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Original Article

EGFR-TKI Sensitizing Mutation Rate in Adenocarcinoma of Lung

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ABSTRACT

Objective: To assess EGFR-TKI sensitizing mutation rate in patients having lung adenocarcinoma and its association with smoking status.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Medical Oncology, Jinnah Postgraduate Medical Center, Karachi Pakistan from Apr to Dec 2019.

Methodology: One eighty-seven patients aged 20-75 years, of either gender presented with confirmed diagnosis of adenocarcinoma of lung were included in the study. The data regarding characteristics of patients such as gender, age, smoking status, ethnicity and religion were recorded on pre-designed proforma. The examination of EGFR mutation in plasma and tissue specimens was done by the Real-Time polymerase chain reaction assays. SPSS version 23 was used to analyze data.

Results: Out of 187, 65(34.8%) patients presented with EGFR TKI-sensitizing mutation and among them 48(73.8%) patients had exon 19 deletion and 17(26.2%) patients had exon 21 L858R point mutation. In patients with positive EGFR, 90.8% were never smokers and 9.2% were smokers or ever smokers. The statistically significant relationship was found between EGFR mutation and smoking status (p=0.001).

Conclusion: This study showed EGFR-TKI mutation frequency as 34.8% which in contrast to western studies where EGFR mutation is less frequent. Further, never smokers are at greater risk of EGFR mutation.

Keywords: Adenocarcinoma EGFR-TKI sensitizing, Exon 21, Exon 19, Lung cancer, Mutation, Smoking status.

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INTRODUCTION

Lung cancer (LC) remains the world's leading cause of cancer mortality, accounting for 19% of all cancer-related mortalities.[1] Non-small cell lung cancer (NSCLC) is more frequent and accounts for 85% of primary LC.[2] Adenocarcinoma (AC) is one of the most common histopathological subtype of NSCLC and comprises almost 40% of all LC.[3]

Among all the mutations found in lung cancer like ALK, PIK3 CA, KRAS, the epidermal growth factor (EGFR) mutation is the most frequent oncogenic driver event in NSCLC. LC with EGFR mutations are more common in non-smokers with AC, young females and Asians. Commonly occurring classical EGFR mutations are Exon 19 deletion (19del) and Exon 21 (L858R) point mutation.[4] These mutation; 19del and L858R point mutation; comprises for 33% and 41% of the cases respectively and are closely related to EGFR inhibitor therapy response.[5]

The etiology of EGFR mutation is still debatable. It could be attributed to environmental or genetic factors. However, the up-regulation of EGFR expression is correlated with tumor growth.[6] The treatment planning for patients with advanced lung carcinoma, specifically NSCLC, is sensitive to EGFR mutations and ALK gene rearrangements.[7] The TKI sensitizing EGFR mutation is responsive to tyrosine kinase inhibitors like gefitinib, erlotinib, and afatinib. Patients who have been provided with EGFR-tyrosine kinase inhibitors to treat advanced NSCLCs in several clinical trials have resulted in increased response rate or prolonged progression free survival (PFS), improved quality of life and better tolerance than platinum-based chemotherapy in the first-line settings.[8]

Owing to the importance of EGFR expression in treatment planning, it is substantial to assess EGFR-TKI sensitizing mutation rate in patients having lung adenocarcinoma and its association with smoking status. This study would add to local statistics of EGFR mutation. As there is dearth of data in this context locally, the study would aid in patient better treatment selection.

METHODOLOGY

The cross-sectional study was carried out at the Department of Medical Oncology, Jinnah Postgraduate Medical Center, Karachi Pakistan, from April to December 2019. Estimated sample size was 187 patients,

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calculated on Open Epi sample size calculator taking frequency of positive EGFR as 39.1%,[9] margin of error as 7% and 95% confidence level. Non-random consecutive sampling technique was applied for sample selection.

Inclusion Criteria: Patients aged 20-75 years, of either gender presenting with confirmed diagnosis of advance adenocarcinoma of lung were included in the study.

Exclusion Criteria: Patients who received previous chemotherapy or radiotherapy were excluded from the study.

