

Investigation of EGFR Mutation and ALK Gene Rearrangement Rates in Lung Adenocarcinoma Patients in Mardin

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Abstract

Objective: Non-Small Cell Lung Cancer (NSCLC) is a heterogeneous group of tumors comprising different histologic subtypes and genetic mutations. Important mutations are EGFR (Epidermal Growth Factor Receptor), ALK (Anaplastic Lymphoma Kinase) rearrangement and ROS 1 rearrangement. This study aimed to determine the mutation rates of lung adenocarcinoma patients admitted to Mardin State Hospital Oncology clinic and to review the literature on the term mutually exclusivity.

Materials and Methods: The records of patients admitted to Mardin State Hospital Medical Oncology Clinic between 2014-2018 were retrospectively analyzed. The descriptive statistics for continuous variables mean/median; for categorical variables, frequency (n) and percentage (%) were shown.

Results: There were 39 lung adenocarcinoma patients (30.2%) among 130 lung cancer patients. The median age of female patients was 49.31 (27-74), while the median age of male patients was 58.87 (43-78). There were 6 EGFR mutant (15.4%) patients and 2 (5.1%) patients with ALK rearrangement. There were no ROS-1 positive patients.

Conclusion: This study indicates that EGFR mutation rates may be very low in Turkey compared to the literature and ALK rates may be close to the literature. To determine the actual mutation rates and factors affecting genetic alterations in Turkey, there are needed to further studies.

Keywords: EGFR, ALK, Mutually Exclusive, Mardin, Turkey

Introduction

Non-Small Cell Lung Cancer (NSCLC) is a heterogeneous group of tumors comprising different histologic subtypes and genetic mutations, accounting for almost 85-90% of lung cancers. (1, 2) Important mutations are EGFR (Epidermal Growth Factor Receptor), ALK (Anaplastic Lymphoma Kinase) rearrangement and ROS-1 rearrangement. Recent studies suggest that molecular tests should be performed in all NSCLC cases. It is even recommended to perform at selected squamous cell carcinomas (non-smoker or mild drinkers). (3) With the detection of ALK gene rearrangement in NSCLC patients in 2007, a new molecular subtype emerged in lung cancer. (4) Approximately 3-5% of ALK re-arrangement is detected in NSCLC patients.

This feature has distinct clinical and pathological features such as adenocarcinoma histology, and the presence of young, non-smoker or low-smoking patients. (5-8) EGFR mutation rate has been reported between 17-50%. (9-12) This mutation is mostly detected in adenocarcinoma histology. ALK re-arrangement and other mutations (EGFR, KRAS) are mainly mutually exclusive with each other (only one is present and the other is not available) (6, 13) Only 3-5% of cases have overlapping (doublet or multiple mutations). (14, 15)

This study aimed to determine the mutation rates of lung adenocarcinoma patients admitted to Mardin State Hospital Oncology clinic and to review the literature on the term mutually exclusive.



Materials and Methods

The records of patients admitted to Mardin State Hospital Medical Oncology Clinic between 2014-2018 were retrospectively analyzed. The local Ethics committee approved the study. Patients over 18 years of age were included in the study. Patients who have not pathological diagnosis were excluded from the study. In addition to age, sex and disease diagnosis, admission and diagnosis stages of the patients were recorded. Statistical analyses were performed over the whole group, followed by male and female patients. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) for Windows v20.0 (SPSS Inc, Chicago, Illinois, USA). The descriptive statistics for continuous variables mean/median; for categorical variables, frequency (n) and percentage (%) were shown. FISH method was used for ALK rearrangement, and real-time (RT) PCR was used for EGFR mutation evaluation.

Results

There were 39 lung adenocarcinoma patients (30.2%) among 130 lung cancer patients. While the median age of these patients was 57.82 (27-78), there were 11 female (28.2%) and 28 male (71.8%) patients. The median age of female patients was 49.31 (27-74), while the median age of male patients was 58.87 (43-78). When the disease stages were examined, There were 4 (10.3%) patients in stage 1; 2 (5.1%) patients in stage 2; 11 (28.2%) patients in stage 3 and 22 (56.4%) patients in stage 4. While 11 (28.2%) of these patients had never smoked, 11 (28.2%) were ex-smokers and 17 (43.6%) were those who continued to smoke at or after diagnosis. The number of patients who had mutation/rearrangement tests performed was 24 (61.5%). 15 (38.5%) of the patients who were not tested / unknown. There were 6 (15.4%) EGFR mutant patients and 2 (5.1%) ALK rearrangement positive patients. Of the 6 patients with EGFR mutation, 3 were female and 3 were male. The ALK-positive patients were equal (1 female and 1 male). While 3 of the EGFR positive patients had never smoked, 1 consisted of active smokers and the other 2 had quit smoking. One of the 2 ALK-positive patients had never smoked and the others had quit. There were no mutations or rearrangements in 16 patients (41%) (Table 1). There were no ROS-1 positive patients.

