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Original research

ANALYSIS OF EGFR GENE MUTATION IN PATIENTS WITH NON - SMALL CELL LUNG CANCER IN HUE CENTRAL HOSPITAL

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ABSTRACT

Objective: *To analyze the EGFR mutation index on the cancer blocs of the patients with non - small cell lung cancer (NSCLC) at the Department of Pathology - Hue Central Hospital.*

Subjects and methods: *A prospective, cross-sectional descriptive study of 227 patients with advanced, metastatic non - small cell lung cancer who were mutated in the EGFR gene. The study were carried out on the cancer parrafin blocs stored in Pathology Department, Hue Central Hospital.*

Results: *Mean age 58.29 ± 9.36 years old, male/female ratio 1.58. Histopathology is mainly adenocarcinoma: 96%, squamous epithelium: 0.9%, large cell: 3.1%. EGFR mutation rate positive 38.3%, negative: 61.7%. The rate of positive EGFR mutations in women: (53.4%) is higher than in men: (28.8%). The rate of positive EGFR mutations in the smoking group: (24.4%), insignificant smoking: (32.8%), the non - smoking group (56.6%). The cases of patients carrying mutations in EGFR gene have 50.6% of LREA deletion mutations in exon 19; 40.23% are L858R substitution mutations in exon 21; 3.45% are G719X mutations and 2.3% are G719S mutations in exon 18; 1.14% are Q787 mutations in exon 20; 1.14% are double mutations S768I + V769L in exon 20 and T790M + L858R in exons 20 and 21.*

Conclusion: *The rate of EGFR gene mutation in NSCLC patients was 38.3%, higher in women than in men and especially high in non - smokers or non - smokers, the difference was statistically significant with p. < 0.05. The most common TKI - sensitive mutations include deletion mutations in exon 19 and substitution mutations in exon 21 (accounting for more than 90%), a percentage less than 5% are mutations.*

Keywords: *EGFR, gene mutation, lung cancer.*

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I. INTRODUCTION

Lung cancer is the most common cancer and the leading cause of death worldwide. Particularly in Vietnam, lung cancer ranks second in terms of both incidence and mortality rates among cancers in both male and female [1]. NSCLC accounts for 75 - 80% of all cancers, the most common is adenocarcinoma type. According to the statistics, about 90% of recorded cases of lung cancer are related to tobacco smoke, the remaining 10% are due to radiation exposure or exposure to carcinogens in the working environment [2]. Studies have shown that smoke contains up to 40 carcinogenic compounds [3]. About 25% of cancer patients have no specific clinical symptoms and can only be detected through physical examination. periodic health. Patients often have symptoms such as cough, chest pain, shortness of breath ..., when

the tumor has metastasized, signs such as bone pain, headache and other atypical symptoms will appear. such as hoarseness, fatigue, weight loss... [4]. In recent years, the development of molecular biology techniques has helped the diagnosis and treatment of NSCLC have significantly improved, most notably the targeted treatment method through the detect mutations in EGFR gene (Epideral Growth Factor Receptor - epidermal growth factor receptor) in patients with NSCLC with the rate from 10 - 20% in European and American patients and 30 - 60% in Eastern ethnicity. Especially, according to many studies, Vietnamese patients with NSCLC have an EGFR mutation rate of 64.2%. Treatment with tyrosin kinase inhibitors (Erlotinib or Gefitinib...) for advanced NSCLC patients with EGFR mutations can delay disease progression and improve quality of life better than chemotherapy. Therefore, according to recommendations from leading cancer organizations in the world such as NCCN (National Comprehensive Cancer Network - US National Cancer Network), ASCO (American Society of Clinical Oncology - Association of Clinical Oncology) USA) or ESMO (European Society for Medical Oncology - European Society of Oncology), patients with advanced, metastatic NSCLC with adenoid pattern should be routinely tested for EGFR mutations to help select choose the target therapy method [1, 5].

II. MATERIALS AND METHODS

A cross - sectional, prospective study was carried out with 260 NSCLC parrafin blocs at Pathology Department, Hue Central Hospital were tested for EGFR mutations from January 2015 to February 2022.

