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Triple Mutation Epidermal Growth Factor Receptor (EGFR) Exon 18 (G719s), 20 (T790m), and 21 (L858r) in A Male Patient with Lung Adenocarcinoma: A Case Report

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ABSTRACT

Background: Lung cancer is one of the deadliest cancers in the world. The percentage of non-small cell lung cancer (NSCLC) is about 80% of the incidence of lung cancer. A type of NSCLC, adenocarcinoma, is usually found in the presence of epidermal growth factor receptor (EGFR) mutations. **Case:** A male patient aged 70 years old, an active smoker, works as a farmer. He experienced shortness of breath and chest pain for three months. There was no family history of suffering from malignancy. The cytology result of the right pleural fluid indicated adenocarcinoma. He was diagnosed with pulmonary adenocarcinoma (D) stage IV positive mutation of EGFR exon 18 (G719S), 20 (T790M), and 21 (L858R) with Karnofsky score of 70. He could survive for more than 11 months with the treatment of EGFR TKI, and received a good therapeutic response. Initially, for the first six months, it was such a progressive disease, and for the next eleven months it became stable. **Discussion:** Lung adenocarcinoma has a higher EGFR mutation rate than that of other types of NSCLC. EGFR mutations usually occur in the first four exons that have a code for Tyrosine Kinase (TK), such as deletion (usually five amino acids) in exon 19 and leucine-to-arginine missens mutations in codon 858 of exon 21 (L858R). **Conclusion:** In addition to exon mutations found in this case, cells in the tumor will continue to grow and develop into new mutants that are immune to drugs and rapidly split themselves into new, different forms. The therapy for complex mutations is still being developed. EGFR TKI therapy in this patient had a relatively good response. Further understanding of molecular biology of lung cancer is seriously required.

Keywords: EGFR mutations, triple mutations, complex mutations

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INTRODUCTION

Lung cancer, in the broadest sense, is all malignancies in the lungs, including the ones originating from the lungs themselves (primary) and those from outside the lungs (tumor metastases in the lungs) and becomes the number one cause of death among all cases of malignancy. Based on pathology, lung cancer is divided into two main categories, namely Small Cell Lung Carcinoma (SCLC) and Non-Small Cell Lung Carcinoma (NSCLC). NSCLC is often found with the percentage of around 80% to 85%. It consists of adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and NOS (not otherwise specified). Adenocarcinoma occupies around 35-40% of the incidence of lung cancer. A mutation in the epidermal growth factor receptor (EGFR)¹⁻⁵ is usually observed in this type of tumor.

EGFR is a transmembrane receptor that plays an important role in the process of cell growth. NSCLC

indicates excessive EGFR expression so that it can be used as a predictor for the success of the therapy of tyrosine kinase inhibitor which is able to improve prognosis. The prevalence of EGFR mutations in adenocarcinoma is around 10% in the United States and about 35% in East Asia.^{1,4-6} EGFR mutations can occur in exon 18, 19, 20, and 21. The most common EGFR gene mutations are exon mutations 19 and 21.^{5,7,8}

EGFR mutations can be either single or complex mutations. Different mutations occur simultaneously in one tumor are called complex mutations. In this case, they can be two mutations (dual), three mutations (triple), or more.¹ A study in Japan found a single mutation incidence around 91% and dual mutations around 9%, while the complex ones have been reported around 6.6%. The causes of mutations are divided into two, namely somatic mutations (obtained during life) and germinal mutations (derived from parents).⁹⁻¹¹

Adenocarcinoma therapy with positive EGFR mutation that is currently being developed is EGFR tyrosine kinase inhibitor, in which its working principle in inhibiting EGFR is competing with ATP to bind the intracellular domain of EGFR catalytic tyrosine kinase, thereby inhibiting cancer cell proliferation and tumor angiogenesis. EGFR TKI as a targeted therapy is used to treat adenocarcinoma and it currently includes gefitinib and erlotinib. A research conducted by Kobayashi, et al. reported that both the dual and triple mutations received a good response from gefitinib and erlotinib with an incidence of around 14% from 5 cases of exon T790M and L858R mutations. On the other hand, the single and dual exon G719S mutations did not get a good response from gefitinib.¹²⁻¹⁵

The following is a case report of uncommon triple positive EGFR exon 18 (G719S), 20 (T790M), and 21 (L858R) mutations found in a patient with pulmonary adenocarcinoma in Dr. Soetomo General Hospital.

CASE

A 65-year-old man experienced shortness of breath for 3 months and got worse 1 week before admission. Coughing up blood and fever were denied, but coughing with thick, white phlegm was noticed. Loss of appetite and body weight was noticed. Night sweating was denied. Right chest pain was on and off. There were no complaints of nausea and vomiting. Bowel movements and urinating were within normal limits.

The patient had never experienced such similar complaints before. Diabetes mellitus had just been noticed since 2 months ago. Hypertension, asthma, and OAT were denied. He was hospitalized in Madiun Hospital for 8 days in August 2015. Yellowish pleural fluid as much as 1000 ml was evacuated. Patient had a history of smoking as many as 2 packs a day for more

than 20 years and had stopped smoking since 3 months ago.