Discussion

In a study that includes 1683 NSCLC patients reported by Gainor et al.(9) EGFR mutation was found in 301 (17.8%) patients and ALK rearrangement in 75 (4.4%) patients. In this study, EGFR mutation and ALK re-arrangement were reported as mutually exclusive. In a study by Won et al. (10) a total of 1445 NSCLC patients were examined for EGFR mutations and ALK translocations, and the mutation rates were detected 42.4% (612/1445) and 6.3% (91/1445), respectively. Simultaneous EGFR and ALK changes were detected in 4 patients (4/91, 4.4% based on ALK-positive group) and 4/612, 0.7% based on EGFR mutant group. In a study by Yank et al.(11) 336 (32.7%) EGFR mutations and 70 (6.8%) ALK gene rearrangement positivity were detected in 977 Chinese NSCLC patients. The frequency of simultaneous EGFR mutation and ALK rearrangement was reported to be 1.3% (13/977 patients). In a meta-analysis conducted by Fengzhi Zhao et al. (16) 6950 patients from 27 retrospective studies were examined. The ALK fusion rate was 6.8% (472/6950). In addition, in terms of male and female gender, the ALK fusion gene was examined in 26 of 27 studies. There was no significant sex difference between the two groups. Mardin's study also showed no difference in terms of sex. However, the number of patients was low in our study. In a meta-analysis by Ying Wang et al. (17) a total of 4511 patients from 17 articles on NSCLC were examined. Considering the current 17 studies involving 4511 cases, the EML4-ALK fusion gene was highly correlated with none or mild smoking, female sex, and adenocarcinoma pathology and was commonly mutually exclusive with EGFR mutation. In a study by Lee et al. (12) 444 lung adenocarcinoma patients were examined for EGFR and ALK status. As a result, EGFR mutation was detected in 228 (51.4%) patients and ALK rearrangement in 34 (7.7%) patients. 4 (0.9%) patients had both EGFR mutation and ALK rearrangement. As can be seen, in some studies, very low rates of mutually exclusivity rules are broken. In a study by Cicek et al in Turkey (18), biopsy specimens of 114 patients (86 adenocarcinoma, 28 NOS) were examined. In this study, EGFR mutation rate was detected 11.4% (n: 13), ALK re-arrangement rate was detected 8% (n: 9) and ROS-1 rearrangement positivity rate was detected 1% (n: 1).

Table 1: Clinical and Demographic Characteristics of Patients

		Female (n:11, %28.2)	Male (n:28, % 71.8)	All Group (n:39)
Age (Median)		49.31 (27-74)	58.87 (43-78)	57.82 (27-78)
		n (%)	n (%)	n (%)
Stage	Stage 1	1(9.1)	3 (10.7)	4 (10.3)
	Stage 2	0	2 (7.1)	2 (5.1)
	Stage 3	3 (27.3)	8 (28.6)	11 (28.2)
	Stage 4	7 (63.6)	15 (53.6)	22 (56.4)
Smoking	No-Smoker	9 (81.8)	2 (7.1)	11 (28.2)
	Active Smoker	1 (9.1)	16 (57.1)	17 (43.6)
	Ex Smoker	1 (9.1)	10 (35.7)	11 (28.2)
EGFR Mutant		3 (27.3)	3 (10.7)	6 (15.5)
ALK positive		1 (9.1)	1 (3.6)	2 (5.1)
All (EGFRALK,ROS-1) Negative		3 (27.3)	13 (46.4)	16 (41)
Unknown/No-Tested		4 (36.4)	11 (39.3)	15 (38.5)

Conclusion

In the Current Study (Mardin's Study), EGFR positivity rate was 15% and ALK rearrangement rate was 5%. These results were close to the results of the study by Cicek et al and these two studies suggest indicates that EGFR mutation rates may be very low in Turkey compared to the literature and ALK rates are may be close to the literature. To determine the actual mutation rates and factors affecting genetic alterations in Turkey, there are needed to further studies.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author's Contributions: AA; Patient examination, research the literature, Collection of the Data. AA; Revision of the article.

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