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A comparative study on erlotinib & gefitinib therapy in non-small cell lung carcinoma patients

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***Background & objectives*: Tyrosine kinase inhibitors (TKIs) targeting the epidermal growth factor receptor (EGFR) have been evaluated in patients with advanced non-small cell lung cancer (NSCLC). Erlotinib and gefitinib are the first-generation EGFR-TKIs for patients with NSCLC. However, there is a paucity of studies comparing the effectiveness of these two drugs. Hence, this study was aimed to compare the effectiveness and safety of erlotinib and gefitinib in NSCLC patients.**

***Methods*: This study included 71 NSCLC patients who received EGFR-TKIs between 2013 and 2016. Adverse drug reaction of both erlotinib (n=37) and gefitinib (n=34) was determined and graded according to Common Terminology Criteria for Adverse Events grading system. Effectiveness was measured using response evaluation criteria in solid tumours and progression-free survival (PFS). Pharmacoeconomic analysis was performed by cost-effective analysis.**

***Results*: When comparing safety profile, both the drugs had similar adverse events except for dermal side effects such as acneiform eruption (51.4%), rash (54.05%) and mucositis (59.5%) for erlotinib and 20.6, 26.5 and 29.4 per cent for gefitinib, respectively. The PFS of the two drugs was compared to differentiate the effectiveness of erlotinib and gefitinib. There was no significant difference between the effectiveness of the two drugs. The pharmacoeconomic analysis showed that gefitinib was more cost-effective than erlotinib.**

***Interpretation & conclusions*: This study showed that erlotinib and gefitinib had similar effectiveness but gefitinib had a better safety profile compared to erlotinib. Therefore, gefitinib could be considered a better option for NSCLC patients compared to erlotinib. However, further studies need to be done with a large sample to confirm these findings.**

Key words Epidermal growth factor receptor inhibitors - erlotinib - gefitinib - non-small cell lung cancer - pharmacoeconomic analysis - treatment response

Lung cancer is the most commonly occurring cancer worldwide and nearly 80-85 per cent of all cases account for non-small cell lung cancer (NSCLC)[1]. Globocan estimate of lung cancer

indicated that incidence of lung cancer in India was 70,275 (for all ages and both genders) with an age standardized incidence rate being 6.9/100,000[2]. Recent advances in the field of lung cancer biology have led to therapies that are personalized based on the molecular characteristics of the tumour, targeting specific genes and pathways[3,4]. One such pathway that is deregulated in some NSCLC patients, particularly non-smokers, is the epidermal growth factor receptor (EGFR) signalling pathway[5].

Tumours with activating EGFR mutations are mainly dependent on continued EGFR signalling for proliferation and survival, which explains their sensitivity to EGFR tyrosine kinase inhibitors (TKIs)[6]. Drugs that target EGFRs include cetuximab, panitumumab (which are monoclonal antibodies that target the extracellular ligand-binding domain of EGFR tyrosine kinase receptor), gefitinib, erlotinib and afatinib (these target the cytoplasmic side of the receptor)[6]. The use of EGFR inhibitors can cause some adverse drug reactions (ADRs) particularly, dermatological *i.e.*, acneiform eruption, nail changes, mucositis, diarrhoea, dryness, rash, paronychia *etc*[7]. EGFR has a role in maintenance of epithelium and is expressed in dermal connective tissue. Inhibition of EGFR leads to abnormal functioning resulting in a loss of integrity of epithelial maintenance, leading to dermatological toxicities[8,9].

Studies involving evaluation of efficacy and safety of erlotinib and gefitinib in India are only a few, and the results have been inconclusive because of the small sample sizes. Therefore, this study was conducted to compare the safety and efficacy of the two drugs in NSCLC patients.

Material & Methods

Between January 2013 and December 2016, an observational study was carried out at Amrita Institute of Medical Sciences and Research Centre (Kochi, Kerala) on NSCLC patients who received erlotinib and gefitinib. A total of 71 patients were selected and the study was conducted over a period of eight months from September 2015 to May 2016. The sample size was estimated based on the prevalence of patients taking erlotinib and gefitinib for treating NSCLC in our study centre for the previous three years. Patients were considered eligible if they met the following criteria: histologically proven NSCLC, patients who have received EGFR-TKI therapy for three months or more and who were on follow up during the study period. The exclusion criteria were as follows: patients allergic to EGFR-TKI therapy, patients with malignancies other than NSCLC and patients who had psychiatric illness. Of the 71 patients, 37 received erlotinib and 34 patients received gefitinib. EGFR was tested from the sample obtained during the biopsy. Clinical characteristics, including patients age, gender, smoking history, present EGFR-TKI therapy *etc*., were recorded. In the present study cytology sample were used which included tissue sample collected during diagnosis (fine needle aspiration) for EGFR mutation testing.

