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COMPARATIVE ASSESSMENT OF GEFITINIB AND ERLOTINIB THERAPY IN SUBJECTS WITH NON-SMALL CELL LUNG CARCINOMA

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ABSTRACT

Background: In subjects with non-small cell lung carcinoma (NSCLC) Tyrosine kinase inhibitors (TKIs) are assessed targeting the epidermal growth factor receptor (EGFR). First-generation epidermal growth factor receptor- tyrosine kinase (EGFR-TKIs) used in subjects with NSCLC are gefitinib and erlotinib.

Aims: The present study was conducted to comparatively assess the efficacy and safety of gefitinib and erlotinib in subjects with non-small cell lung carcinoma.

Methods: The study included a total of 70 subjects having NSCLC who received gefitinib and erlotinib. In the present study, 36 subjects received erlotinib, and 34 subjects gefitinib. Adverse drug reactions were noted for both the drugs and were graded based on the Common Terminology Criteria for Adverse Events grading system. Progression-free survival (PFS) and response evaluation criteria in solid tumors were measured to assess the effectiveness of the drugs.

Results: Mucositis was seen in 32.35% (n=11) subjects with gefitinib and 58.33% (n=21) subjects using erlotinib. In gefitinib group, diarrhea, nail brittleness, Nail pigmentation, koilonychia, paronychia, alopecia, rash, dryness, itching, and acneiform eruptions were seen in 26.47% (n=9), 17.64% (n=6), 23.52% (n=8), 8.82% (n=3), 23.52% (n=8), 35.29% (n=12), 26.47% (n=9), 44.11% (n=15), 61.76% (n=21), and 23.52% (n=8) study subjects respectively. In erlotinib group, diarrhea, nail brittleness, Nail pigmentation, koilonychia, paronychia, alopecia, rash, dryness, itching, and acneiform eruptions were seen in 22.22% (n=8), 11.11% (n=4), 27.7% (n=10), 8.33% (n=3), 25% (n=9), 11.1% (n=4), 58.3% (n=21), and 41.66% (n=15) study subjects (Table 3). For the response to the drug therapy, statistically significant difference was seen from initial drug response to follow-up drug response for gefitinib, erlotinib, and total EGFR therapy in the study subjects with $p<0.001$

Conclusions: The present study concludes that gefitinib and erlotinib have similar efficacy, whereas, a better safety profile is seen with gefitinib compared to erlotinib. Hence, a better treatment modality for subjects with non-small cell lung carcinoma is gefitinib compared to erlotinib.

Keywords Erlotinib, gefitinib, Epidermal growth factor receptor inhibitors, non-small cell lung cancer, pharmacoeconomic analysis, treatment response

INTRODUCTION

One of the most commonly seen cancer globally is lung cancer contributing nearly 80% of all the carcinomas of the lung are non-small cell lung carcinoma (NSCLC). It is reported that in subjects with lung carcinoma, the incidence is nearly 70000 cases in both the genders and all age groups with incidence seen in 7 cases per 1 lakh subjects as depicted by Globocan estimation. In the field of lung cancer biology owing to the recent advancements, various therapies have been

developed that target pathway, specific genes, and molecular tumor characteristics. The epidermal growth factor signaling pathway is one such pathway especially of importance in non-smokers having NSCLC.[1]

Tumors that activate mutations in EGFR mainly depend on EGFR signaling for survival and proliferation show their EGFR tyrosine kinase inhibitors (TKIs) sensitivity. Drugs targeting EGFRs are panitumumab and cetuximab that are monoclonal antibodies targeting the extracellular ligand-binding domain of EGFR tyrosine kinase receptor, and afatinib, erlotinib, and gefitinib targeting the cytoplasmic receptor side.[2]

Use of the drugs that are EGFR inhibitors can lead to various adverse reactions due to drugs especially dermatologic effects including paronychia, rash, dryness, diarrhea, mucositis, nail changes, and/or acneiform eruption. EGFR is expressed in the connective tissue of the skin and has a vital role in maintaining epithelium. EGFR inhibition can cause abnormal function leading to loss of epithelial integrity and dermatologic toxicities. The data assessing the safety and efficacy of gefitinib and erlotinib in the Indian population is scarce in the literature and has a small sample size, monitoring periods, and inconclusive results.[3] Hence, the present study was conducted to comparatively assess the efficacy and safety of gefitinib and erlotinib in subjects with non-small cell lung carcinoma.

