DOI: 10.7860/JCDR/2023/59489.17433

Original Article

Internal Medicine Section

Comparison of Treatment Outcome in EGFR Positive and Negative Patients with Non Small Cell Lung Cancer: A Longitudinal Study

FARZANA KHANUM[1], NAFEES AHMAD KHAN[2], HUMA FIRDAUS[3], RAKESH BHARGAVA[4], ZUBER AHMAD[5], MOHAMMAD SHAMEEM[6], KAFIL AKHTAR[7]

ABSTRACT

Introduction: Lung cancer is one of the most common malignancies to occur worldwide. Two main subtypes of lung cancer include small cell lung cancer and Non Small Cell Lung Cancer (NSCLC). Patients with advanced stage NSCLC who achieve good response with Tyrosine Kinase Inhibitors (TKI) have been found to have Epidermal Growth Factor Receptor (EGFR) mutation. The first biomarker identified for targeted treatment in lung cancer was EGFR and patients of NSCLC with EGFR mutation have superior survival outcome when treated with targeted therapy as compared to conventional chemotherapy.

Aim: To compare the outcome of targeted therapy to mutation to EGFR and conventional therapy in non mutant lung cancer patient of NSCLC.

Materials and Methods: The present longitudinal study was conducted in the Department of TB and Respiratory Diseases, Jawaharlal Nehru Medical College and Hospital, Aligarh, Uttar Pradesh, India, from July 2017 to November 2019 on a sample size of 80. Patients diagnosed with NSCLC and EGFR mutation status were included in the study. They were started on TKI if tumour was EGFR positive and on conventional chemotherapy (cisplatin plus paclitaxel) if no mutation was detected on histopathology. Among the study group, 35 patients were EGFR positive and started on gefitinib (group I), 45 were EGFR negative and received platinum-based chemotherapy (group II). Outcomes were measured in terms of progression-free survival, Overall Survival (OS), and toxicities. Statistical analysis of data was done using Statistical Package for the Social Sciences (SPSS) version 20.0.

Results: Among the study group, 35 patients were EGFR positive and started on gefitinib (group I), 45 were EGFR negative and received platinum-based chemotherapy (group II). The mean age of EGFR positive patients was 58.91 years and for EGFR negative patients was 60.11 years. In group I, there was no complete response while 28.5% had partial response, 45.5% had stable disease and 25.7% had progressive disease. In group II, 15.5% patients had complete response, 33.3% had partial response, 17.7% had stable disease and 33.3% had progressive disease. Mean progression-free survival in group I (5.65 months) was significantly higher than group II (4.26 months). The mean OS in group I (7.85 months) was slightly higher than group II (6.72 months). Both haematological and non haemaotlogical toxicities were significantly higher in group II.

Conclusion: Patients with EGFR positive expression subjected to gefitinib had significant mean progression-free survival with an acceptable range of non haematological toxicities and no haematological toxicities, as compared to the EGFR negative patients on conventional chemotherapy.

Keywords: Chemotherapy toxicity, Epidermal growth factor receptor, Gefitinib, Lung carcinoma, Platinum-based chemotherapy, Survival

INTRODUCTION

Lung cancer causes more deaths worldwide than any other cancer. According to GLOBACON report 2018, 11.6% cases were of lung cancer in both males and females combined and 18.4% of cancer related deaths were due to lung cancer. According to this report in 2018, 5.9% of all cases were lung cancers amounting to a total of 67,795 new lung cancer cases in India and caused 8.1% deaths among all cancer related deaths [1]. Relative incidence of various histological subtypes of lung cancer has been gradually changed in the recent past. Squamous cell type was the most (49%) common subtype in past few decades, but in recent years adenocarcinoma has become the most common subtype in the United States and most of the Western and Asian countries [2]. However, Squamous Cell Carcinoma (SCC) is still reported as the most common histological subtype in India [3]. Overall, 30-40% of lung cancer patients are diagnosed at an advanced stage, which accounts for losing the most effective timing for surgery, which leads to high mortality [4].

