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THE INITIAL TREATMENT RESULTS OF 6 PATIENTS WITH NON-SMALL CELL LUNG CANCER WITH EGFR AND ALK CONCURRENT MUTATIONS, AT NATIONAL LUNG HOSPITAL

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ABSTRACT

Purpose: *Evaluate the initial treatment results of non-small cell lung cancer with EGFR and ALK concurrent mutations.*

Subjects and methods: *A prospective study, non-controlled description, and longitudinal follow-up of 6 patients with stage IIIB-IV non-small cell lung cancer, with EGFR and ALK concurrent mutations, at the National Lung Hospital, from January 2022 to July 2023.*

Results: *The average age of patients was 65.5 years, the male/female gender ratio was 5/1, and the proportion of patients who smoked was 83.3%. Patients were mainly admitted to the hospital due to symptoms of cough (100%), chest pain (50.0%), and dyspnea (33.3%); the majority of patients with stage IV cancer (83.3%); all patients had adenocarcinoma (100%). The average disease-free survival time was 11.36 months. The common unwanted effects were mainly skin rash (83.3%) and diarrhea (66.7%). Elevated liver enzymes and renal failure occurred in the group of patients using a combination of EGFR-TKIs and ALK-TKIs and were the reasons for discontinuation of ALK-TKIs.*

Keywords: Lung cancer, EGFR, ALK, concurrent mutations, targeted therapy.

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1. INTRODUCTIONS

The EGFR gene mutation in patients with non-small cell lung cancer (NSCLC) is the most common mutation. In the Asian population, EGFR gene mutations account for 40-60%, while ALK gene mutations only account for 3-5% [1]. The concomitant mutations rate of EGFR and ALK occurs in 0.06-1.6% of NSCLC patients [2], [3]. Two common gene mutations need to be tested before targeted therapy. With the advancement of molecular biology technology, next-generation sequencing (NGS) allows the identification of multiple gene mutations simultaneously. The choice of tyrosine kinase inhibitors (TKIs) for the treatment of patients with concurrent EGFR and ALK mutations is a matter of discussion. Many studies have shown that the use of EGFR-TKIs from the beginning brings better treatment effects compared to ALK-TKI treatment. The intracellular transmission pathways of the EGFR and ALK genes are different, the simultaneous occurrence of these two mutations is considered a factor affecting the treatment results of TKIs in NSCLC patients.

In the world, there have been studies on the groups of patients with these two gene mutations, but the effectiveness remains unclear. In Vietnam, there have not been any studies evaluating the effectiveness of initial treatment when both types of mutations appeared simultaneously. We conducted this study to evaluate the initial treatment results of

advanced stage NSCLC patients with concurrent EGFR and ALK mutations at the National Lung Hospital.

2. SUBJECTS AND METHODS

2.1. Subjects

Six patients diagnosed with advanced stage NSCLC (stage IIIB-IV), testing positive for concurrent EGFR and ALK gene mutations, were treated with TKIs and monitored for treatment response at the National Lung Hospital from January 2022 to July 2023.

Exclusion criteria: patients with more than two types of cancer; patients with insufficient research information.

2.2. Methods

- Study design: A prospective study, non-controlled description with longitudinal follow-up.

- Diagnosis of NSCLC by histopathology (through transthoracic biopsy under computed tomography guidance); disease classification according to WHO in 2021.

- Study parameters:

+ Age, gender, smoking status, reason for hospitalization, clinical symptoms, tumor size, histopathology, treatment drugs, progression-free survival (PFS), overall survival (OS), and unwanted effects of the treatment regimen.

- Treatment regimens: three patients treated with EGFR-TKIs, and three patients treated with a combination of EGFR-TKIs and ALK-TKIs. The EGFR-TKIs and ALK-TKIs drugs (Erlotinib, Gefitinib, Afatinib, Crizotinib) are authorized for use in cancer treatment in Vietnam.

- Treatment results assessment: regular monitoring of clinical and subclinical signs monthly; evaluation of lesions on CT scans according to RECIST 1.1 criteria every three months. Reassessment of gene mutations when patients show clinical or radiological progression.

- Data processing: Data collecting, entering, and coding with Microsoft Excel 2010; analysis using SPSS 20.0 software with medical statistical tests.

- Research ethics: The research protocol approved by the Ethics Board of Hanoi Medical University (document number 912/GCN-HĐĐĐNCTSH-ĐHYHN). Patients were informed, understood the purpose, and provided consent to participate in the study. All personal patient information kept confidential.