The approval from Ethical Review Committee [Ltr no. F.2-81/2019-GENL/19159/JPMC] was taken before the conduct. The data regarding characteristics of patients such as gender (male/female), age (<50 years/ ≥50 years), smoking status (Current or ever smokers/ never smokers), ethnicity (Sindhi/Punjabi/ Pathan/ Balochi/Urdu Speaking) and religion (Muslims/Non-Muslims) were recorded on pre-designed proforma. The examination of EGFR mutation in plasma and tissue specimens was done by the RT-PCR (Real-Time polymerase chain reaction) assays.

SPSS ver 23 was used to analyze data. Frequency and percentage was reported for qualitative variables like age groups, gender, ethnicity, religion, smoking status and EGFR mutations. Chi-square/Fisher exact test was applied to see the difference in the frequency of EGFR with respect to age, gender, ethnicity, religion and smoking status. The *p*-value ≤0.05 was taken as statistically significant.

RESULTS

Total 187 patients presenting with lung adenocarcinoma were included in the study. About 71 patients were of age <50 years (38%) and 116 patients were of age ≥50 years (62%). Majority of the patients were males 116(62%), Sindhi 90(48.1%) and Muslims 160 (85.6%). Out of 187, 52 patients were current smokers or ever smokers (27.8%) whereas 135 patients were never smokers (72.2%) (Table-I).

Out of 187, 65(34.8%) patients presented with EGFR TKI-sensitizing mutation and among them 48 (73.8%) patients had exon 19 deletion and 17(26.2%) patients had exon 21 L858R point mutation (Figure).

Most of the patients with EGFR positive mutation were of age ≥50 years 43(66.2%), males 42(64.6%), Sindhi 28(43.1%) and Muslims 57(87.7%). No statistically significant relationship was found between EGFR positive and negative groups in terms of age (*p*=0.397), gender (*p*=0.595), ethnicity (0.093) and religion (*p*=0.545). In patients with positive EGFR, 59 were never smokers (90.8%) and 6 were current smokers or ever smokers (9.2%). The statistically significant rela-tionship was between EGFR mutation and smoking status (*p*=0.001) (Table-II).

Table-I: Descriptive Statistics of Study Variables (n=187)

Age groups	n(%)
<50 years	71(38)
≥50 years	116(62)
Gender	
Male	116(62)
Female	71(38)
Ethnicity	
Sindhi	90(48.1)
Punjabi	26(13.9)
Pathan	17(9.2)
Baloch	12(6.5)
Urdu Speaking	42(22.7)
Religion	
Muslim	160(85.6)
Non-Muslim	26(14.1)
Smoking Status	
Current smoker or ever smoker	52(27.8)
Never smoker	135(72.2)

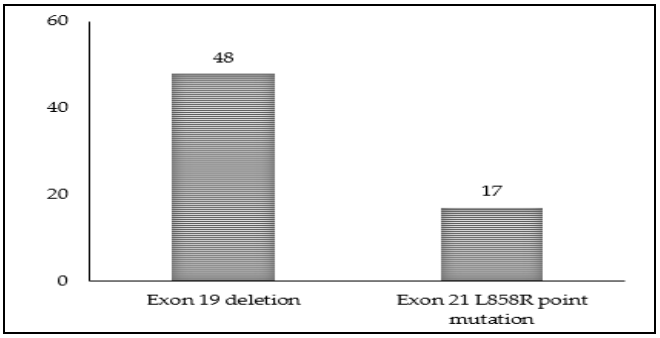

Figure: Frequency Distribution of Mutation Subtypes (n=187)

Table-II: Frequency of EGFR Mutations with respect to different variables (n=187)

Variables	EGFR Mutations		*p*-value
	Positive	Negative	
Age group			
< 50 years	22(33.8%)	49(40.2%)	0.397
≥50 years	43(66.2%)	73(59.8%)	
Gender			
Male	42(64.6%)	74(60.7%)	0.595
Female	23(35.4%)	48(39.3%)	
Ethnicity			
Sindhi	28(43.1%)	62(50.8%)	0.093
Punjabi	10(15.4%)	16(13.1%)	
Pathan	2(3.1%)	15(12.3%)	
Balochi	5(7.7%)	7(5.7%)	
Urdu speaking	20(30.8%)	22(18%)	
Religion			
Muslim	57(87.7%)	103(84.4%)	0.545
Non-Muslim	8(12.3%)	19(15.6%)	
Smoking Status			
Current smoker or ever smoker	6(9.2%)	46(37.7%)	0.001
Never smoker	59(90.8%)	76(62.3%)	