Mok TS et al., Mitsudomi T et al., Maemondo M et al., and several other studies showed that patients with Epidermal Growth Factor Receptor (EGFR) mutation had better response with erlotinib and gefitinib which are EGFR- Tyrosine Kinase Inhibitors (TKI) compared to conventional chemotherapy in patients of advanced Non Small Cell Lung Cancer (NSCLC) [5-10]. Testing for EGFR mutation in advanced NSCLC is now recommended before initiating first line therapy [11,12]. Approximately, 30% of Asian (Japanese) have EGFR mutation as against 20% among white population [13,14]. Frequency of mutation is higher in Asian females and who are never smokers as compared to Asian males and smokers however prevalence is still higher than white population [15-17]. EGFR-TKI targets the active adenoine triphosphate binding site of EGFR kinase. One of the first generation EGFR-TKI used for treatment of NSCLC is gefitinib [18].

The EGFR mutation causes increased downstream signaling which leads to proliferation, differentiation and growth of cells. Tyrosine kinase inhibitors block EGFR derived signal transduction and is a

good prognostic marker in many patients with EGFR mutations. However, the outcome may vary due to presence of uncommon mutation and resistance to TKI's, small sample size [19].

The purpose of this study was to investigate and compare the outcomes of targeted therapy in EGFR mutated NSCLC and conventional chemotherapy in non mutant NSCLC and also evaluate the toxicity profile in mutated and non mutated NSCLC.

MATERIALS AND METHODS

This longitudinal study was conducted in the Department of TB and Respiratory Diseases, Jawaharlal Nehru Medical College and Hospital (JNMCH), Aligarh, Uttar Pradesh, India, involving diagnosed cases of NSCLC. The study was done from July 2017 to November 2019. The study was approved by the Institutional Ethical Committee (1024/FM). Written informed consent was taken from each participant of this study.

Inclusion criteria: Histopathologically-confirmed cases of NSCLC with stage >IIIB on radiology and a mutation status confirmed on Immunohistochemistry (IHC) were included in the study.

The stages were defined according to the stage grouping of eighth edition of TNM as [20]:

- Stage IIIB (tumour size more than 5 cm with involvement of ipsilateral mediastinal or subcrinal nodes or tumour size less than 5 cm with involvement of contralateral mediastinal or hilar; ipsilateral/contralateral scalene or supraclavicular lymph nodes)
- Stage IIIC (tumour size more than 5 cm with involvement of contralateral mediastinal or hilar nodes or ipsilateral/contralateral scalene or supraclavicular nodes)
- Stage IV (any size of tumour with distant metastasis).

Exclusion criteria: Patients with confirmed diagnosis of cancer other than NSCLC on histopathology, patients having history of chemotherapy and radiotherapy and those who refused treatment or did not give consent for the chemotherapy were excluded from the study.

Study Procedure

Patients with symptoms of shortness of breath, chest pain, cough, haemoptysis, loss of appetite and fever were studied. After detailed history and thorough investigations like chest radiograph, Contrast-enhanced Computed Tomography (CECT) thorax, Ultrasonography (USG) guided Fine Needle Aspiration Cytology (FNAC)/biopsy, bronchosocopy-guided FNAC/biopsy, histopathological diagnosis were confirmed. Finally, 120 patients diagnosed with NSCLC on histopathological examination were enrolled. Out of 120 patients 14 patients were excluded due to their unknown EGFR status, 12 patients died before start of treatment, 14 patients were lost to follow-up. Thus, 80 patients were enrolled in the study. After histopathological diagnosis staging of lung cancer done on CECT thorax. NSCLC samples were immunostained with primary and secondary EGFR antibodies and the intensity and proportion of immunoexpression were classified according to the criteria proposed by Kountourakis P et al., [21]:

1+=>10% of cell exhibited weak membranous staining.

2+=>10% of cells exhibited moderate membranous staining.

3+=>10% of cells exhibited intense and complete membranous staining.

Patients were divided into two groups based on treatment:

- Group I: Patients were EGFR positive and started on gefitinib and
- Group II: Patients were EGFR negative and received platinum-based chemotherapy.