MATERIAL & METHODS

The present study was conducted to comparatively assess the efficacy and safety of gefitinib and erlotinib in subjects with non-small cell lung carcinoma. The study was conducted at Government Medical College, Nagpur, Maharashtra Government Medical College, Akola, Maharashtra after obtaining clearance from the concerned Ethical committee. The study population was comprised of the subjects visiting the Institute with non-small cell lung carcinoma. The study included a total of 70 subjects from both genders who received gefitinib and erlotinib for non-small cell lung carcinoma.

The inclusion criteria for the study were subjects with a confirmed histologic diagnosis of non-small cell lung carcinoma, subjects on recall phase, and subjects who received either gefitinib or erlotinib for a minimum of 1 month. The exclusion criteria for the study were subjects having psychotic diseases, subjects with malignancies other than NSCLC, and subjects allergic to the therapy for EGFR-TKIs. In 70 study subjects, 36 subjects received erlotinib, and 34 subjects gefitinib. After explaining the detailed study design, informed consent was taken from all the subjects in both written and verbal form.

After the final inclusion of the study subjects, detailed history was recorded for all the subjects followed by a general examination. Characteristics recorded were EGFR-TKI therapy, present history, smoking history, gender, and age. The samples used in the present study were tissue samples obtained by FNAC (fine needle aspiration cytology) during disease diagnosis for testing mutation of EGFR.

Adverse drug reactions were assessed with the direct interview of the subjects and caretakers or were extracted from the previous medical records assessed on the Naranjo ADR probability scale. CTCAE (Common Terminology Criteria for Adverse Events) was used to assess the severity or extent of the adverse drug reactions. For mutations in EGFR, FNAC was guided by endobronchial ultrasound of lesions of pulmonary mass for each study subject. For FNAC, the skin was prepared with povidone-iodine followed by the insertion of the long spinal needle through a transthoracic/ percutaneous approach, and smears were immediately prepared from the aspirate. Following smear preparation, they were dried with air and were stained and examined under the microscope.

Response to treatment was evaluated based on RECIST (Response evaluation criteria in solid tumors) group criteria. After three months of follow-up, for each subject imaging was done to detect the target lesion size. Depending on these findings, the status of the disease was classified into progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR). The PFS (progression-free survival) rate for both drugs was assessed and compared.

The collected data were subjected to the statistical evaluation using SPSS software version 21 (Chicago, IL, USA) and one-way ANOVA and t-test for results formulation. The data were expressed in percentage and number, and mean and standard deviation. The level of significance was kept at $p<0.05$. Figure 1 depicts one completed case.

RESULTS

The present observational study was conducted to comparatively assess the efficacy and safety of gefitinib and erlotinib in subjects with non-small cell lung carcinoma. The study included a total of 70 subjects from both genders who received gefitinib and erlotinib for non-small cell lung carcinoma. In 70 study subjects, 36 subjects received erlotinib, and 34 subjects gefitinib. The demographic and disease-related characteristics of the study subjects are described in Table 1. There were 41.42% (n=29) smokers and 58.57% (n=41) non-smokers in the present study. The mean age of the study subjects was 64.01±0.62 years. Adenocarcinoma was seen in 81.42% (n=57) subjects, squamous cell carcinoma in 18.57% (n=13) subjects, and stage 4 NSCLC in 91.42% (n=64) study subjects. EGFR mutation was seen in 55.71% 9n=39) subjects, absent in 22.85% (n=16) subjects, and inconclusive results due to tissue collapse were seen in 21.42%

(n=15) subjects. In EGFR positive subjects there were 31.42% (n=22) males and 24.28% (n=17) females. The dosage of erlotinib was 150 mg OD and for gefitinib was 250 mg OD.