Chest examination in the thorax region started from the anterior. Lung inspection obtained right asymmetrical pulmonary motion lagged behind. Palpation found fremitus decreased. Percussion found dullness in the right lung and chest auscultation found the sound of vesicular breath decreased in the right lung. No Rhonchi and wheezing was detected. Cardiac examination findings were as follows: no appearance of ictus cordis, impalpable heart pulses, and no thrill. Right heart border was in the right sternal line, and left heart border was in the left midclavicular line. Heart sounds (S1 and S2) were single, regular, neither murmur nor gallop noise.

Contrasting chest X-ray CT scan was carried out on September 21, 2015 in Madiun Hospital, and indicated the massive right pleural effusion with right pulmonary atelectasis and suspected peripheral lung mass in the right upper lobe measuring around 50x47x63 mm, periaortic lymphadenopathy, simple cysts in the right lobe of the liver with stadium T3N2M1.

During the treatment, the patient was in stable conditions, and sometimes complained of shortness of breath and right chest pain. The total volume of the pleural fluid that had been evacuated was ±2000 ml. No chest tube was applied because it was rejected. Antidiabetic therapy was given and blood sugar test was provided to control the level of blood glucose. Hypo albumin was well corrected.

The result of the pleural fluid cytology on October 9, 2015 indicated adenocarcinoma (figure 2). The cytology preparations were then examined by EGFR and the results were positive mutations of exon 18 (G719S), exon 20 (T790M), and exon 21 (L858R).

After the application of gefitinib treatment for five months, the patient's clinical condition was stable. His complaints of shortness of breath and coughing decreased. His itching and diarrhea had gone. Then, on April 18, 2016 (figure 3), thoracic CT scan was carried out to evaluate the condition. After that, the results were compared with the thoracic CT scan of January 11, 2016. It indicated that the enhancing solid mass (± 9.05x8.10x8.43 cm) still appeared to relatively increase in size in the posterior segment of the right lobe of the

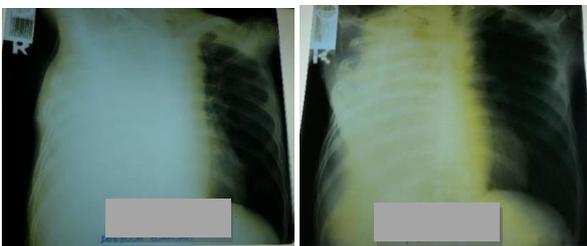


Figure 1. Chest X-Ray Patient before and after thoracentesis



Figure 2. Pleural fluid cytology of the patient. The appearance of anaplastic cell groups with pleomorphic nuclei of hyperchromation shows an adenocarcinoma

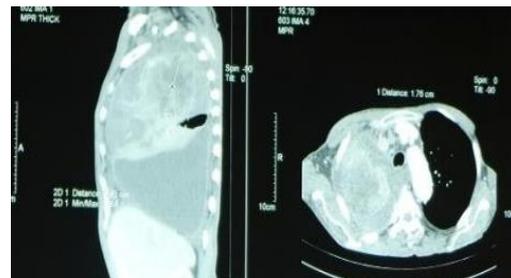


Figure 3. Thoracic CT scan of the patient on April 18, 2016

right lung which caused the superior vena cava, obliterated the right bronchus, and caused distortion/electectasis of the medius lobe which desensitizes the superior vena cava, lubricates the right bronchus, and causes distorted lobe medius and inferior lobe of the right lung resulting in superior vena cava partial thrombus with satellite nodules in the posterior segment of the inferior lobe of the left lung. Para tracheal lymphadenopathy, parahiler and sub-carina, right pleural effusion, multiple cystic lesion in the liver, degenerative disease of the spine were still visible. Recist criteria was progressive disease.

The treatment of gefitinib 250 mg every 24 hours, codeine tablets 10 mg/4 hours, paracetamol tablets 500 mg/4 hours was continued. After six months treatment of gefitinib, the patient complained of swelling face and right arm, sometimes requiring some assistance to do activities, coughing, and on and off shortness of breath.

Seven months after gefitinib therapy, no complaints of coughing, swelling face and arms, diarrhea, and itching were noticed by the patient. Shortness of breath rarely occurred. His body weight was still 46 kg. His Karnofsky score was more than 70 or score 1 according to WHO. Thoracic CT scan with contrast and bone survey were planned to administer. Treatment of gefitinib 250 mg/24 hours and vitamin B complex/24 hours was continued to the eighth month.

The result of thoracic CT scan with contrast on June 24, 2016 (figure 4) indicated that the mass in the posterior segment of the superior lobe of the right lung got smaller in size (not more than 30%) if it was compared with that of April 18, 2016. There was still the appearance of distelectasis lobe medius and inferior lobe of the right lung; pleural thickening, partially organized right pleural effusion, pleural nodules (relatively fixed), and nodules in the posterior segment of the inferior left lung (relatively fixed). Recist criteria: Stable disease. Thrombus in the superior vena cava, subclavian vein to the right jugular vein (increased), multiple cystic lesion in the liver, degenerative disease of the spine.

