Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Advanced Non-Small Cell Lung Cancer

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Key Words

Epidermal growth factor receptor mutation · Epidermal growth factor receptor tyrosine kinase inhibitors · Personalized medicine · Pathological and molecular profile

Abstract

The advent of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) has led to a paradigm shift in the management of advanced adenocarcinoma of the lung. The key to success of these therapies lies in the precise identification of their molecular targets, i.e. sensitizing EGFR mutations. The variations in the prevalence of these mutations among different ethnicities necessitate regional studies for a better understanding of the molecular epidemiology of the disease and clinical decision-making. This is even more relevant for countries like India where genetic heterogeneity is a rule. Here, we make an attempt to review the epidemiology of EGFR mutations in India versus other Asian countries and the West. We also review the clinical experience with EGFR TKIs and suggest the way forward in a resource-limited setting.

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Introduction

Lung cancer is the most common cancer among males and a major cause of cancer-related deaths all over the world. It accounts for 13% of all new cancer cases [1]. In India, lung cancer constitutes 6.9% of all new cancer cases and 9.3% of all cancer-related deaths in both sexes [1]. The prevalence pattern and pathological profile of the disease vary significantly among various ethnicities and geographic locations and largely reflect smoking pattern, genetic heterogeneity and possibly other environmental factors. During the past decade, with better understanding of molecular biology, newer targets and driver mutations have been identified. This has led to the development of novel epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs). These are currently being recommended in the treatment of advanced/metastatic disease in eligible patients. This is based on the results of a number of randomized, metacentric studies in a large number of patients. In this review, we make an attempt to summarize the available data from India on frequency and type of EGFR mutations, clinical experience with EGFR TKIs and its potential impact on outcome.

Table 1. Pathological profile: Indian data

Study	Patients, n	Median age, years	M:F ratio	Smoker:non-smoker ratio	Histological characterization
Behera and Balamugesh [8]	1,009	54.3	4.5:1	2.7:1	Sq: 34.3% Ade: 25.9% Others: 39.8%
Prasad et al. [12]	400	57	4.3:1	2.5:1	Sq: 46.5% Ade: 18.2% Others: 35.3%
Khan et al. [13]	321		11.3:1	7.6:1	Sq: 77.3% Ade: 5.3% Others: 17.4%
Singh et al. [9]	250	57.9	4.4:1	2.67:1	Sq: 34.8% Ade: 26% Others: 18.4%
Noronha et al. [11]	489	56	3.5:1	0.9:1	Sq: 26.2% Ade: 43.8% Others: 30%
Malik et al. [10]	434	55	4.6:1	2.1:1	Sq: 29.4% Ade: 45.41% Others: 25.1%
Sq = Squamous cell carcinoma; Ade = adenocarcinoma.					

Pathological Profile of Lung Cancer: The Changing Paradigm

In recent years, the histological characterization of lung cancer has become important in view of genomic classification of lung carcinoma and histologically guided therapeutic intervention [2, 3]. In Europe, North America and most of the Asian countries, the incidence of adenocarcinoma has already surpassed that of squamous cell carcinoma [4, 5]. This shift has been attributed partly to the smoking pattern and increasing incidence of lung cancer in females and non-smokers [4, 6, 7]. This shift in histology subtype has also been observed in India. While the earlier and even a few recent hospital-based studies have described squamous cell carcinoma as the most common histology [8, 9], recent data from two major centers have shown a changing pattern, i.e. adenocarcinoma as the most common histological subtype, similar to the West [10, 11] (summarized in table 1). Many patients who were earlier classified as non-small cell carcinoma not otherwise specified (NSCLC NOS), can be further subclassified after careful review of the pathology with the appropriate use of immunohistochemistry. In a recent

study, in an independent pathology review of 174 biopsy specimens, the histological subtype was changed in 24% of cases. [10].