Patients of NSCLC with positive EGFR expression were given oral gefitinib 250 mg once a day and EGFR negative NSCLC patients were subjected to cisplatin (75 mg/kg BSA) plus paclitaxel (175 mg/kg BSA) for six cycles at 21 days interval. Treatment protocol was discussed in the board meeting for every patient. The therapy was given till disease progression or till any intolerable toxicity. Both groups were then followed-up clinically and radiologically.

All the biopsy tissues were routinely processed paraffin embedded, 3-4 µmm thick sections cut and stained with Haematoxylin and Eosin (H&E) stains. All the NSCLC on histopathological diagnosis were immunostained with primary and secondary EGFR antibodies and the intensity and proportion of immunoexpression were studied.

Detection of EGFR mutation: Retrieval of antigen was done by microwaving 0.01 M citrate buffer for 15 minutes at 650 W at a pH of 6.0. Three percent hydrogen peroxide in menthol for 15 minutes was used to quench endogenous peroxidase activity. After incubation for 10 minutes blocking solution sections were incubated at 4°C with primary antibodies for 12 hours followed by incubation with biotinylated secondary antibody and with streptavidin horsereadish peroxidase for further 10 minutes. Staining and counterstaining was done by diaminobenzidine chromogen and Mayer's haematoxylin, respectively. Rabbit polyclonal p-Akt (ser473) antibody and rabbit polyclonal p-p44/42 MAPK (Thr 202/Thr 2014) antibody purchased from Thermo (USA) were primary antibodies. Secondary antibody, blocking solution, streptavidin horseradish peroxidase and diamino-benzidine chromogen were all from Thermo (USA).

Outcome Measures

Assessment of tumour for response to treatment was assessed by Computed Tomography (CT) every two months.

a. Primary end points:

Progression free survival: Measured as time from start of treatment to worsening of disease.

Overall response: Measured radiologically as sum of partial response (>30% decrease in sum of diameters of target lesion), complete response (disappearance of all target lesions) and stable disease (does not meet other criteria) according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria version.

1.1. Progressive disease was not included in calculating response rate [22].

b. Secondary end points:

Overall survival (OS): Calculated from start of treatment till death of the patient.

Toxicity profile: Assessed as per the Common Terminology Criteria for Adverse Events version 5.0 [23].

Baseline performance status and ability of the patient to tolerate therapies under cancer therapies were measured by Eastern Cooperative Oncology Group (ECOG) [24]. An ECOG score of 0 indicated patients were asymptomatic and could carry out all their daily activities.

- ECOG 1: Indicated symptomatic but completely ambulatory.
- ECOG 2: Indicated ambulatory and capable of all self-care but unable to perform any work activities up and about more than 50% of waking hours.
- ECOG 3: Indicated perform limited self-care and confined to bed or chair >50% of waking hours.
- ECOG 4: Indicated completely disabled and totally confined to bed.
- ECOG 5: Indicated death [24].

STATISTICAL ANALYSIS

Statistical analysis of data were done using Statistical Package for the Social Sciences (SPSS) version 20.0. Comparison between responses to treatment was measured with the help of independent t-test. Other categorical measurement was calculated using Chi-square test and Fisher's-exact test. Results with p-value <0.05 were considered as statistically significant.

RESULTS

Total 80 patients of NSCLC were studied in which 35 (44%) patients were EGFR positive (group I) and 45 (56%) were EGFR negative (group II) [Table/Fig-1]. The majority of the patients in both the groups were males (80% vs 87%). Total number of adenocarcinoma cases in group I i.e., 19 (54.28%) were higher as compared to group II i.e., 8 (17.7%) and number of SCC cases in group II were higher than group I i.e., 82.22% vs 45.71%. And this difference was significant with p-value of <0.001. The smokers in group II (45) were significantly higher than group I (15) (p-value=0.001). The number of pack years in group II patients were significantly higher than group I (p-value<0.001) [Table/Fig-2]. All the stages (IIIB, IIIC, IV) were distributed independently in both the groups and the difference calculated was not significant (p-value=0.930) [Table/Fig-1]. The performance status in both the groups did not differ significantly with majority of the patients fell under ECOG performance score between 2-4 [Table/Fig-1]. In group I, 51.14% patients had EGFR membranous positivity of 1+, 42.85% patients had 2+ and only 5.71% had 3+ membranous positivity [Table/Fig-1].