The occurrence of ADR was determined by direct interview with patients/ close relatives or from electronic medical records and their probability was measured using Naranjo ADR Probability Scale[10]. The extent or severity of ADRs was assessed using Common Terminology Criteria for Adverse Events (CTCAE)[11]. For EGFR mutation, endobronchial ultrasound-guided fine needle aspiration cytology (FNAC) of pulmonary mass lesions from each case were performed. From each patient, written informed consent was taken. The skin surface was cleaned with povidone iodine, and then, long spinal needle was introduced through percutaneous/transthoracic approach. The aspirate was obtained, and smears were prepared immediately from the sample. Air-dried smears were stained and examined with the aid of a microscope[12]. The study protocol was approved by the Institutional Ethics Committee.

Assessment of effectiveness: Treatment response evaluation was performed according to the Response evaluation criteria in solid tumours (RECIST) group criteria[13]. The follow up period for each patient was three months after which imaging studies were performed to assess the size of target lesions. Based on these, the disease status was classified into complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The progression-free survival (PFS) rate of both drugs were determined and compared.

Assessment of cost-effectiveness: Cost-effective analysis was determined by calculating Incremental Cost Effectiveness Ratio (ICER) and Average Cost Effectiveness Ratio (ACER)[14].

ICER = (Cost of erlotinib – Cost of gefitinib)/
(Effectiveness of erlotinib – Effectiveness of gefitinib)

ACER = Health care cost/clinical outcome

The cost of therapy of one drug is calculated by multiplying cost of standard dose of that drug with number of days of use (PFS - number of days of drug discontinuation) of every patient.

Statistical analysis: The data were analysed using IBM SPSS 20.0 (SPSS Inc., Chicago, IL, USA). For all the continuous variables, the results were given in mean±standard deviation, and for categorical variables as percentage. To obtain the association of categorical variables, Chi-square test was applied. For the comparison of PD and overall response (OR) between two treatment groups, McNemar test was used. PFS was estimated by using the Kaplan-Meier method with log-rank test. PFS is described as the total duration of drug use without disease progression, death or change in therapy. Time to disease progression was calculated from the date of administration of the first dose of EGFR-TKI to the date of occurrence of disease progression. Log rank test was used for comparison of survival rate between two drugs. Student's paired *t*-test was used to compare the mean between PFS and EGFR mutation.

Results

Of the 71 patients who received EGFR-TKIs treatment (34 gefitinib, 37 erlotinib), 39 (55%) were males and 16 (41.03%) were smokers. Most of the patients were in the age group of 55-75 yr with mean age of 64.03±0.42 yr. A total of 58 patients (81.7%) were diagnosed with adenocarcinoma followed by squamous cell carcinoma (n=13, 18.3%), and Stage IV NSCLC was found in 66 (93%) patients; 56.3 per cent (n=40) harboured EGFR mutation, 22.5 per cent (n=16) were non-mutated and the remaining 21.1 per cent (n=15) were not tested because of non-availability of tissue or exhaustion of tissue. Among the 40 EGFR-positive patients, 23 patients were male and 17 patients were female. There were 31 (43.7%) patients who received EGFRI therapy as first-line treatment, while the remainder used EGFRI as salvage therapy after failing previous chemotherapy and radiation therapy. Among the 37 patients who received erlotinib, the dose of drug mostly used was 100 mg OD (75.7%) than 150 mg OD (24.3%) and the dose of gefitinib was 250 mg. In the analysis of relationship between EGFR mutation and effectiveness of EGFRI therapy, it was observed that the patients who harboured EGFR mutations showed a better PFS compared to non-mutated patients with EGFRI therapy (P<0.05) (Table I). A significant association was found between *EGFR* mutation and smoking (P<0.01) (Table II). Among patients with EGFR-positive mutation, 97.5 per cent (n=39) were non-smokers. On the other hand, the majority of non-mutated patients developed NSCLC due to smoking (62.5%).