EGFR Mutations: Frequency

The incidence of EGFR mutations varies among different ethnic and geographical populations. In Caucasian populations 10% of patients harbor these mutations, while in East Asian patients the frequency has been reported to be as high as 60% [14, 15]. In the Indian population, where there is genetic diversity, a frequency of 23–50% has been reported (table 2) [16–23]. The techniques of mutation testing as well as the type of referrals have varied in these studies. In a recent multinational study among patients with advanced adenocarcinoma of the lung from Asian countries, it was reported that the frequency of mutations in Indians is lower: 22.2 versus 47.2–67.2% compared to data of other Asian countries [24]. These differences highlight the importance of molecular epidemiology and the need for regional studies.

Table 2. Frequency of EGFR mutations in Indian, Western and other Asian populations

Study	Patients, n	Technique	Prevalence of mutations	Mutation subtypes	Ethnicity
Sahoo et al. [16]	220	Scorpion ARMS PCR	51.8%	Exon 19: 51.6% Exon 21: 26.2% Exon 18: 7.9% Exon 20: 3.0%	Indian
Doval et al. [17]	166	Direct sequencing	25.9%	Exon 19: 51.2% Exon 21: 34.9% Exon 18: 4.6% Exon 20: 2.3%	Indian
Chougule et al. [18]	907	TaqMan PCR	23.2%	Exon 19: 50% Exon 21: 42% Exon 18: 7% Exon 20: 3%	Indian
Noronha et al. [19]	111	TaqMan PCR	35%	Exon 19: 74.3% Exon 21: 23% Exon 18: 2.5% Exon 20:	Indian
Bhatt et al. [20]	106	Direct sequencing	39.6%	Exon 19: 76.2% Exon 21: 7 % Exon 18: 2.4% Exon 20: 4.8%	Indian
Veldore et al. [21]	1,036	Scorpion ARMS PCR	40.3%	Exon 19: 61% Exon 21: 31.8% Exon 18: 4.5% Exon 20: 4%	Indian
Mehta et al. [22]	367 (analyzable)	PCR-RFLP	32%	Exon 19 : 76% Exon 21 : 24%	Indian
Jain et al. [23]	206	IHC (using mutation-specific antibodies)	26.6%	Exon 19: 60% Exon 21: 40%	Indian
Dogan et al. [25]	3,026	PCR	20%	Exon 19: 59% Exon 21: 41%	American
Reinersman et al. [26]	121	PCR	19%	Exon 19: 78.2% Exon 21: 21.8%	African American
Douillard et al. [27]	1,060	Scorpion ARMS PCR	14%	Exon 19: 65% Exon 21: 31%	Caucasian

ARMS = Amplification-refractory mutation system; PCR = polymerase chain reaction; RFPL = restriction fragment length polymorphism; IHC = immunohistochemistry.

EGFR TKIs: Clinical Experience

Protein kinases are attractive therapeutic targets for cancer cells because of frequent dysregulation. Small molecules like gefitinib and erlotinib are the first-generation TKIs of EGFR, which blocks binding of adenosine-5'-triphosphate (ATP) to the tyrosine kinase catalytic do-

main and thereby inhibits the downstream signaling. In 2004, three groups of researchers identified that the subgroup of NSCLC tumors which harbored a mutation in the EGFR gene, detected by direct sequencing, were highly sensitive to EGFR TKIs [28–30]. Although the initial clinical experience of EGFR TKIs was analyzed in an unselected patient population and later on in a clinically se-

lected population (Asian ethnicity, non-smoker, female gender and adenocarcinoma histology), nowadays, the clinical efficacy of these drugs is usually indicated by the molecular selection. Table 3 summarizes the major clinical studies on EGFR TKIs.

Unselected Population

ISEL (Iressa Survival Evaluation in advanced Lung cancer) is a large phase III study in which gefitinib was compared with placebo in patients who were refractory or intolerant to chemotherapy [31]. Here, gefitinib did not improve the survival as compared to placebo; however, there was some evidence of a benefit among never-smokers and patients of Asian origin. In a retrospective ad hoc analysis of 77 Indian patients included in the ISEL study, the median survival was observed to be 6.4 months with gefitinib and 5.1 months with placebo. The response rates were also better with gefitinib (14 vs. 0%) [32].