Collect information on clinical, paraclinical, and stage of the patient's disease according to a unified information collection form.

The patient's specimen was histological diagnosis with by routine HE staining and by immunohistochemistry.

Determination of EGFR gene mutations by real-time PCR method.

Data were processed using SPSS 16.0 software.

3. RESULTS

Table 1: Patient characteristics

Patient characteristics		N = 227	100%	EGFR mutation		EGFR: no mutation	
				N = 87	%	N = 140	%
Gender	Male	139	61.2	40	28.8%	99	71.2%
	Female	88	38.8	47	53.4%	41	46.6%
		P = 0.001		P = 0.001			
Average age = 58.29 ± 9.36	< 50	44	19.4	14	31.8%	30	68.2%
	50 - 65	131	57.7	55	42.0%	76	58.0%
	> 65	52	22.9	18	34.6%	34	65.4%
		P = 0.4		P = 0.845			
Pathology	Adenocarcinoma	218	96.0	85	39.0%	133	61.0%
	Squamous cell carcinoma	2	0.9	2	100.0%	0	0.0%
	Large cell carcinoma	7	3.1	0	0.0%	7	100.0%
				P = 0.115			

The mean age of the disease is 58.29 ± 9.36, mainly in the age group of 50 - 65 years old (57.7%). The proportion of male patients with the disease (61.2%) was higher than that of female patients (38.8%) (male/female ≈ 1.58). The rate of patients carrying EGFR mutations was 38.3%, of which the percentage of patients carrying genetic mutations in women (53.4%) was higher than in men (28.8%). Histopathology was mainly adenocarcinoma (96%). The rate of EGFR mutations was higher in non-smokers (56.6%) than in smokers (24.4%) ($p < 0.05$).

Table 2: Clinical symptoms of patients with NSCLC

Expression signs	n	Tỷ lệ (%)
Cough lasts	104	45.8
Chest pain	85	37.4
Shortness of breath	21	9.3
Fatigue, weight loss	17	7.5
Total	227	100.0

Most of the patients with NSCLC had symptoms such as cough (45.7%) and chest pain (37.4%), a small percentage of patients were hospitalized for some other reasons such as fatigue, weight loss or shortness of breath.

Table 3: The site where specimen were taken

Specimen taken site	n	Tỷ lệ (%)
Lung	186	81.9
Nodal/metastatic site	32	14.1
Pleural fluid	9	4.0
Total	227	100.0

There are many places where samples can be taken for EGFR mutation testing (primary tumor, lymph node or metastatic site, pleural fluid), however, there are many samples taken for EGFR mutation test. The most is still in the primary tumor with the rate of 81.9%.

Table 4: Characterític of EGFR mutations

Mutation site Muta	Mutation type	n	Ratio (%)
Exon 19	LREA 19del	44	50.60
Exon 21	L858R	35	40.23
Exon 18	G719X	3	3,45
Exon 18	G719S	2	2,30
Exon 20	Q787	1	1.14
Exon 20 + Exon 20	S768I + V769L	1	1.14
Exon 20 + Exon 21	T790M + L858R	1	1.14
Total		87	100

In patients with EGFR gene mutation, exon 19 deletion mutation (50.6%) and L858R substitution mutation in exon 21 (40.23%) account for the majority; a small percentage are rare mutations G719X,G719S in exon 18 (5.75%); Q787 in exon 20 (1.14%); 2 double mutations S768I + V769L in exon 20(1.14%) and T790M + L858R (1.14%) in exon 20 + 21.

IV. DISCUSSION

Results of our study on 227 NSCLC patients, 61.2% of patients were male; 38.8% of patients are female; male/female ratio ≈ 1.58. The mean age was 58.29 ± 9.36; The age group is mainly 50 - 65 years old with 131 patients, accounting for 57.7%; This result is consistent with domestic and foreign studies [6, 7].

Analysis of patients with NSCLC by gender showed that, although the rate of male patients was higher than that of female patients, 53.4% of female patients carried the mutated gene 1.85 times higher than that of males (28.8%). This study is similar to the research results of Mai Trong Khoa and al [8], the study of Shi Y (2014) on Asian lung cancer patients also showed that EGFR gene mutations

were more common in female patients than in male patients (64) 9% [4].