Safety profile: Table III illustrates the major toxicities of both drugs. All 71 patients experienced several ADRs with grades varying from I to III according to CTCAE grading system. The adverse reactions most commonly observed during EGFRI (erlotinib and gefitinib) therapy were mucositis, rash, acneiform eruption and dryness. Less frequently observed ADR

Table I. Relationship between epidermal growth factor receptor (*EGFR*) mutation and effectiveness of EGFRI therapy

EGFR mutation	NSCLC patients (n=56)	(Mean±SD) PFS
Positive	40	2.46±0.302*
Negative	16	2.29±0.230

*P<0.05 compared to those with negative *EGFR* mutation.

Table II. Association of epidermal growth factor receptor (*EGFR*) mutation and smoking

EGFR mutation	Total number of patients	Smoking status	
		Smokers, n (%)	Non-smokers, n (%)
Positive	40	1 (2.5)	39 (97.5)**
Negative	16	10 (62.5)	6 (37.5)

**P<0.01 compared to patients with no mutation

Table III. Comparison of adverse drug reaction (ADR) between erlotinib and gefitinib

ADR	Erlotinib (n=37) n (%)	Gefitinib (n=34) n (%)
Acneiform eruption	19 (51.4)	7 (20.6)
Itching	16 (43.2)	20 (58.8)
Dryness	16 (43.2)	16 (47.06)
Rash	20 (54.05)	9 (26.5)
Alopecia	5 (13.5)	11 (32.4)
Paronychia	8 (21.6)	9 (26.5)
Koilonychia	3 (8.1)	3 (8.8)
Nail pigmentation	9 (24.3)	8 (23.5)
Nail brittleness	5 (13.5)	6 (17.7)
Diarrhoea	7 (18.9)	10 (29.4)
Mucositis	22 (59.5)	10 (29.4)

Table IV. Response evaluation criteria in solid tumours (RECIST) scoring

Drug	Response	RECIST score		*P* value
		OR (%)	PD (%)	
Erlotinib	Initial response	14 (37.8)	23 (62.2)	<0.001
	Follow up response	30 (81.1)	7 (18.9)	
Gefitinib	Initial response	9 (26.4)	25 (73.5)	<0.001
	Follow up response	29 (85.2)	5 (14.7)	
Total EGFRI therapy	Initial response	23 (32.4)	48 (67.6)	<0.001

PD, progressive disease; OR, overall response

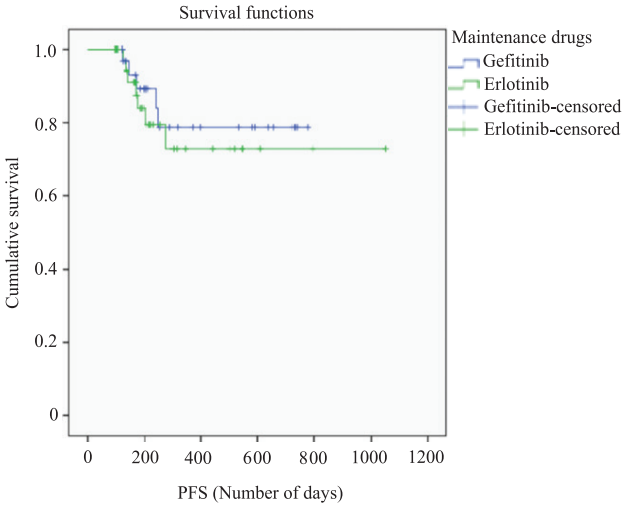

Figure. Comparison of progression-free survival of erlotinib and gefitinib.

were koilonychias and nail brittleness. All the ADRs were confirmed as probable (5-8) 95.7 per cent and definite (>9) 4.3 per cent using Naranjo Probability ADR Scale. When ADRs were graded according to CTCAE scale, of the total ADR profile, majority of the patients who were taking erlotinib and gefitinib had grade II ADRs with occurrence of 48 and 55 per cent, respectively, whereas grade III ADRs were lesser for the two drugs (12% for erlotinib and 13.3% for gefitinib). Grade IV ADRs were not observed in any of the study participants.

When comparing safety profile, both the drugs had similar adverse events except for dermal side effects such as acneiform eruption, rash and mucositis with percentage of 51.4, 54.05 and 59.5 per cent for erlotinib and 20.6 (P<0.01), 26.5 (P<0.01) and 29.4 per cent (P<0.01) for gefitinib, respectively.

Effectiveness of erlotinib and gefitinib

Response evaluation criteria in solid tumours (RECIST) scoring: According to RECIST criteria, the initial response and follow up response were compared and categorized into CR, PR, SD and PD. To obtain significance between the number of patients who got complete/partial/stable responses and PD states, they were categorized into two groups *i.e.*, PD as group with no response and CR+PR+SD as group with OR. The number of patients who had PD was found to be decreased from 67.6 to 16.9 per cent and those obtained OR were found to be increased from 32.4 to 83.1 per cent (Table IV).