Another randomized phase III study (INTEREST) compared gefitinib with docetaxel in 1,433 previously treated NSCLC patients [33]. This study endorsed the non-inferiority of gefitinib to docetaxel in a second-line setting. On the other hand, in a Japanese study (V-15-32) gefitinib was compared with docetaxel in 489 patients with advanced NSCLC who had failed one or two lines of therapy [34]. However, this study could not demonstrate a non-inferiority of gefitinib in terms of overall survival (OS) (primary endpoint) according to pre-defined criteria, but there was no statistically significant difference in OS. Gefitinib fared better compared to docetaxel in terms of tumor response and improvement in quality of life.

In the BR.21 study, erlotinib was compared with placebo in previously treated NSCLC patients and was found to be superior in terms of progression-free survival (PFS) (2.2 vs. 1.8 months) and median survival time (6.7 vs. 4.7 months) [35]. Another phase III trial, TITAN, compared erlotinib with second-line chemotherapy (docetaxel or pemetrexed) for previously treated patients with advanced NSCLC and showed a similar OS (5.3 vs. 5.5 months) [36].

Clinically Selected Population

In a preplanned subgroup analysis of the ISEL study, gefitinib was shown to improve survival in patients of Asian origin and in non-smokers [37]. Therefore in 2006,

the Iressa® Pan-Asia Study (IPASS) was initiated to investigate the effectiveness of first-line gefitinib in previously untreated patients in East Asia who had advanced pulmonary adenocarcinoma and who were light smokers or non-smokers [38]. In this study, 1,217 patients from Asian countries were randomized to receive gefitinib 250 mg or a combination of carboplatin and paclitaxel. The study met its primary endpoint of non-inferiority of gefitinib as compared to chemotherapy in terms of PFS. The PFS at 12 months was 24.9% with gefitinib and 6.7% with chemotherapy. However, a subgroup of 261 patients with EGFR mutations (detected by ARMS PCR) had a significant PFS benefit with gefitinib. On the other hand, in 176 patients with mutation-negative disease, gefitinib was associated with an inferior outcome as compared to chemotherapy [38].

Selection by EGFR Mutation

In March 2006, at the same time when the IPASS study was started, two other phase III trials, the North East Japan (NEJ) 002 study [39] and the West Japan Thoracic Oncology Group (WJTOG) 3405 [40], were initiated, which compared gefitinib with standard chemotherapy in first-line treatment for EGFR-mutated NSCLC. NEJ 002 confirmed as the primary endpoint that PFS was significantly longer in the gefitinib group than in the carboplatin plus paclitaxel group [10.8 vs. 5.4 months; hazard ratio (HR) 0.30, $p < 0.001$]. The WJTOG 3405 study also demonstrated a superior PFS with gefitinib as compared to cisplatin plus docetaxel (9.2 vs. 6.3 months; HR 0.489, $p < 0.0001$).

Similarly, erlotinib was evaluated in a phase III trial (OPTIMAL) of Chinese patients with advanced NSCLC with an EGFR mutation. Erlotinib was associated with significantly better PFS compared to gemcitabine plus carboplatin (13.1 vs. 4.6 months; HR 0.16, $p < 0.0001$) [41]. Another phase III study (EURTAC) compared erlotinib to the standard chemotherapy in European patients with advanced NSCLC [42]. Erlotinib resulted in significantly better PFS as compared to the standard chemotherapy (9.7 vs. 4.2 months; HR 0.37, $p < 0.0001$) [42].

Afatinib, an irreversible and more potent TKI, has also been evaluated in mutation-positive patients. It was found to improve PFS as compared to chemotherapy (LUX-Lung 3 and LUX-Lung 6) [43, 44].

