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Review Article

Frequency of EGFR mutation and EML4-ALK fusion genes in patients with non-small cell lung carcinoma

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ABSTRACT

Lung cancer ranks among the top causes of mortality worldwide. Non-small cell lung cancer (NSCLC) accounts for the majority of cases. Advances in genomics have identified potential biomarkers to predict therapeutic strategies in lung cancer. Despite the availability of targeted drugs such as tyrosine kinase inhibitors, a substantial proportion of patients still experience problems such as drug resistance. Mutations in genes like epidermal growth factor receptor (EGFR) and EML4ALK have already been established with altered clinical outcomes in NSCLC patients. With a focus on non-small cell lung cancer (NSCLC),the study was conducted at indraprastha apollo hospital in new delhi. With their informed agreement, 90 patients who were admitted between january 2012 and december 2015 and who had been diagnosed with fine-needle aspiration cytology (FNAC)/biopsy utilizing computed tomography (CT) guidance were included in the study. Excluded from the study were those receiving radiation therapy or chemotherapy concurrently. Information on age, gender, a thorough medical history, a history of smoking, and any additional co-morbidities were taken from medical records. Investigation of EGFR mutation and EML4-ALK gene fusion in NSCLC patients was done. Eleven (11%) were positive and (89%) were negative for EGFR mutations. The positive cases were analyzed for exon 19 deletion and exon 21 (L858R) substitution and found positive for (60%) and (40%) of cases, respectively. Amongst 90 EGFR-negative patients, 4 (4.4%) had the EML4-ALK fusion gene, while 86 (95.5%) were negative for EML4-ALK. This study's EML4-ALK fusion gene incidence was only (4%). Females have a higher occurrence of EGFR mutations than males (p=0.003) and the frequency of EGFR mutation was higher in non-smokers. The overall incidence of the EML4-ALK fusion gene was (4.44%) and was higher in patients below 60 years of age.

Keywords: Non-small cell lung cancer (NSCLC), Mutations, Epidermal growth factor receptor (EGFR), EML4-ALK fusion gene

INTRODUCTION

Treatment of cancer continues to present challenges due to its intricate nature and diverse mutations affecting multiple genes that drive its development. Approximately, 90% of global lung cancer cases result from smoking and tobacco abuse, making it the foremost cause of cancer-related deaths. Progression of lung cancer is also impacted by factors like exposure to radon gas, asbestos, air pollution, and chronic infections.[1] Although there has been development in the diagnosis and treatment of lung cancer, prognosis remains low, with a reported 15% survival rate and a life expectancy of up to 5 years.[2] In India, 1,392,179 cases of lung cancer were reported in 2020.[3] Lung cancer is generally categorized histologically as non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC).[4] Among NSCLC patients, adenocarcinoma is the most common histological form, which originates in the outer edges of the lung and is generally diagnosed at an advanced stage, and it has limited treatment options.[2] Various cytotoxic chemotherapeutic drugs like taxane, platinum, and gemcitabine are used for treatment but have shown poor clinical outcomes and are associated with various side effects, creating challenges for both clinicians and patients who are dealing with advanced NSCLC.[5]

Mutations in several genes have already been established in association with altered therapeutic outcomes in advanced NSCLC patients. These include lung cancer can be caused by various gene mutations and alterations, including those in EGFR, MET, VEGF, KRAS, HER2, EML4-ALK, PIK3CA, BRAF, IGF1R, ROS1, and KIF5B, among others.[6,7]

Epidermal growth factor receptor (EGFR) regulates epithelial tissue development and maintains homeostasis. Mostly in

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pathological settings, lung EGFR is a driver of tumorigenesis.[8] Bioinformatics has been playing a key role by connecting the gap between initial discovery phases like an experimental draft to result in analysis and independent validation of identified markers or pathways.[9] Some of the databases are PubChem, ChemSpider, and Kyoto Encyclopedia of Genes and Genomes (KEGG).[10] It has been found that activating mutations in NSCLC is associated with the prediction of response to tyrosine kinase inhibitors (TKIs). In addition to this fusion gene, EML4-ALK is associated with altered response to ALK and cMET inhibitors, with the introduction of targeted therapies.[11,12] The individualized, targeted therapy requires accurate histological and pathological findings accompanied by genomic testing of certain biomarkers predictive of therapeutic response. EGFR is being increasingly acknowledged as a biomarker for resistance in tumors, as drug pressure can lead to its amplification or the emergence of secondary mutations.[2] EGFR-mutant lung squamous cell carcinoma (SCC) exhibits a more unfavorable outlook compared to EGFR-mutant adenocarcinoma.[13]

