of the epidermal growth factor receptor (EGFR) subfamily. The principal available therapeutic options for the treatment of lung cancer were surgical intervention, platinum-based chemotherapy and radiotherapy but with the description of epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer in the past decade and also the response of these tumors tissues to tyrosine kinase inhibitors such as gefitinib and erlotinib, a new hope has arisen in making a significant difference in the survival of cancer patients [5-6].

Epidermal Growth Factor Receptor (EGFR) is a membrane bound signaling protein belonging to the ErbB family. It is essential for the normal development of various tissues such as bone [7], mammary ducts [8] and vascular system [9]. Owing to its role in development, EGFR is normally found at low levels in most of the tissues where it is regulated both transcriptionally and mechanically by existing as an inactive monomer, requiring dimerization that is facilitated by the binding of extracellular signals such as Epidermal Growth Factor (EGF) [10-11]. The epidermal growth factor receptor (EGFR) cascades the signaling pathway that regulates tumor-cell proliferation, invasion, angiogenesis, metastasis, and apoptosis. EGFR plays a central role in lung carcinogenesis. Stimulation by its ligand, EGFR initiates signal transduction cascades, which promote proliferation, invasion, metastasis, angiogenesis and inhibition of apoptosis. EGFR plays an important role in tumor biology and to be an attractive therapeutic target.

EGFR Mutation- EGFR gained pharmaceutical significance with the discovery of its involvement in a number of cancers including Non-Small Cell Lung Cancer, head and neck cancers. It has been found that the EGFR is up-regulated in several types of cancers. It has also been implicated in the development of several types...
of cancer. Hence it has become an important target because of its involvement in the number of cancers where EGFR may be found up-regulated or mutated [12]. It has been reported that the common mutations of the tyrosine kinase coding domain are the exons 18–21 of the EGFR gene. The most common mutations found in the EGFR gene are the deletion in exon 19 and L858R point mutation. EGFR mutations are important due to their diagnostic value as well as the presence of EGFR mutations has also a significant impact on cancer responds to the tyrosine kinase inhibitor such as gefitinib [13]. EGFR has been shown to be an important therapeutic target in several types of cancer including NSCLC, colorectal cancer, head and neck squamous cell carcinoma and pancreatic cancer [14-15].

**EGFR and Tyrosine Kinase Inhibitor (TKI)-**

Erlotinib and gefitinib are orally administered small molecules which acts as inhibitors of the tyrosine kinase domain of the intracellular part of EGFR and are used in patients with advanced NSCLC. It has been shown by several studies that the EGFR mutations are predictive factors of response to EGFR-TKI treatment. The discovery of these mutations in tumors of NSCLC patients are associated with the gefitinib response. [5,6] It is found that the mutational status of lung cancer patients has also been correlated with patient outcomes. [16]

Since EGFR is often over-expressed in NSCLC and the level of EGFR expression correlates with poor prognosis, EGFR inhibitors have been developed as a novel therapy for NSCLC. Gefitinib is the first molecular targeted agent approved for the treatment of advanced NSCLC. It is a highly effective EGFR TK inhibitor (TKI) selectively blocks the signal transduction pathways implicated in cancer growth.

**EGFR Structure and Mechanism of action-** EGFR is a member of the transmembrane receptor family, EGFR is composed of three important regions. The extracellular ligand binding domain binds to EGFR ligands viz., EGF, Heparin-binding EGF-like growth factor (HB-EGF), transforming growth factor-α (TGFα), betacellulin, epiregulin and amphiregulin. The transmembrane domain of EGFR links the ligand-binding domain to intracellular tyrosine kinase signalling domain. Binding to the ligands EGFR undergoes auto-dimerization and hetero-dimerization with the other HER/erbB family of tyrosine kinases, such as HER1 (EGFR/erbB1), HER2 (neu, erbB2), HER3 (erbB3), and HER4 (erbB4) and triggers the EGFR signalling and targeted functions [17]

Growth and metastasis of tumors involve EGFR-dependent activations of Ras/Mitogen activated Protein kinase cascade (MAPK) and phosphatidylinositol-3 kinase/Akt (PI3K/AKT) pathways. PI3K/AKT is a pro-proliferative signalling pathway which promotes the cellular multiplication and attenuates apoptosis in SCLC and NSCLC [18]. Activated-EGFR also triggers the enhanced expression of the angiogenic growth factors such as vascular epidermal growth factor (VEGF), basic-fibroblast growth factor, platelet-derived endothelial cell growth factor and interleukin-8 [19].

**CONCLUSIONS**

Epidermal growth factor Receptor Mutation status is the most valuable indicator for the screening of non-small cell lung cancer patients for tyrosine kinase inhibitor (TKI) therapy. It has been reported from the previous study that the Lung cancer patients of adenocarcinoma subtypes and non-smoker as well as female gender are more likely to contain mutation in the EGFR gene and therefore may show better response to gefitinib. The testing of EGFR mutation in non-small cell lung cancer patients with adenocarcinoma subtype is helpful in selection of specific therapy. Those lung cancer patients where only small biopsies or
cytological material are available may be benefited from molecular testing in determining the choice of drugs for target therapy.

REFERENCES