3. RESULTS

3.1. Characteristics of study patients (SP)

- Age: Patients ranged from 50 to 75 years, with an average age of 65.5 years.

- Gender: One female patient (16.7%) and five male patients (83.3%).

- The clinical characteristics of the study group:

Table 1. Reasons for hospital admission, clinical symptoms, and smoking status of the SP

SP	Reason for hospitalization	Clinical symptoms	Smoking status
SP1	Cough, chest pain	Chest pain, coughing up phlegm, fever	Smoking pipe tobacco
SP2	Coughing up blood, chest pain	Chest pain, Coughing up blood	Active smoking
SP3	Cough, dyspnea	Dry cough, dyspnea, fatigue	Active smoking
SP4	Cough, chest pain	Chest pain, dry cough, fatigue	Passive smoking
SP5	Cough, chest pain, dyspnea	Chest pain, dry cough, dyspnea	No smoking
SP6	Cough	Chest pain, dry cough	Active smoking

Common reasons for hospital admission were cough (100%) and chest pain (66.7%). Prominent clinical symptoms included chest pain (83.3%) and dry cough (66.7%). In the study group, 5 out of 6 patients were smokers, including one case of pipe tobacco smoking.

- Histopathological characteristics:

Table 2. Histological subtypes and stages of the SP group

Patient	Histological disease	Disease stage	EGFR mutation type
SP1	Adenocarcinoma	IV	L858R point mutation
SP2	Adenocarcinoma	IIIB-IIIC	Exon 19 deletion
SP3	Adenocarcinoma	IV	L858R point mutation
SP4	Adenocarcinoma	IV	Exon 19 deletion
SP5	Adenocarcinoma	IV	Exon 19 deletion
SP6	Adenocarcinoma	IV	Exon 19 deletion

All SP (100%) had adenocarcinoma histology. The predominant disease stage was Stage IV (83.3%), with a mutation type mostly involving exon 19 deletion (66.7%).

3.2. Treatment results

- Duration of drug usage by SP (as of August 1, 2023):

Table 3. Duration of drug usage by SP

Drug type	Duration of drug usage (months)					
	SP1	SP2	SP3	SP4	SP5	SP6
EGFR-TKI	12.4	13.5	5.3	15.6	13.4	8.0
ALK-TKI	-	8.5	3.0	-	-	8.0

Three patients were treated with EGFR-TKIs alone, while the remaining three received a combination of EGFR-TKIs and ALK-TKIs. 2/3 patients treated with the combination had a longer duration of EGFR-TKIs usage compared to ALK-TKIs.

- Progression-free survival (PFS):

Table 4. Progression-free survival of patients

Time	PFS (months)					
	SP1	SP2	SP3	SP4	SP5	SP6
PFS	12.40	13.47	5.27	15.60	13.43	8.00
Average	11.36					

The average progression-free survival of the six patients was 11.36 months. The patient with the longest PFS had 15.6 months, while the one with the shortest had 5.27 months.

- The unwanted effects of drugs in research patients:

Table 5. The unwanted effects of TKIs therapy

Patient	Treatment drug	Adverse effect	Grade	Note
SP1	EGFR-TKIs	Skin rash	1	
		Diarrhea	1	
SP2	EGFR-TKIs và ALK-TKIs	Skin rash	1	
		Diarrhea	1	
SP3	EGFR-TKIs và ALK-TKIs	Skin rash	1	
		Nausea, vomiting	1	
		Elevated liver enzymes	3	Reason for stopping ALK-TKIs
		Renal failure	2	Reason for stopping ALK-TKIs

SP4	EGFR-TKIs	Skin rash	1	
		Nausea, vomiting	1	
		Hair loss	1	
SP5	EGFR-TKIs	Diarrhea	1	
		Paronychia	1	
SP6	EGFR-TKIs và ALK-TKIs	Skin rash	1	
		Diarrhea	1	

The most common adverse effects were skin rash (83.3%) and diarrhea (66.7%). Patient SP3, treated with a combination of two TKIs, experienced Grade 3 elevated liver enzymes and Grade 2 renal failure, leading to discontinuation of ALK-TKIs and a switch to EGFR-TKIs alone.