DISCUSSION

In Pakistan, LC is ranked 3rd most prevalent malignancy, with almost 9,771 new cases and 9,260 LC-related deaths recorded in GLOBOCAN Pakistan in 2018.[10] The function of EGFR TKIs in patients with NSCLC having EGFR mutations has come out as an essential oncogenic outcome and EGFR status has become a significant prognostic factor in LC.[11] Several researches have revealed that frequency of EGFR mutation is higher in Asia-Pacific countries ranging from 20-70% (Average 47%).[12-14] Hence, in the present we have evaluated the frequency of EGFR mutation among patients with advance adenocarcinoma of lung.

In the present study from Karachi Pakistan tertiary care hospital, which caters mainly to Sindh patients; especially from the interior of Sindh, the overall frequency of EGFR TKI-sensitizing mutation was 34.8%. This is almost similar to the study conducted in India, which revealed an average prevalence of 32% of EGFR mutations.[11] Other researchers conducted studies in the central and southern parts of India also showed a frequency of EGFR TKI-sensitizing mutation ranging between 16-43%.[15,16] It indicates that these variations can be due to discrepancies in environmental, ethnic and geographic differences. In region of Asia-Pacific, Singapore showed the lowest frequency of EGFR mutation as 40% ranging from 39-43%, whereas Taiwan had the highest frequency of EGFR mutation of 57% ranging from 36-76%. However, in south-east Australia lowest frequency of EFGR TKI-sensitizing mutation was noted ranging from 7-36%.[17,18] In South America the widest range of frequency of EGFR mutation was reported from 9-67%.[13,19] In Europe also great variation was observed in EGFR mutation ranging from 7.3-41%.[12,14,16,20]

In the present research, we found del19 to be higher than L858R point mutation with 73.8% and 26.2%. In a Pakistani study, ninety-four patients were enrolled having lung adenocarcinoma. The studied showed that 29% patients had EGFR mutation positive; where in 48% mutations were on L858R point mutation whereas 44% patients had del19.[21] We found discordance in results might be because it was a lab-based study whereas our study was hospital based. Further dissimilar frequency of higher L858R point mutation than del19 has been found in the Indian study by Kumari *et al.* which showed frequency of L858R point mutation as 51% whereas del19 as 39% among total EGFR TKI sensitizing mutation.[11] Similarly in the study by Kim *et al.* (53% versus 40%) and Yotsukura *et al.* (56% versus 40%) also showed higher L858R point mutation than del19.[12,14] The differences in EGFR mutation frequencies among countries are more likely due to variations in case number of tested groups, case selection for testing and ethnicity.[22]

Irrespective of region female gender showed significantly higher proportion of positive EGFR mutation. However, in present study we found higher proportion of male gender with positive EGFR mutation than females. Similar results were obtained in a study conducted at Bangladesh which showed positive EGFR mutations in 25.5% of males and 14.3% of females.[23] Ahmed *et al*. also found proportion of males higher than females (60% vs 40%).[24] But in several western studies higher percentage of females with positive EGFR mutations were found than males.[13]

Several studies have found significant relationship between smoking status and EGFR mutations frequency in NSCLC patients.[22] We also found similar findings among Pakistani patients, 90.8% of the patients with positive EGFR mutations were non-smokers and only 9.2% were smokers, hence smoking status was strongly associated with positive EGFR mutations with p-value=0.001. Similarly in a study by Kumari *et al*. 36.8% of the patients with EGFR mutation were smokers whereas 63.2% were non-smokers (p=0.05).[11] Further, in a systematic review of African and Middle East countries also showed higher frequency of positive EGFR mutations among non-smokers as compared to ever-smokers.[22] Whereas in a Pakistani study conducted on patients with lung AC showed that positive EGFR mutation was present in 25% of the patients, but they found insignificant difference in frequency of EGFR mutation with respect to smoking status (p=0.95).[25]

CONCLUSION

This study showed the frequency of EGFR-TKI mutation was 34.8% which in contrast to western studies where EGFR mutation is less frequent. Further, never smokers are at greater risk of EGFR mutation.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

SS & GH: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

BR & VR: Data acquisition, data analysis, concept, critical review, approval of the final version to be published.

TA & BM: Critical review, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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