Characteristics (%)	EGFR positive n (%)	EGFR negative n (%)
Number of patients	35 (44)	45 (56)
Mean age (years)	58.91	60.11
Histological type		
Adenocarcinoma	19 (54.28)	8 (17.7)
Squamous cell carcinoma	16 (45.71)	37 (82.22)
Smoking history		
Yes	15 (42.85)	35 (77.77)
No	20 (57.14)	10 (22.22)
Clinical stage		
IIIB	15 (42.85)	19 (42.22)
IV	12 (34.28)	16 (35.55)
ECOG performance score		
1	5 (14.28)	5 (11.11)
2	13 (37.14)	21 (46.66)
3-4	17 (48.57)	19 (42.22)
EGFR membranous positivity		
1+	18 (51.14)	
2+	15 (42.85)	
3+	02 (5.71)	

[Table/Fig-1]: Comparison of patient's characteristics.

Pack years	EGFR positive (n=15) n (%)	EGFR negative (n=35) n (%)
0-20	14 (40)	13 (28.8)
21-30	1 (2.85)	14 (31.1)
31-40	0	5 (11.1)
41-50	0	3 (6.6)

[Table/Fig-2]: Smoking history of the patients.

Comparison of efficacy of gefitinib (group I) vs cisplatin plus paclitaxel (group II): All types of responses, excluding progressive disease, were taken in calculating response to treatment. The response rate in group I patients were slightly higher than group II patients (74% Vs 67%) but they did not differ significantly (p-value=0.461) [Table/Fig-3]. In group I patients on gefitinib therapy no complete response was observed. Number of patients with partial response and progressive disease were significantly higher in group II patients on conventional chemotherapy but the number of patients with stable disease were significantly higher in group I (p-value=0.009).

Response	EGFR positive n (%)	EGFR negative n (%)	p-value (t-test)
Complete response	0	7 (15.5)	0.009*
Partial response	10 (28.5)	15 (33.3)	
Stable disease	16 (45.7)	8 (17.7)	
Progressive disease	9 (25.7)	15 (33.3)	

[Table/Fig-3]: Showing overall response rate.
*p-value <0.05 was considered statistically significant (individual p-value not calculated)

Out of 35 EGFR positive patients on gefitinib, patients with weaker membranous positivity (IHC EGFR 1+) had significantly higher number of progressive and stable diseases (p-value=0.015). Complete response was not observed in any patient [Table/Fig-4].

IHC intensity	Partial Response (PR)	Stable Disease (SD)	Progressive Disease (PD)	Total	p-value
1+	2 out of 18	8 out of 18	8 out of 18	18	0.015*
2+	6 out of 15	8 out of 15	1 out of 15	15	
3+	2 out of 2	0	0	2	
Total	10 out of 35	16 out of 35	9 out of 35	35	

[Table/Fig-4]: Types of response based on immunohistochemistry intensity in EGFR Positive NSCLC.
*p-value <0.05 was considered statistically significant

Mean progression free survival in EGFR positive patients on gefitinib were significantly higher than EGFR negative patients on cisplatin plus paclitaxel (5.65 months vs 4.26 months). The mean OS and OS at one year in EGFR positive patients of NSCLC on gefitinib were slightly higher than EGFR negative patients on conventional chemotherapy but not significantly [Table/Fig-5].

Outcome measurement	EGFR positive patients	EGFR negative patients	p-value
Mean progression free survival (months)	5.65	4.26	0.013*
Mean overall survival (months)	7.85	6.72	0.145
Overall survival at one year	22%	15%	0.406

[Table/Fig-5]: Outcome measurement in EGFR positive and negative patients of NSCLC.
*p-value <0.05 was considered statistically significant

The mean progression free survival and mean OS in EGFR positive adenocarcinoma were significantly higher than EGFR positive SCC both on gefitinib [Table/Fig-6].

