Targeting Epidermal Growth Factor Receptor in the Management of Lung Cancer

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The epidermal growth factor receptor (EGFR) mutation is a potent oncogenic driver that accounts for carcinogenesis and tumor growth of pulmonary adenocarcinoma. Targeting EGFR with tyrosine kinase inhibitors (TKIs) is highly effective in terms of tumor response rate, progression-free survival (PFS), and quality of life. Multiple randomized studies have confirmed the superiority of EGFR TKIs over platinum-based chemotherapy and established EGFR TKIs as standard first-line therapy for patients with EGFR mutation-positive non-small cell lung cancer (NSCLC). However, almost all patients will develop resistance to EGFR TKIs and post progression therapy may include a combination of local therapy, systemic chemotherapy, and second-generation EGFR TKIs.
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The epidermal growth factor receptor (EGFR) has been a focus of research for over four decades before the eventual discovery of its activating mutation in 2004.[1,2] This discovery is now the foundation for personalized therapy for management of advanced stage non-small cell lung cancer (NSCLC). It is standard practice to analyze a NSCLC tumor for the presence or absence of an activating EGFR mutation, and direct therapy according to mutation status. EGFR mutation-positive lung cancer is now recognized as a distinguished disease entity that is dissimilar to EGFR wild-type lung cancer or lung cancer defined by another oncogenic driver. Being a separate disease entity since 2004, questions remain as to the optimal management of EGFR mutation-positive NSCLC patients and if the standard approach to the management of lung cancer is applicable to this unique patient population. For example, it is common knowledge that chemotherapy should be stopped whenever there is clinical or radiological evidence of disease progression. But for patients with an EGFR mutation, EGFR tyrosine kinase inhibitors (TKIs) are frequently given beyond disease progression. We are in the process of learning and discovering the best way to manage this specific disease. The objectives of this review are to summarize the existing knowledge on targeted therapies approved for the treatment on EGFR mutation NSCLC, to examine the optimal sequence of therapy, to explore the potential combination of chemotherapy and EGFR TKIs, to discuss the management of TKI resistance, and to project on future developments in the field.

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EGFR AS A TARGET FOR BIOLOGIC THERAPY

EGFR is an important growth signal receptor that controls cell proliferation and survival. The discovery of epidermal growth factor by Stanley Cohen in 1964 led to a Nobel prize,[3] but its receptor was not isolated until almost two decades later when Mendelsohn and colleagues first proposed EGFR as a potential anti-cancer target.[4] Based on this concept, monoclonal antibodies (Mabs) targeting EGFR and TKIs targeting the intracellular domain were developed. Cetuximab (Erbitux; Merck Serono, Geneva, Switzerland) is an IgG1 Mab that binds to the extracellular ligand-binding domain of EGFR inhibiting EGFR signaling. It is approved as a standard first-line therapy in combination with chemotherapy for patients with KRAS wild-type metastatic colorectal cancer and in combination with radiotherapy for patients with head and neck cancer. A number of randomized studies were conducted assessing combination chemotherapy plus cetuximab compared to

Table 1. 4 Combination of Chemotherapy Plus Cetuximab Versus Chemotherapy in Patients With Advanced-Stage NSCLC

Authors	No. of Patients	Tumor Response Rate(%)	Median PFS (mo)	Median OS (mo)
Butts et al[5]	131	28 *v* 18	5.1 *v* 4.2	12 *v* 9
Rosell et al[6]	86	35 *v* 28	5.0 *v* 4.6	8.3 *v* 7.3
Lynch et al[7]	676	26 vs17	4.4 *v* 4.2	9.7 *v* 8.4
Pirker et al[8]	1,125	36 *v* 29	4.8 *v* 4.8	11.3 *v* 10.1

chemotherapy alone in patients with advanced-stage NSCLC (Table 1). The randomized phase II studies demonstrated a modest but statistically insignificant difference in overall survival (OS) favoring combination therapy, which was confirmed in the phase III study.[5–8] However, the small benefit was not recognized by approval agencies and the drug has not been approved for use in lung cancer patients. Further data have demonstrated that while EGFR is a potential target in NSCLC, not all patients with expression of EGFR will benefit from anti-EGFR therapy with cetuximab.

Gefitinib was one of the first EGFR TKIs designed to target the intracellular domain of EGFR. Initial clinical development was met with excitement as there were selective patients with dramatic tumor response. However, phase II studies in unselected patients reported tumor response rates (RRs) of 18.4%–19% in the Japanese population and 9%–12% in the western population.[9,10] The low response rate is explained by the low incidence of EGFR mutations in unselected patient populations but this was not evident until Lynch and colleagues and Paez and colleagues independently discovered EGFR mutations in almost all responders to gefitinib.[1,2] Their discovery showed that the true target of EGFR TKIs, such as gefitinib, is the EGFR with either a deletion in exon 19 or point mutation in exon 21. Multiple phase II studies were performed to investigate the efficacy of EGFR TKIs as second-/third-line therapy for biomarker-selected populations.[11–14] Tumor response rates were consistently above 60% irrespective of patients' age, gender, and ethnicity. Clinical observations have confirmed that the real target is the mutated EGFR receptor and not the wild-type receptor.

EFFICACY OF EGFR TKIs IN PATIENTS HARBORING EGFR MUTATIONS

Early investigations of the clinical efficacy of EGFR TKIs focused on patients with specific clinical features including Asian ethnicity, female gender, never/light smoker, and adenocarcinoma. Only retrospectively was it confirmed that these patient subgroups were associated with a higher incidence of activating EGFR mutations.[15,16] IPASS (Iressa Pan-ASia Study) was the first randomized phase III study that confirmed the role of EGFR TKIs as first-line therapy in patients with EGFR mutations.[17] Patients were accrued according to clinical features for enrichment of a study population with activating EGFR mutations and tumor samples were analyzed retrospectively for the presence or absence of the mutation. This study confirmed the EGFR mutation to be a potent predictive biomarker for response to EGFR TKIs. Tumor RR to gefitinib in patients with EGFR mutations was 71.2%, which was significantly higher than the RR to chemotherapy ($P < .001$). The primary endpoint of progression-free survival (PFS) was prolonged in the gefitinib treatment group (hazard ratio [HR] 0.48, $P < .0001$). The interaction-test of the HR between the EGFR mutation-positive and -negative subgroup was statistically significant, thus confirming the EGFR mutation as the predictive biomarker. The majority of patients treated with first-line chemotherapy were crossed over to gefitinib at time of progression, thus accounting for the lack of OS benefit. A Korean study with a similar design reported comparable results but was limited by the small sample size of patients with known EGFR mutation status.[18] Subsequent studies enrolled only patients with EGFR mutations and randomized patients to either an EGFR TKI or chemotherapy. A total of four studies conducted in biomarker-selected patient populations with activating EGFR mutations have confirmed the superiority of EGFR TKIs over standard platinum-based doublet chemotherapy (Table 2).[19–22] The significantly higher RR and magnitude of prolongation of PFS were persistent across these randomized studies, thus establishing the unequivocal evidence of EGFR TKIs as standard treatment for patients with EGFR mutations.

FIRST- VERSUS SECOND-/THIRD-LINE TREATMENT WITH EGFR TKIs

Irrespective of the extensive data on the use of first line EGFR TKIs, many argue that second-line