Table 3. Major clinical studies on EGFR TKIs

Study	Study population	Patients, n (M:F)	Drug and comparison arm	Response rates	PFS	OS
ISEL [31]	Unselected patients who progressed or were intolerant after chemotherapy	1,692 (1,129:563)	Gefitinib vs. placebo	–	–	5.6 vs. 5.1 months HR 0.89 (95% CI 0.77–1.02)
INTEREST [33]	Unselected patients previously treated with platinum-based chemotherapy	1,433 (723:710)	Gefitinib vs. docetaxel	–	–	7.6 vs. 8 months HR 1.02 (96% CI 0.905–1.150)
V-15-32 [34]	Unselected patients who failed one or more lines of chemotherapy	490 (245:244) 1 patient excluded	Gefitinib vs. docetaxel	22.5 vs. 12.8% ($p = 0.009$)	2 vs. 2 months HR 0.90 (95% CI 0.72–1.12)	11.5 vs. 14 months HR 1.12 (95.24% CI 0.89–1.40)
BR.21 [35]	Unselected patients who failed one or two lines of chemotherapy	731 (488:243)	Erlotinib vs. placebo	8.9 vs. <1% ($p < 0.001$)	2.2 vs. 1.8 months HR 0.61 (95% CI 0.51–0.74)	6.7 vs. 4.7 months HR 0.70 (95% CI 0.58–0.85)
TITAN [36]	Unselected patients who progressed after platinum-based doublet chemotherapy	424 (203:221)	Erlotinib vs. pemetrexed or docetaxel	34.5 vs. 43% ($p = 0.073$), disease control rate	6.3 vs. 8.6 weeks HR 1.19 (95% CI 0.97–1.46)	5.3 vs. 5.5 months HR 0.96 (95% CI 0.78–1.19)
IPASS [38]	Clinically selected (adenocarcinoma, Asians, former light smokers or non-smokers) treatment-naïve patients	1,217 (609:608)	Gefitinib vs. paclitaxel carboplatin	43 vs. 32.2% ($p < 0.001$) in overall population, 71.2 vs. 47.3% in EGFR mutation-positive patients	5.7 vs. 5.8 months HR 0.74 (95% CI 0.65–0.85) in overall population 9.5 vs. 6.3 months HR 0.48 (95% CI 0.36–0.64) in EGFR mutated patients	18.6 vs. 17.3 months HR 0.91 (95% CI 0.76–1.10)
NEJ 002 [39]	EGFR-mutated treatment-naïve patients	230 (115:115)	Gefitinib vs. paclitaxel carboplatin	73.7 vs. 30.7% ($p < 0.001$)	10.4 vs. 5.5 months HR 0.36 (95% CI 0.25–0.51)	30.5 vs 23.6 months ($p = 0.31$)
WJTOG 3405 [40]	EGFR-mutated treatment-naïve patients	177 (88:89)	Gefitinib vs. docetaxel cisplatin	62.1 vs. 32.2% ($p < 0.0001$)	9.2 vs. 6.3 months HR 0.489 (95% CI 0.336–0.71)	30.9 months vs. NR HR 1.638 (95% CI 0.75–3.58)
OPTIMAL [41]	EGFR-mutated treatment-naïve patients	165 (83:82)	Erlotinib vs. Gemcitabine Carboplatin	83 vs. 36% ($p < 0.0001$)	13.1 vs. 4.6 months HR 0.16 (95% CI 0.10–0.26)	Data not mature
EURTAC [42]	EGFR-mutated treatment-naïve patients	173 (86:87)	Erlotinib vs. cisplatin and docetaxel or gemcitabine	64 vs. 18% ($p < 0.0001$)	9.7 vs. 4.2 months HR 0.37 (95% CI 0.25–0.54)	19.3 vs. 19.5 months HR 1.04 (95% CI 0.65–1.68)
LUX-Lung 3 [43]	EGFR-mutated treatment-naïve patients	345 (230:115)	Afatinib vs. pemetrexed Cisplatin	56 vs. 23% ($p = 0.01$)	11.1 vs. 6.9 months HR 0.58 (95% CI 0.43–0.78)	Median NR
LUX-Lung 6 [44]	EGFR-mutated treatment-naïve patients	364 (242:122)	Afatinib vs. gemcitabine cisplatin	66.9 vs. 23% ($p < 0.0001$)	11.0 vs. 5.6 months HR 0.28 (95% CI 0.20–0.39)	22.1 vs. 22.2 months HR 0.95 (95% CI 0.68–1.33)

CI = Confidence interval; NR = not reported.