Outcome measurement	EGFR positive adeno carcinoma (19)	EGFR positive squamous cell carcinoma (16)	p-value
Mean progression free survival (months)	7.05	4	<0.001
Mean overall survival (months)	9.89	5.43	<0.001

[Table/Fig-6]: Outcome measurement in EGFR positive adeno and squamous cell carcinoma.

Comparison of toxicity profile: The haematological toxicity in EGFR negative patients on cisplatin plus paclitaxel was significantly higher than EGFR positive patients on gefitinib (p-value=0.05)). No haematological toxicities were reported in gefitinib group [Table/Fig-7].

Toxicities	Common Terminology Criteria (CTC)		p-value
	Grade 1-2 n (%)	Grade 3-4 n (%)	
Leucopenia	6 (13%)	0	0.05
Anaemia	20 (44%)	9 (20%)	
Thrombocytopenia	15 (33%)	0	

[Table/Fig-7]: Hematological toxicities EGFR negative (cisplatin+paclitaxel) n=45.

In non haematological toxicities, EGFR patients on gefitinib had only grade 1-2 toxicity and no grade 3-4 toxicity were noted according to Common Terminology Criteria (CTC) version 5.0. Patients on

cisplatin plus paclitaxel showed significant grade 3-4 nausea and vomiting. They also showed significantly higher number of patients with alopecia, weightloss and grade 1-2 neuropathy. Grade 1-2 acne like skin rash and deranged liver enzymes were significantly higher in gefitinib group than cisplatin plus paclitaxel group, but it was not life threatening and was subsided by itself [Table/Fig-8].

Toxicity	CTC grade 1-2		p-value	CTC grade 3-4	p-value
	EGFR negative n (%)	EGFR positive n (%)		EGFR negative n (%)	
Nausea	18 (40%)	9 (26%)	0.180	5 (11%)	0.064
Vomiting	12 (27%)	5 (14%)	0.179	6 (13%)	0.032
Alopecia	34 (75%)	0	<0.01*	0	-
Weightloss	15 (33%)	0	<0.01*	0	-
Haematuria	4 (8%)	0	0.070	0	-
Neuropathy	7 (15%)	0	0.016*	2 (4%)	0.502
Diarrhea	5 (11%)	5 (14%)	0.670	0	-
Deranged LFT	0	4 (11%)	0.019*	0	-
Skin rash	0	4 (11%)	0.019*	0	-

[Table/Fig-8]: Non haematological toxicities.
*p-value <0.05 was considered statistically significant

DISCUSSION

The study presents the comparison of treatment outcome in patients of EGFR positive NSCLC on gefitinib and EGFR negative NSCLC patients on cisplatin plus paclitaxel. It was found that EGFR mutant NSCLC patients treated with gefitinib showed a better progression free survival benefit with an acceptable range of haematological and non haematological toxicities and better objective response than EGFR negative patients on conventional chemotherapy. Also, the OS and progression free period were significantly higher in mutant adenocarcinoma than mutant SCC patients.

In this study, the EGFR expressions was seen in 35 (44%) out of 80 patients with no significant difference in frequency of expression between adeno and non adenomatous carcinomas with adeno and SCC in EGFR positive patients were (54.28% Vs 45.71%). The findings are consistent with the results of Chou TY et al., who found EGFR expression in 33 (61.1%) out of 54 of cases with no significant difference in frequency of expression between adenocarcinoma (29 of 43) and non adenocarcinomas (4 of 11; *P*=0.085) [25]. The prevalence of smokers in EGFR positive group were significantly lower than EGFR negative group (42% Vs 78% with p-value=0.001) and also the EGFR positive patients had history of significantly lesser number of pack years (p-value <0.001) of smoking. This was consistent with the study by Sequist LV et al., in which the most prominent predictor of somatic mutations in EGFR was lack of cigarette smoking. Never smokers were 5.6-fold more likely to have an EGFR mutation than ever-smokers (p-value <0.0001). There were no significant association of EGFR expression with age (p-value=0.37) and gender (p-value=0.422) reported in this study which was again consistent with the study by Sequist LV et al., in which no significant association of EGFR expression with age (p-value=0.91) or female gender (p-value=0.91) were observed [26]. The mean progression free survival in EGFR positive patients on gefitinib was 5.65 months which was less from the results of the study by Verduyn SC et al., which was 10.5 months [27]. The less progression free survival may be due to the less number of patients in the study group with most of the patients with poor ECOG performance score (17 out of 35 in ECOG score 3-4) and advanced stage disease and almost equal distribution of the EGFR positive SCC and adenocarcinoma in the first group. Type of EGFR mutation, overexpression and resistance to TKI also plays a major role on progression free survival and OS.