Table 6. Treatment methods and progression in SP

SP	Treatment tesponse with TKIs	PFS (months)	Retesting for genomic mutation after TKIs resistance	Discovery of lesions at the time of drug resistance	Subsequent treatment method
SP1	PR	12.40	Yes	Increased size of the primary tumor, appearance of new lesions	Paclitaxel - Carboplatin
SP2	PR	13.47	Yes	Increased size of the primary tumor	Paclitaxel - Carboplatin
SP3	SD	5.27*		Non-resistant to drug	
SP4	PR	15.60	Yes	Brain metastasis	Osimertinib
SP5	PR	13.43	Yes	Increased size of the primary tumor	Take care of mitigation
SP6	PR	8.0	Yes	Pleural/pericardial effusion	Osimertinib
Note: PR - Partial response; SD - Stable disease; ** Progression-Free survival (PFS) for SP3 (as of August 1, 2023)*					

83.3% of patients partially responded to targeted therapy. In cases of TKI resistance, all patients retested for genomic mutations. The two subsequent treatment methods, Paclitaxel - Carboplatin and Osimertinib, were chosen with equal proportions (both 33.3%).

4. DISCUSSIONS

4.1. Characteristics of SP group

EGFR and ALK mutations were the most common mutations in targeted therapy for lung cancer in Vietnam and worldwide. ALK gene mutations often found in younger individuals who did not smoke. According to Shaw et al., the average age of ALK-positive NSCLC patients was 55 years, and approximately 70% of cases have never smoked [4]. While the average age of patients in this study was 65.5 years, nearly equivalent to the average age of EGFR-positive patients in the study by Yoon et al. (66.8 years [5]). Additionally, 83.3% of patients in this study have a history of smoking, either actively or passively. This rate was significantly higher than in previous studies, possibly due to the small sample size in this study.

The mutations in the study group with NSCLC were considerable diversity. Deletion mutation in exon 19 and L858R point mutation in exon 21 were the two most common mutations, accounting for 90% of all EGFR mutations. In this study, exon 19 deletion mutation was appeared frequently (4/6 patients, accounted for 66.7%), while L858R point mutation in exon 21 accounted for 33.3% (2/4 patients.

According to a multinational epidemiological study in Asia, the prevalence of solitary exon 19 deletion mutation is 22.1%, occurring concurrently with other mutations was 24.3%, and the prevalence of solitary L858R point mutation in exon 21 and concurrent mutations was 20.9%

and 22.9%, respectively [1], [2]. Next-generation sequencing (NGS) was commonly employed as a standard method to investigate and identify single or concurrent mutations due to its high sensitivity and specificity.

4.2. Treatment results

The emergence of concurrent EGFR and ALK mutations poses a clinical challenge in treatment selection. Most advanced-stage NSCLC patients with concurrent mutations were treated with targeted therapy. In particular, researchs around the world still prioritize the use of EGFR-TKIs. If it is effective, ALK will use it in the next treatment steps. In this study, ALK inhibitors were not used in subsequent steps because one patient's biopsy conducted after progression did not detect ALK gene rearrangement, and another patient with severe clinical deterioration was shifted to supportive care [6]. However, treating according to a sequential process or using different ALK-TKI drugs from the beginning and gradually increasing them over time can promote the development of ALK resistance mutations [7]. According to Yang et al., the response rate to EGFR-TKIs in patients with concurrent EGFR/ALK mutations was 80% (8/10 patients), with an average progression-free survival (PFS) of 11.2 months [3]. In our study, the response rate to TKIs was 83.3% (5/6 patients), with one patient showing stable disease. The average progression-free survival (PFS) was 11.36 months.

The initial results of targeted therapy with EGFR-TKIs demonstrated good efficacy. However, when combined with ALK mutation treatment using ALK-TKIs, patients experienced more adverse effects, especially elevated liver enzymes, which might lead to a change in treatment regimen [8].

There were no specific recommendations regarding whether to start treatment with EGFR-TKIs or ALK-TKIs because both drugs were accepted. Although NGS technology detects more concurrent EGFR/ALK mutations, there is a need for general treatment guidelines for this patient group. Further clinical trials and comprehensive genomic sequencing studies are required to guide appropriate treatment decisions.

5. CONCLUSIONS

Treatment with EGFR-TKIs was effective and associated with fewer adverse effects compared to combined treatment with EGFR-TKIs and ALK-TKIs in advanced-stage NSCLC patients with concurrent EGFR and ALK mutations.

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