EGFR TKIs in Patients with Poor Performance Status and Advanced Age

Patients with poor performance status (PS; ECOG PS >2), as a group, are mostly unsuitable for chemotherapy and have been under-represented in clinical trials. TKIs offer a safer option for this group of patients. TOPICAL was a phase III double-blind randomized study conducted in the UK and tested erlotinib against placebo for patients with advanced NSCLC and poor PS who were unsuitable for chemotherapy [45]. OS did not differ between the erlotinib and placebo groups, but patients who developed a skin rash after 1 month of therapy had a significantly better survival with erlotinib (HR 0.76, $p = 0.0058$).

Another multi-center phase II NEJ 001 study has investigated the efficacy and feasibility of gefitinib treatment for advanced NSCLC patients harboring EGFR mutations but who were ineligible for chemotherapy due to poor PS [46]. The overall response rate was 66%, and the median PFS and median survival time were 6.5 and 17.8 months, respectively. The PS improvement rate was 79% ($p < 0.00005$); in particular, 68% of the 22 patients improved the PS from ≥ 3 to 0 or 1.

The Tarceva Lung cancer Survival Treatment (TRUST) was an open-label phase IV study of unselected patients with advanced NSCLC [47]. In a subpopulation of elderly patients (≥ 70 years) receiving first-line erlotinib ($n = 485$) in TRUST, the disease control rate was 79%, median PFS was 4.57 months, and OS was 7.29 months.

Thus, in a mutation-enriched population like ours, offering TKIs upfront to this poor-risk subgroup along with best supportive care seems to be a reasonable option. Incorporation of clinical predictors like non-smoker, female sex, adenocarcinoma histology and development of rash in the therapeutic decision-making might be further helpful in such difficult situations.

EGFR TKIs as Maintenance after Response to First-Line Chemotherapy

Maintenance treatment after platinum-based doublet chemotherapy has been gaining a place in the management of advanced NSCLC in recent years. Two paradigms, continuation or switch maintenance, have emerged in this context. SATURN was a phase III randomized trial comparing maintenance treatment with erlotinib versus placebo in unselected patients with advanced NSCLC who had non-progressive disease after

first-line chemotherapy [48]. Maintenance erlotinib was associated with an improvement in PFS (HR 0.71, $p < 0.0001$) and OS (HR 0.81, $p = 0.01$). The benefit was demonstrated in both the mutation-positive and overall population. Along with these two studies from Asia, WJTOG0203 and INFROM using gefitinib as maintenance demonstrated a benefit in terms of PFS [49, 50]. However, the subgroup analysis of both SATURN and INFROM shows that the maximum benefit is gained by mutation-positive patients and further reinforces the utility of predictive biomarkers in deciding treatment. Since all these studies included unselected patients irrespective of mutation status and still demonstrated a benefit, it is acceptable to use maintenance TKIs, more so in a mutation-enriched population like ours.

Experience from India

There are very few studies on the use of TKIs from India. Parikh et al. [32] analyzed 77 Indian patients enrolled in the ISEL study. The median survival and objective response rates in Indian patients were better with gefitinib compared to placebo (6.4 vs. 5.1 months; 14 vs. 0%). The tolerance among Indians was no different. Louis et al. [51] reported their experience of first-line use of gefitinib in 47 clinically selected patients from southern India and compared their outcome with 73 patients who were treated with chemotherapy at the same time. They reported a better PFS in the gefitinib group compared to chemotherapy (10 vs. 4 months; $p = 0.014$) despite the fact that there were more patients with poor PS and higher stage (stage 4) in the gefitinib group.

Noronha et al. [19] retrospectively analyzed 111 patients who were treated with EGFR TKIs. They performed EGFR mutation testing in these patients and found that 39 of 111 had evidence of mutation. The response rate was 74% in patients with activating mutation compared to 5% in mutation-negative patients. Median PFS was 10 versus 2 months and median OS was 19 versus 13 months in mutation-positive and -negative patients, respectively.

In our experience (unpubl. data), in 50 patients treated between 2008 and 2011, TKIs were used as upfront treatment based on clinical parameters, and the clinical benefit rate (complete, partial and stable response) was 54%. The majority of patients in this cohort (80%) had a poor PS (ECOG PS ≥ 2). Median PFS and OS in this poor-risk population were 7.5 and 12.7 months, respectively. The decision of TKI use was mostly based on clin-

ical parameters: 62% of patients were females, 72% non-smokers and 82% had adenocarcinoma and bronchoalveolar histology. EGFR mutation results were available in 7 patients only, and 3 of them had a sensitizing mutation.