Comparison of effectiveness (PFS) of erlotinib and gefitinib: The PFS for each drug was estimated from the number of days without disease progression and was compared (Figure). There was no significant difference between PFS of erlotinib and gefitinib. Hence, these were similar in effectiveness in NSCLC patients.

Cost-effectiveness analysis (CEA): The cost-effectiveness analysis was done using PFS and cost of erlotinib and gefitinib (Table V). The ICER was 1019.55 ₹/day. As the incremental cost obtained in ICER calculation was positive (54209.26) and incremental effect was negative (−53.17), gefitinib (drug B) was considered to be more cost-effective than erlotinib because of achieving better outcome at lower cost.

The ACER of erlotinib was 307.7 ₹/day, and that of gefitinib was 99 ₹/day. The average cost per day for obtaining effectiveness of gefitinib was lesser than that of erlotinib indicating that gefitinib was more cost-effective than erlotinib.

Table V. Total cost of progression-free days of erlotinib (n=37) and gefitinib (n=34)

Dose	Erlotinib dose		Gefitinib dose
	100 mg	150 mg	250 mg
Average cost (₹)	77775.1	97590.63	33473.65
Total average (₹)	87682.86		33473.65
Mean PFS (days)	284.95		338.12

PFS, progression-free survival; SD, standard deviation

Discussion

Most patients in our study were in the age group of 55-75 yr, as also observed by Yoshida *et al*[13]. Rocha *et al*[15] showed that lung cancer occurred more commonly in individuals above 40 yr of age. The number of males was slightly higher (55%) than females (45%). This could be mainly attributed to the different patterns of smoking which is one of the risk factors for NSCLC.

Adenocarcinoma was the most common type of NSCLC seen in our study (82%) as also observed by Lim *et al*[16]. This is mainly because EGFR-TKI is used in cases of adenocarcinoma. Due to the fact that early symptoms of NSCLC such as coughing and fatigue is often misinterpreted as other causes and also because severe symptoms such as respiratory tract infections, dyspnoea and haemoptysis are manifested in later stages, a large proportion of patients was diagnosed at the metastatic stage (Stage IV) of NSCLC. Thus, most of our patients (93%) received EGFRI (erlotinib/gefitinib) therapy during the progressive stage (Stage IV) of NSCLC followed by 5.6 per cent in Stage III.

The EGFR mutation status and smoking status of patients were mainly analysed. In our study, 56 per cent were found to be EGFR mutated, 22.5 per cent were non-mutated and others were not tested for EGFR mutation due to non-availability of tissue. According to a study conducted by Shi *et al*[17], there is increased prevalence of EGFR mutation in Asians (60%) compared to only 10 per cent in Caucasians. As concluded from previous studies, EGFR mutations are most often detected from female adenocarcinoma patients without the history of smoking[13,15]. Among our study participants, 41 per cent of male patients were found to be smokers and all the female patients were non-smokers. A high proportion of EGFR-positive patients were non-smokers; on the other hand, majority of patients without mutation were smokers. Hence, it may be possible that in non-smokers, lung cancer develops due to genomic alterations and molecular pathways (such as cell signalling due to EGFR).

In the safety analysis, all our patients experienced several ADRs with grades varying from I to III. EGFR has a role in maintenance of epithelium and is expressed in dermal connective tissue[8]. Inhibition of EGFR leads to abnormal functioning resulting in a loss of integrity of epithelial maintenance, leading to dermatological toxicities.

Gefitinib was found to be more tolerable than erlotinib which was consistent with the study conducted by Ma *et al*[18]. The PFS of the two drugs were compared and the values were similar. Hence both drugs showed similar effectiveness similar to a study conducted by Lim *et al*[14]. In pharmacoeconomic analysis using ICER and ACER calculation, it was found that gefitinib was more cost-effective than erlotinib which was in concordance with a study done by Ma *et al*[18].

In conclusion, the present results showed that though both erlotinib and gefitinib had similar effectiveness but gefitinib had a better safety profile compared to erlotinib. Therefore, gefitinib could be a better option for NSCLC patients compared to erlotinib. However, these findings were based on a small sample of patients and further studies with a large sample size should be conducted to confirm these findings.

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***Conflicts of Interest*:** None.

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