The response to EGFR-TKIs is more favorable in NSCLC patients with adenocarcinoma histology, female gender, asian ethnicity, and nonsmokers compared to others.[14] The presence of EML4-ALK is common in adenocarcinoma patients (nonsmokers), with an incidence rate of 2–7% among all NSCLC patients. The prevalence of EGFR mutations in indian NSCLC patients has been in the range of 23–44%.[15]

MATERIALS AND METHODS

This study was carried out at indraprastha apollo hospital in new delhi, focusing on non-small cell lung carcinoma (NSCLC). It included 90 patients admitted between january 2012 and december 2015, diagnosed using CT-guided FNAC/biopsy, and who participated with their informed consent. Due to severe illness, patients already on chemotherapy or radiotherapy were excluded from the study, as they have not given consent to participate in the study. The data were obtained from medical records, including age, gender, detailed history along with history of smoking and any other comorbidities.

The NSCLC pathway analysis and clinical databases were downloaded from the KEGG pathway database and PubMed as study material for future analysis. EGFR mutation analysis was done by polymerase chain reaction (PCR) method using biopsy, fine-needle aspiration cytology (FNAC), or pleural fluid specimen, and EML4-ALK fusion was done by fluorescence in situ hybridization (FISH) technique on biopsy/cell block specimen. EGFR mutation analysis was carried out by PNAClamp™ EGFR Mutation Detection Kit (Panagene Korea, PNAClamp™ EGFR Mutation Detection Kit ver. 2) that allows for quick and sensitive detection of EGFR mutations within just 2 hours. It exhibits high sensitivity, even with a small DNA sample (25–50 ng). The kit's detection limit for mutated genes mixed with wild-type DNA is less than 1%.

The study of ALK gene rearrangement in non-small cell lung cancer (NSCLC) employed the tricolor ZytolightSPEC ALK/EML4 TriCheck Probe. This probe is specifically designed to identify inversions [inv (2) (p21p23)], a common occurrence in NSCLC. Detection of inv (2) (p21p23) involves a distinct green/orange fusion signal from ALK, leading to separate green and orange signals, along with a split in the EML4-specific blue signal, resulting in an additional blue signal. This kind of inversion is difficult to identify using dual-color FISH probes, where ALK and EML4 genes are closely mapped, making the gap between the orange and green signals tiny. To overcome errors in signal interpretation, especially in borderline cases, the SPEC ALK/EML4 TriCheckTM Probe allows for simultaneous checking of the EML4 rearrangement status. The kit offers accuracy in detecting these inversions when compared to traditional dual-color FISH probes.

To interpret ALK/EML4, the invasive part of the NSCLC specimen was identified on a corresponding hematoxylin and eosin-stained slide. The evaluation process includes counting a minimum of 50 nonoverlapping cells from two specific areas with well-distributed and distinguishable nuclei. ALK rearrangement was detected by either ALK break apart (one green/one orange). Number of cells with one green, one separate orange and one additional blue signals indicates abnormal cells, while two fusion signals and two blue signals indicates for normal cells. A positive ALK test result was achieved if 15% of the counted cells exhibited ALK rearrangements.

RESULTS

Throughout the study, 90 patients were examined for EGFR mutation and EML4-ALK fusion gene. Among them, 56 (62.2%) were males, and 34 (37.8%) were females. The median age was 60 years (range). Smoking history was reported in 12 patients (13.3%), while 78 (86.7%) were nonsmokers. Table 1 demonstrates the patient characteristics included in the study. The study found EGFR mutation in 10 (11%) patients, and the most frequently detected mutation was exon 19 deletion (60%) followed by exon 21 substitutions (40%) [Table 2].

EGFR mutation was more prevalent in females (80%) compared to males (20%), and this difference was statistically significant ($p = 0.003$) according to Table 3. In addition, nonsmokers had a higher frequency of EGFR mutation than smokers, though no statistical significance was seen ($p=0.188$). Among the other parameters assessed, age and incidence among indians and patients from other countries did not show any statistical significance. The overall incidence of the EML4-ALK fusion gene in our study was 4.44%. EML4-ALK

Table 1: Patient demographics

Patient characteristics	Patient number (N = 90)	
	N	Percentage (%)
Age group		
More than 60 years	52	57.8
Less than 60 years	38	42.2
Sex		
Male	56	62.2
Female	34	37.8
History of smoking		
Smoker	12	13.3
Non smoker	78	86.7
Nationality		
Indian	72	80
Others	18	20
Histology	Adenocarcinoma	
Stage at diagnosis	Stage IV	