In EGFR positive subjects mean PFS was 2.48±0.304 and in EGFR negative subjects, PFS was 2.27±0.232. This was significantly higher in EGFR positive subjects with p<0.001. Based on the smoking status, there was 1 smoker and 38 non-smokers in EGFR positive subjects. In EGFR negative subjects, there were 5 smokers and 11 non-smokers. This was statistically significant between smokers and non-smokers with p<0.001 as shown in Table 2.

On assessing the adverse drug reaction in the study subjects, mucositis was seen in 32.35% (n=11) subjects with gefitinib and 58.33% (n=21) subjects using erlotinib. In gefitinib group, diarrhea, nail brittleness, Nail pigmentation, koilonychia, paronychia, alopecia, rash, dryness, itching, and acneiform eruptions were seen in 26.47% (n=9), 17.64% (n=6), 23.52% (n=8), 8.82% (n=3), 23.52% (n=8), 35.29% (n=12), 26.47% (n=9), 44.11% (n=15), 61.76% (n=21), and 23.52% (n=8) study subjects respectively. In erlotinib group, diarrhea, nail brittleness, Nail pigmentation, koilonychia, paronychia, alopecia, rash, dryness, itching, and acneiform eruptions were seen in 22.22% (n=8), 11.11% (n=4), 27.7% (n=10), 8.33% (n=3), 25% (n=9), 11.1% (n=4), 58.3% (n=21), and 41.66% (n=15) study subjects (Table 3). For the response to the drug therapy, statistically significant difference was seen from initial drug response to follow-up drug response for gefitinib, erlotinib, and total EGFR therapy in the study subjects with p<0.001 (Table 4).

DISCUSSION

The present observational study was conducted to comparatively assess the efficacy and safety of gefitinib and erlotinib in subjects with non-small cell lung carcinoma. The study included a total of 70 subjects from both genders who received gefitinib and erlotinib for non-small cell lung carcinoma. In 70 study subjects, 36 subjects received erlotinib, and 34 subjects gefitinib. There were 41.42% (n=29) smokers and 58.57% (n=41) non-smokers in the present study. The mean age of the study subjects was 64.01±0.62 years. Adenocarcinoma was seen in 81.42% (n=57) subjects, squamous cell carcinoma in 18.57% (n=13) subjects, and stage 4 NSCLC in 91.42% (n=64) study subjects. EGFR mutation was seen in 55.71% 9n=39) subjects, absent in 22.85% (n=16) subjects, and inconclusive results due to tissue collapse were seen in 21.42% (n=15) subjects. In EGFR positive subjects there were 31.42% (n=22) males and 24.28% (n=17) females. The dosage of erlotinib was 150 mg OD and for gefitinib was 250 mg OD. These demographics were comparable to the studies by Ma Y et al[4] in 2013 and Shi Y et al[5] in 2014 where authors assessed subjects with the demographics comparable to the present study.

In EGFR positive subjects mean PFS was 2.48±0.304 and in EGFR negative subjects, PFS was 2.27±0.232. This was significantly higher in EGFR positive subjects with p<0.001. Based on the smoking status, there was 1 smoker and 38 non-smokers in EGFR positive subjects. In EGFR negative subjects, there were 5 smokers and 11 non-smokers. This was statistically significant between smokers and non-smokers with p<0.001. These results were in agreement with the studies by Lim SH et al[6] in 2014 and Kimura M et al[7] in 2018 where similar results for PFS and smoking status were seen in subjects with NSCLC.