Post-TKI Progression

Secondary Resistance

Despite good initial response, almost all patients treated with EGFR TKIs have disease progression due to the development of secondary resistance. For more than 60% of cases, a plausible mechanism of resistance has been identified [52]. A second-site EGFR mutation, particularly T790M, is the most common mechanism of acquired resistance accounting for almost 50% of cases. The T790M substitution alters proper binding of the drug to the ATP pocket of EGFR and/or restores the affinity for ATP versus the drug back to the level of wild-type EGFR [53]. Another 5–10% of cases demonstrate MET amplification [53]. A development of new mutations in the downstream signaling pathway like PIK3CA (5%) and BRAF (1%) is less frequently observed [54]. Rarely, a histological change to small cell carcinoma or epithelial to mesenchymal transition can be observed [54].

In recently published phase I–II trials, two third-generation TKIs (AZD9291 and rociletinib) have been demonstrated to be highly active in patients with a T790M mutation and showed impressive response rates of 61 and 59%, respectively [55–56]. Several specific combinations directed against the genetic makeup of individual tumors are currently under evaluation (e.g. adding a MET inhibitor for tumors displaying no EGFR T790M but MET amplification, or adding a PI3K inhibitor for tumors displaying a secondary PIK3CA mutation, and so on).

Continuation of EGFR TKI beyond disease progression is a controversial issue. In a phase II study (ASPIRATION), continuation of erlotinib beyond progression was feasible, if patients had slow progressive disease (>6 months of partial response/stable disease), asymptomatic minimal progressive disease, or new brain metastasis controlled locally [57]. However, on the other hand, the IMPRESS trial found no benefit for continuing treatment with gefitinib plus chemotherapy versus chemotherapy alone in patients with EGFR-mutated NSCLC who had disease progression on treatment with gefitinib. Progression was defined according to the RECIST criteria in the IMPRESS trial, and not by clinical symptoms or metastatic spread [58].

Personalized Medicine in a Resource-Limited Setting: Challenges and the Way Forward

In this new era, the validation of targeted therapeutic compounds should be paralleled to the development of predictive biomarkers. In order to address that, well-accessible centralized laboratories can generate quality epidemiological data as well as support policies of incorporation of high-cost targeted drugs in clinical practice.

Presently, most of the molecular testing facilities in India are in the private sector. The accessibility of such testing is limited for the majority of the Indian population due to the high cost. In addition, poor or lack of quality control and standardization among various laboratories are other issues. Such facilities are limited to the government sector or teaching institutions. These problems can be overcome by establishing centralized laboratories where standardized uniform techniques can be used. A bulk use of technique may reduce the cost of individual tests. Implementation of quality control policies and their scrutiny would also be easier and more practical in such centralized facilities. Use of techniques like dHPLC (denaturing high-performance liquid chromatography), HRMA (high-resolution melting analysis) and immunohistochemistry (using mutation-specific antibodies) as a screening procedure before whole-exon sequencing can reduce the cost and the turnaround time [59].

The availability of a generic version of TKIs has made these drugs easily accessible to larger number of patients. A better understanding of the molecular biology of NSCLC and EGFR mutation would be helpful to develop guidelines on the use of TKIs and therapy duration. In situations where mutation testing facilities are not readily available or accessible, TKIs should be used judiciously based on clinical judgment. In patients with advanced NSCLC and good PS, TKIs can be used as maintenance or second-line treatment after platinum-based doublet chemotherapy. The upfront treatment use of TKIs should be restricted to EGFR-mutated patients only. On the other hand, in patients who are not suitable candidates for cytotoxic chemotherapy because of poor PS, advanced age or comorbidities, TKIs may be a reasonable option. In such situations, clinical predictors like female sex, non-smoker, adenocarcinoma histology and development of rash after treatment can be used in the therapeutic decision-making.

Disclosure Statement

The authors declare no conflicts of interest.

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