The mean progression free survival was significantly higher in EGFR positive NSCLC than EGFR negative NSCLC (5.65 months vs 4.26 months; p=0.013). It was comparable with the study by Chou TY et al., in which EGFR positive patients as compared to EGFR negative patients showed significantly better progression-free survival (median: 7.6 vs 1.7 months) and OS (median, 14.7 versus 4.7 months) [25]. But the present study showed no significant OS benefit in both the groups. The findings are consistent with the study of Verduyn SC et al., and Fukuoka M et al., who showed similar OS of gefitinib and doublet chemotherapy [27,28]. All the studies allowed for further treatments at disease progression which included cross over of patients on chemotherapy to gefitinib or any other TKI and vice versa which may have leads to similar OS. Second line therapy affects OS which makes it difficult to interpret OS differences between initial treatments. In the present study, the response rate (sum of partial response, complete response and stable disease divided by the total number of patients in the same group) was 74% with EGFR positive patients and 68% with EGFR negative patients on conventional chemotherapy. This was slightly different with a second randomised phase 3 clinical trials by Costanzo R et al., where response rate was 84.6% in mutation positive patients and 51.9% in EGFR negative patients [29]. The discrepancy in the results may be due to less number of patients or geographic, ethnic and histologic variances between the studies.

In the present study, in EGFR positive patients on gefitinib there were no complete response noted and percentage of patients with progressive disease, partial response and stable disease were higher. This is different from the study by Takeda M et al., in which results were 9% patients with complete response, 62% with partial response, 21% with stable disease and 9% with progressive disease [30]. The better response may be due to more number of patients with majority of patients with mutation type of deletion of exon 19 (50%). In the present study, the type of EGFR mutation was not known. The progression free survival and OS in EGFR positive adenocarcinomas were significantly higher than EGFR positive SCC. The results are concordant to the study by Chou TY et al., where all four non adenocarcinomas with EGFR mutations had no response to gefitinib [25].

The most striking difference between the groups was in the toxicity profile of the drugs used in the study. No haematological toxicities were reported in EGFR positive patients on gefitinib as compared to platinum doublet chemotherapy. In non haematological toxicities; alopecia, weightloss, neuropathy, haematuria were significantly higher (p-value <0.05) in conventional chemotherapy and deranged liver enzymes and skin rash were significantly higher in gefitinib group (p-value <0.05). The toxicities were similar as reported by Mitsudomi T et al., in an open label, randomised phase 3 trial where myelosuppression, alopecia, and fatigue were more frequent in the cisplatin plus docetaxel group, but skin toxicity, liver dysfunction, and diarrhea were more frequent in the gefitinib group [6]. The finding is also comparable with two phase III studies-ISEL and IRESSA NSCLC Trial Evaluating Response and Survival versus Taxotere (INTEREST). The studies evaluated the role of gefitinib monotherapy in pretreated patient in which gefitinib was well tolerated, with the most common adverse events being rash (37% vs 10%) and diarrhea (27% vs 9%); mostly CTC grade 1 or 2 in severity [31].

Limitation(s)

The sample size was small and also exact mutation position like exon-19 could be done to further study the response of tumour cells against tyrosin kinase inhibitors.