Concerning the adverse drug reaction in the study subjects, mucositis was seen in 32.35% (n=11) subjects with gefitinib and 58.33% (n=21) subjects using erlotinib. In gefitinib group, diarrhea, nail brittleness, Nail pigmentation, koilonychia, paronychia, alopecia, rash, dryness, itching, and acneiform eruptions were seen in 26.47% (n=9), 17.64% (n=6), 23.52% (n=8), 8.82% (n=3), 23.52% (n=8), 35.29% (n=12), 26.47% (n=9), 44.11% (n=15), 61.76% (n=21), and 23.52% (n=8) study subjects respectively. In erlotinib group, diarrhea, nail brittleness, Nail pigmentation, koilonychia, paronychia, alopecia, rash, dryness, itching, and acneiform eruptions were seen in 22.22% (n=8), 11.11% (n=4), 27.7% (n=10), 8.33% (n=3), 25% (n=9), 11.1% (n=4), 58.3% (n=21), and 41.66% (n=15) study subjects. For the response to the drug therapy, statistically significant difference was seen from initial drug response to follow-up drug response for gefitinib, erlotinib, and total EGFR therapy in the study subjects with p<0.001. These results were consistent with the studies of Hickman M et al[8] in 2017 and Reck M et al[9] in 2014 where authors reported similar adverse drug reactions and response to drug therapy.

CONCLUSION

Within its limitations, the present study concludes that gefitinib and erlotinib have similar efficacy, whereas, a better safety profile is seen with gefitinib compared to erlotinib. Hence, a better treatment modality for subjects with non-small cell lung carcinoma is gefitinib compared to erlotinib. However, the present study had a few limitations including a small sample size, short monitoring period, use of IOPAR, and geographical area biases. Hence, more longitudinal studies with a larger sample size and longer monitoring period will help reach a definitive conclusion.

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TABLES

S. No	Characteristics	Percentage (%)	Number (n)
1.	**EGFR-TKIs therapy**		
2.	Gefitinib	48.57	34
3.	Erlotinib	51.42	36
4.	**Smoking status**		
5.	Smokers	41.42	29
6.	Non-smokers	58.57	41
7.	**Mean age**	64.01±0.62	
8.	**Diagnosis**		
9.	Adenocarcinoma	81.42	57
10.	Squamous cell carcinoma	18.57	13
11.	Stage IV NSCLC	91.42	64
12.	**EGFR mutation**		
13.	Present	55.71	39
14.	Non-mutated	22.85	16
15.	Inconclusive	21.42	15
16.	**Gender (EGFR present)**		
17.	Males	31.42	22
18.	Females	24.28	17
19.	**Dosage(mg)**		
20.	Erlotinib	150	
21.	Gefitinib	250	

Table 1: Demographic and disease characteristics of the study subjects

S. No	EGFR mutation	Positive (n=39)	Negative (n=16)	p-value
1.	**PFS**	2.48±0.304	2.27±0.232	<0.001
2.	**Smoking status % (n)**			
3.	Smokers	1	5	<0.001
4.	Non-smokers	38	11	

Table 2: Assessment of the relationship of EGFR receptor to PFS and smoking status in the study subjects

S. No	Adverse drug reactions	Gefitinib (n=34) n (%)	Erlotinib (n=36) n (%)
1.	**Mucositis**	11 (32.35)	21 (58.33)
2.	**Diarrhea**	9 (26.47)	8 (22.22)
3.	**Nail brittleness**	6 (17.64)	4 (11.11)
4.	**Nail pigmentation**	8 (23.52)	10 (27.7)
5.	**Koilonychia**	3 (8.82)	3 (8.33)
6.	**Paronychia**	8 (23.52)	9 (25)
7.	**Alopecia**	12 (35.29)	4 (11.1)
8.	**Rash**	9 (26.47)	21 (58.3)
9.	**Dryness**	15 (44.11)	15 (41.66)
10.	**Itching**	21 (61.76)	15 (41.6)
11.	**Acneiform eruption**	8 (23.52)	20 (55.55)

Table 3: Adverse drug reactions following Gefitinib and Erlotinib in the study subjects

Drug therapy	Response	p-value
Gefitinib	**Initial response**	<0.001
	Follow-up response	
Erlotinib	**Initial response**	<0.001
	Follow-up response	
Total EGFR therapy	**Initial response**	<0.001

Table 4: Response to the therapy using RECIST scores in the study subjects