Table 2: Frequency of EGFR mutation and EML4-ALK fusion gene

Mutation type	Patient number (N = 90)	
	N	Percentage
EGFR negative	80	88.9
EGFR positive	10	11.1
• Exon 19 deletion	6	60
• Exon 21 (L858R) substitution	4	40
EML4-ALK fusion gene	4	4.44

EGFR: Epidermal growth factor receptor.

fusion gene incidence was observed to be higher in patients below 60 years of age. However, no statistical significance was seen for age, gender, history of smoking, and Indian/nonIndians [Table 4].

Table 3: Patients demographics, according to EGFR mutation

Patient characteristics	EGFR mutated		EGFR wild		p value
	N (10)	Percentage	N (80)	Percentage	
Age group					0.293
More than 60 years	4	40	46	57.5	
Less than 60 years	6	60	34	42.5	
Sex					0.003
Male	2	20	54	67.5	
Female	8	80	26	32.5	
History of smoking					0.188
Smoker	0	0	12	15	
Non smoker	10	100	68	85	
Nationality					1.000
Indian	8	80	64	80	
Others	2	20	16	20	

EGFR: Epidermal growth factor receptor.

Table 4: Patient demographics, according to EML4-ALK fusion gene

Patient characteristics	ALK positive		ALK negative		p value
	N (4)	Percentage	N (86)	Percentage	
Age group					0.81
More than 60 years	1	50	48	55.8	
Less than 60 years	3	50	38	44.2	
Sex					0.60
Male	2	50	54	62.8	
Female	2	50	32	37.2	
History of smoking					0.42
Smoker	0	0	12	13.95	
Non smoker	4	100	74	86.05	
Nationality					0.12
Indian	2	50	70	81.4	
Others	2	50	16	18.6	

DISCUSSION

With ongoing research in pulmonary oncology and the introduction of target therapies for patients with advanced stages of NSCLC, the overall survival has improved to more than 1 year.[11] Molecular profiling of the tumor serves as a guide for optimizing clinical treatment decisions and better management in cases of NSCLC.[16] NSCLC serves as a perfect disease for map-based and pathway-based studies. For this study, the KEGG pathway database served as the source of understanding the interconnection of EGFR and EML4-ALK with NSCLC in the beginning. The precision medicine is totally based on molecular characterisation in advance non-small cell lung cancer (NSCLC). Determination of biomarkers (EGFR, ALK, ROS1, BRAF, RET, NTRK and PD-L1 gene) is mandatory to tailor the therapy.[17]

The occurrence of EGFR mutations has been studied in various ethnicities, which revealed different incidence rates. Previous studies have reported rates of 10–15% in north americans and europeans, 10% in african americans, 24% in koreans, 50.5% in taiwanese, 26.3% in japanese, and 38% in chinese populations.[7] In our study, we observed a 11% incidence of EGFR mutations, with a significantly higher frequency among females (p=0.003) compared to males. These findings align with previous research indicating a female predominance in EGFR mutations.[7,18,19] Epidemiological studies conducted in india and other countries have reported EGFR mutation incidences ranging from 23% to 51.8%, with a female predominance in india, 13% in caucasians, and 47% among asians. Notably, the south indian population exhibited a higher incidence rate (47%) compared to the north indian population (27%).[20] While our study found a higher frequency of EGFR mutations in nonsmokers, no statistically significant correlation was observed. Several studies have consistently reported a higher occurrence of EGFR mutations among nonsmokers or individuals who have never smoked in NSCLC.[14]

The potential implications of EGFR mutations in association with therapeutic outcomes and the patient's benefit have already been established.[18,21] The "Iressa Pan-Asia Study (IPASS)" enrolled east asian patients with untreated stage IIIB or IV adenocarcinoma, comparing gefitinib to carboplatin and paclitaxel chemotherapy. The study examined the clinical outcome of EGFR mutations, which were present in 60% of the patients.[22]

Moreover, various clinical trials have documented treatment outcomes and consistently found that targeted therapies such as gefitinib, erlotinib, or afatinib provide superior results when compared to chemotherapy, particularly in cases of EGFR-mutated NSCLC. The identification of mutations and subsequent selection of targeted therapy have been firmly established and are widely employed to achieve enhanced clinical outcomes. The second-generation TKI drug afatinib is recommended to manage advanced NSCLC in patients with EGFR mutations in exon 19 or exon 21 (L858R). Conversely, chemotherapy remains the preferred option for NSCLC patients without targetable driver mutations in EGFR.[23] Consequently, multiple reports have demonstrated that the subset of EGFR mutation-positive patients who receive TKIs exhibit improved response rates, better quality of life, and increased survival.[20,23]