CONCLUSION(S)

Epidermal growth factor receptor positive and negative patients were almost equally distributed among Increase spaces between words smokers or smokers with less number of pack years. Patients with EGFR positive expression subjected to gefitinib had significant mean progression free survival benefit with an acceptable range of non haematological toxicity and no haematological toxicities than EGFR

negative patients on conventional chemotherapy. No significant OS benefit or difference in response rate were noted between EGFR positive patients on gefitinib and EGFR negative patients subjected to conventional chemotherapy but patients on gefitinib had an acceptable range of toxicity. There were significant progression free survival and overall survival benefit in EGFR positive adenocarcinoma as compared to EGFR positive SCC both on gefitinib.

REFERENCES

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
[2] Wahbah M, Boroumand N, Castro C, El-Zeky F, Eltorky M. Changing trends in the distribution of the histologic types of lung cancer: A review of 4,439 cases. Ann Diagn Pathol. 2007;11(2):89-96.
[3] Behera D. Epidemiology of lung cancer-Global and Indian perspective. JIACM. 2012;13(2):131-37.
[4] Sathiakumar N, Delzell E, Morrisey MA, Falkson C, Yong M, Chia V, et al. Mortality following bone metastasis and skeletal-related events among patients 65 years and above with lung cancer: A population-based analysis of US Medicare beneficiaries, 1999-2006. Lung India. 2013;30(1):20-26.
[5] Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361(10):947-57.
[6] Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, et al. West Japan Oncology Group. Gefitinib versus cisplatin plus docetaxel in patients with non small-cell lung cancer harbouring mutations of the EGFR (WJTOG3405): An open label, randomised phase 3 trial. Lancet Oncol. 2010;11(2):121-28.
[7] Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. North-East Japan Study Group. Gefitinib or chemotherapy for non small-cell lung cancer with mutated EGFR. N Engl J Med. 2010;362(25):2380-88.
[8] Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non small-cell lung cancer (OPTIMAL, CTONG-0802): A multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2011;12(8):735-42.
[9] Han JY, Park K, Kim SW, Lee DH, Kim HY, Kim HT, et al. First-SIGNAL: First-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. J Clin Oncol. 2012;30(10):1122-28.
[10] Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Spanish Lung Cancer Group in collaboration with Groupe Français de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13(3):239-46.
[11] D'Addario G, Felip E; ESMO Guidelines Working Group. Non small-cell lung cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2008;19 Suppl 2:ii39-40.
[12] Azzoli CG, Baker S Jr, Temin S, Pao W, Aliff T, Brahmer J, et al. American Society of Clinical Oncology. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non small-cell lung cancer. J Clin Oncol. 2009;27(36):6251-66.
[13] D'Angelo SP, Pietanza MC, Johnson ML, Riely GJ, Miller VA, Sima CS, et al. Incidence of EGFR exon 19 deletions and L858R in tumour specimens from men and cigarette smokers with lung adenocarcinomas. J Clin Oncol. 2011;29(15):2066-70.
[14] Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, et al. Spanish Lung Cancer Group. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med. 2009;361(10):958-67.
[15] Mitsudomi T, Kosaka T, Endoh H, Horio Y, Hida T, Mori S, et al. Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non small-cell lung cancer with postoperative recurrence. J Clin Oncol. 2005;23(11):2513-20.
[16] Shigematsu H, Lin L, Takahashi T, Nomura M, Suzuki M, Wistuba II, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. J Natl Cancer Inst. 2005;97(5):339-46.
[17] Saijo N, Takeuchi M, Kunitoh H. Reasons for response differences seen in the V15-32, INTEREST and IPASS trials. Nature reviews. Clinical Oncology. 2009;6(5):287-94.
[18] Ettinger DS, Wood DE, Akerley W, Bazhenova LA, Borghaei H, Camidge DR, et al. NCCN Guidelines Insights: Non Small Cell Lung Cancer, Version 4.2016. J Natl Compr Canc Netw. 2016;14(3):255-64.
[19] Yoon HY, Ryu JS, Sim YS, Kim D, Lee SY, Choi J, et al. Clinical significance of EGFR mutation types in lung adenocarcinoma: A multi-centre Korean study. PLoS One. 2020;15(2):e0228925.
[20] Lababede O, Meziane MA. The eighth edition of TNM staging of lung cancer: Reference chart and diagrams. Oncologist. 2018;23(7):844-48.
[21] Kountourakis P, Pavlakis K, Psyrri A, Rontogianni D, Xiros N, Patsouris E, et al. Clinicopathologic significance of EGFR and Her-2/neu in colorectal adenocarcinomas. Cancer J. 2006;12(3):229-36.
[22] Schwartz LH, Litière S, De Vries E, Ford R, Gwyther S, Mandrekar S, et al. RECIST 1.1-Update and clarification: From the RECIST committee. European Journal of Cancer. 2016;62:132-37.
[23] US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Published November 27, 2017.
[24] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.
[25] Chou TY, Chiu CH, Li LH, Hsiao CY, Tzen CY, Chang KT, et al. Mutation in the tyrosine kinase domain of epidermal growth factor receptor is a predictive and prognostic factor for gefitinib treatment in patients with non small cell lung cancer. Clin Cancer Res. 2005;11(10):3750-57.
[26] Sequist LV, Joshi VA, Jänne PA, Muzikansky A, Fidias P, Meyerson M, et al. Response to treatment and survival of patients with non small cell lung cancer undergoing somatic EGFR mutation testing. Oncologist. 2007;12(1):90-98.
[27] Verduyn SC, Biesma B, Schramel FM, van der Scheer FW, Langenfeld MK, de Peuter MA et al. Estimating quality adjusted progression free survival of first-line treatments for EGFR mutation positive non small cell lung cancer patients in The Netherlands. Health Qual Life Outcomes. 2012;10:108.
[28] Fukuoka M, Wu YL, Thongprasert S, Sunpaweravong P, Leong SS, Sriuranpong V, et al. Biomarker analyses and final overall survival results from a phase III, randomised, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non small-cell lung cancer in Asia (IPASS). J Clin Oncol. 2011;29(21):2866-74.
[29] Costanzo R, Piccirillo MC, Sandomenico C, Carillio G, Montanino A, Daniele G, et al. Gefitinib in non small cell lung cancer. J Biomed Biotechnol. 2011;2011:815269.
[30] Takeda M, Okamoto I, Nakagawa K. Survival outcome assessed according to tumour response and shrinkage pattern in patients with EGFR mutation-positive non small-cell lung cancer treated with gefitinib or erlotinib. J Thorac Oncol. 2014;9(2):200-04.
[31] Armour AA, Watkins CL. The challenge of targeting EGFR: experience with gefitinib in nonsmall cell lung cancer. Eur Respir Rev. 2010;19(117):186-96.