The main clinical symptoms that cause patients to come to the hospital for examination are cough and chest pain with the rate of 45.8% and 37.4%, respectively, in addition, a smaller proportion of patients find lung cancer because of other symptoms. with rates below 20%. A study by Nguyen Minh Hai in 2013 [9] also showed that patients mainly came to the hospital because of dry cough and chest pain.

Regarding the histopathological characteristics of the patients tested for EGFR mutations, 96% were adenocarcinomas; The remaining 4% include squamous cell carcinoma and large cell cancer. Previous studies also noted that adenocarcinoma accounted for the highest percentage of all types of NSCLC [4, 10].

EGFR gene mutations were detected in 87 patients, accounting for 38.3%, compared with some other reports in Vietnam, almost equivalent to the study of Hoang Anh Vu in 2011 (42%; n = 71) [11], research by Mai Trong Khoa in 2016 (40.5%; n = 479) [1], higher than research by Nguyen Ngoc Quang in 2014 (30.3%; n = 380) [12]. However, these results are lower than PIONEER study when the common gene mutation rate in 7 Asian countries is 51.3% (n = 1450) in which Vietnam is 64.2% (n = 120) [4], the difference is mainly because the piooner study has special criteria for selecting patients while the national studies are counted on the whole population.

Among the patients with EGFR mutation, deletion mutation in exon 19 LREA and replacement mutation L858R in exon 21 are 2 mutations appearing with the highest rate of 50.6% and 40.23%, respectively, these are also drug - sensitive mutations of TKIs; This result is equivalent to the study Mai Trong Khoa (2016) when the rate of EGFR mutations in exon 19 (53.3%) and exon 21 (40.8%) [1], is nearly 1.3 times high than ours is 1.25 times; at the same time, it is equivalent to some other studies in the world when the ratio between deletion mutations in exon 19 and L858R in exon 21 is about 1.1 [4].

In the treatment of NSCLC, EGFR mutations are divided into 2 groups: group related to drug sensitivity and group resistant to TKIs. In this study, the rate of patients with TKIs resistance mutations is less than 5%, this result is equivalent to the results of Inukai et al., with a resistance rate of 3.6%; according to the PIONEER study, the rate of drug resistance gene mutation was 2.9%, in which the author mentioned the combination between drug sensitivity and resistance mutations was 2.3% [3, 13]; In our study, there was also 1 case carrying a drug - resistant mutation T790M (in exon 20) and a drug-sensitive mutation L858R (in exon 21) accounting for 1.14%. Analysis of mutations on exons of the EGFR gene associated with susceptibility or resistance to TKIs are very important results to help physicians make the right treatment orientation.

According to previous reports in Vietnam and around the world, the proportion of patients carrying EGFR mutations varies by age, sex (higher rate in women than in men), smoking history (in the smokers group). Drug is not significantly lower than the non - smoker/smoker group [4, 5]. In our study, the rate of gene mutation has a clear difference between the sexes, in women, the rate of EGFR mutations is higher than that of men (53.4% versus 28.8%); mutations gene was also more common in never - smokers (56.6 percent)/insignificant smokers (32.8%) than in ever - smokers (24.4%).

V. CONCLUSION

Through the study of 227 NSCLC blocs, the EGFR gene mutation test showed that: The mean age of the disease was 58.29 ± 9.36. The proportion of male patients was higher than that of female patients (61.2% compared with 38.8%) 38.3% of patients had EGFR mutations; the rate of EGFR mutations is higher in women than in men (53.4% versus 28.8%); in non - smokers/smokers was not significantly higher than in smokers; The difference was statistically significant ($p < 0.05$). Most of the patients with the disease were adenocarcinoma (96%). Among patients with EGFR mutations, the LREA deletion mutation in exon 19 and the L858R substitution mutation in exon 21 are the two most common mutations with the rates of 50.6% and 40.23%, respectively, are drug - sensitive mutations; a small percentage are resistant or less sensitive mutations, accounting for less than 5%.

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