We report 60% and 40% mutation frequencies in exon 19 deletion and exon 21 of the EGFR gene in our study population which is per previous studies.[24] The incidence of EGFR mutations in our results corroborates with those reported in previous studies, with 67% and 29% frequencies in exon 19 mutation and exon 21, respectively.[24] Studies show that exon 19 EGFR mutations benefit from TKIs (response 86% vs. 67%; p = 0.171) compared to exon 21 mutations.[22,23] Most EGFR-positive patients benefit from TKIs.

In our study, we analyzed EML4-ALK mutations among NSCLC patients. The inversion in the short arm of chromosome 2 causes fusion among the ALK gene and EML4 gene, most observed in lung cancer.[7] This gene rearrangement transforms/results into transfusion/chimeric protein, which constitutively expresses ALK kinase activity. The therapeutic options are designed to target and inhibit ALK mutations and were first reported in anaplastic large cell lymphomas and subsequently in myofibroblastic tumors and a subset of NSCLC.[25]

We found a 4.44% frequency of EML4-ALK positivity in our study, and a similar trend has been reported in the asian and western populations.[26] The reported overall frequency of the EML4-ALK fusion gene in patients with NSCLC is around 14.5%–44.5% in previous studies.[27] Doval *et al.*, have reported the incidence of EML4-ALK positivity as 2.7%.[7] Similarly, they have also reported the incidence of EML4-ALK positivity as 3%.[7]

ALK fusion gene-positive lung carcinomas have been observed more commonly among younger age groups and adenocarcinomas.[28] Similar findings were seen in our study of ALK fusion gene frequency; however, the further subgroup analysis did not show any statistical significance. Among the other parameters assessed for ALK fusion gene frequency, we did not find any significant difference in incidence when compared between smoker and nonsmoker subgroups, males and females, and between indians and others.

In addition to this study have reported the incidence of the EML4-ALK fusion gene, especially high in adenocarcinoma lacking EGFR/K-RAS mutation. The discovery of mutually

exclusive occurrences of EML4-ALK and EGFR mutations implies that ALK mutations could serve as a promising therapeutic target in EGFR wild-type lung cancer.[29,30] Patients with NSCLC and EGFR mutations, ALK, or ROS1 rearrangements commonly display reduced PD-L1 levels and fewer tumor mutations. Immunotherapy targeting PD-1/PD-L1 pathway has revolutionized the treatment landscape of NSCLC. Nevertheless, most patients with EGFR mutation responded poorly to anti–PD-1/PD-L1 inhibitors.[31] Immune checkpoint inhibitors (ICIs) that target programmed cell death protein-1/programmed cell death ligand-1 axis have significantly shifted the treatment paradigm in advanced NSCLC, clinical benefits of these agents are limited in patients with EGFR-mutated NSCLC. Several predictive biomarkers (e.g., programmed cell death ligand-1 expression, tumor mutation burden), which have been validated in EGFR-wild type NSCLC, however, are not efficacious in EGFR-mutated tumors, suggesting the unique characteristics of tumor microenvironment of EGFR mutated NSCLC.[32,33,34]

CONCLUSION

The advancement of tools used for genomic expression and identification of small mutations in cancer cells improved the relationship between cancer progression and clinical outcomes of target-based treatment. The study shows the concomitant EGFR mutation and ALK gene along with other clinical and pathological correlations that would help in improving targeted treatment beneficial for NSCLC patients. However, in the future, there will be a need for precise studies to find other alterations caused due to the mutation explained above using recent advanced tools.

In recent times, the treatment landscape of NSCLC has undergone significant changes with the introduction of targeted therapies and immunotherapies. Molecular and immunological methods have proven to be successful in diagnosing NSCLC. Numerous studies have identified mechanisms of resistance to various TKIs targeting EGFR, c-MET, and ALK, These mechanisms include the development of mutations in the drug target as well as the activation of alternative signaling pathways. In addition, there have been proteomics studies focused on mutational investigations in NSCLC. To date, a total of 35 differential metabolites and 2202 genes with significant differences have been identified. Osimertinib is currently the widely accepted first-line treatment for NSCLC with EGFR mutations.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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