PARTICULARS OF CONTRIBUTORS:
1. Consultant, Department of TB and Respiratory Diseases, Asarfi Multispeciality Hospital, Ballia, Uttar Pradesh, India.
2. Assistant Professor, Department of TB and Respiratory Diseases, JN Medical College, Aligarh, Uttar Pradesh, India.
3. Assistant Professor, Department of TB and Respiratory Diseases, Shri Atal Bihari Vajpayee Government Medical College, Faridabad, Haryana, India.
4. Professor, Department of TB and Respiratory Diseases, JN Medical College, Aligarh, Uttar Pradesh, India.
5. Professor, Department of TB and Respiratory Diseases, JN Medical College, Aligarh, Uttar Pradesh, India.
6. Professor, Department of TB and Respiratory Diseases, JN Medical College, Aligarh, Uttar Pradesh, India.
7. Professor, Department of Pathology, JN Medical College, Aligarh, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Huma Firdaus,
Assistant Professor, Department of TB and Respiratory Medicine, Shri Atal Bihari Vajpayee Government Medical College, Faridabad, Haryana, India.
E-mail: huma2107@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Aug 05, 2022
- Manual Googling: Oct 29, 2022
- iThenticate Software: Nov 08, 2022 (22%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Aug 04, 2022**
Date of Peer Review: **Sep 14, 2022**
Date of Acceptance: **Nov 09, 2022**
Date of Publishing: **Jan 01, 2023**