During the treatment of gefitinib in the ninth month in August 2016, the patient clinically still showed a stable condition. The complaints were reduced and his Karnofsky score remained 70. The diagnosis was positive lung Adenocarcinoma stage IV (D) EGFR mutations exon 18, 20 T790M, and 21, and Iressa treatment was administered at that time. Therapy of gefitinib 250 mg/24 hours, codeine tablets 10 mg/4 hours, paracetamol tablets 500 mg/4 hours, and vitamin B complex everyday was still continued.

From September to December 2016, the patient did not come to Dr. Soetomo General Hospital to control his condition at the Polyclinic of Onchology, but he took chemotherapy drugs although he did not want to take the medication anymore. He only wanted to seek the traditional treatment in the village. When visiting the patient's home, his general condition was weak and still refused to go to the hospital.

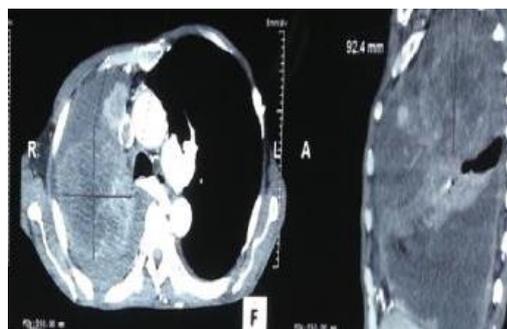


Figure 4. Thoracic CT scan of the patient on June 24, 2016

DISCUSSION

Lung adenocarcinoma has a higher EGFR mutation rate than that of other types of NSCLC. EGFR mutations are found in about 10% to 15% of all NSCLC cases in Western Europe and 35% of NSCLC cases in East Asia. EGFR mutations can occur on exon 18, 19, 20 and 21. EGFR mutations can be either single or complex mutations (dual, triple, or more).^{4, 5, 9} A research in France indicated that the most common data of EGFR exon mutation were the data of EGFR in-frame del exon. As many as 19 incidences of mutations EGFR in-frame del exon occurred around 85%-90% and 21 incidences of Leu858Arg (L858R) substitution in exon occurred around 40%-45%.^{1, 8} Exon 18 mutation (G719S) is one of the rare mutations, either as a single or a complex mutation. The data distribution of the study by Li S, et al. indicated that from 2,368 patients who had EGFR mutations, 18 patients had single mutations of exon with the percentage of as much as 2.57%. The incidence of a single mutation in other exons such as exon 19 was recorded as high as 48.11%, in exon 20 around 3.92%, and exon 21 around 45.40%.^{8, 9, 11}

Multiple or dual mutations are found in exon 18 (G719S) and exon 21 (L858R), and also exon 19. There is, however, no complete data related to the number of occurrences of these complex mutations.^{8, 15} Exon 18 mutations, both as double and triple forms, were found in about 4% of all cases of EGFR mutations in a research in Japan.⁹ The patient in this case experienced a rare triple mutation of exon 18 (G719S) mutation along with exon 20 (T790M) and exon 21 (L585R). The incidence of this kind of mutation, as it occurred in the patient of this case, has not been found.

Exon 20 mutations (T790M) occur around 5% of EGFR mutations and rarely occur as a single form.¹⁶ These exon mutations must be in the form of complex mutations in order to develop as a malignant cancer.¹⁵ In some studies in French (figure 8), the incidence of T790M was 1% of all EGFR mutations.⁸ The study of Yannyan, *et al.* described that exon T790M mutations occurred in cancer patients with white races and were considered as germinal mutations. The researchers also found several cases of this exon mutation in the form of dual mutations. T790M exon as the primary one was

found together with other secondary mutations such as T790M + G719S, T790M + L858R.¹⁵ EGFR exon 20 mutations (T790M) were found to have a greater incidence of complex mutations than those of as a single form of mutation. Primary mutation or *de novo mutation* exon 20 (T790M) is a mutation that includes a genetic disorder, in which a person has a mutation in all cells but does not have a family history of the disease.¹⁶ In this case, the patient was not a white race and had no history of the same disease in the family. He denied that his parents had cancer. In this case, the mutation of exon T790M can be as the primary or *de novo* and as the secondary mutation i.e. exon 18 (G719S) and exon 21 (L858R).

Around 45.40% of Exon 21 (L858R) as a single mutation occurs and it can occur in conjunction with other exon mutations. Exon 21 usually occurs simultaneously with exon 19 and 20. This exon mutation is more common in double or dual forms and is rarely found in triple form. A study by Li S, *et al.* stated that there were four cases of exon 21 (L858R) occurring together with exon 20 (S768I),¹⁰ whereas in this case the patient had exon 21 (L858R) mutation which occurred simultaneously with exon 18 (G719S) and exon 20 (T790M). The report of triple mutation case includes the complex mutations that are rarely found. Its incidence in the Asian region is still low and it is in the form of different exon mutations (figure 5). The incomplete data greatly influences to note the rate of the triple mutation so that the distribution is not particularly clear in Indonesia.

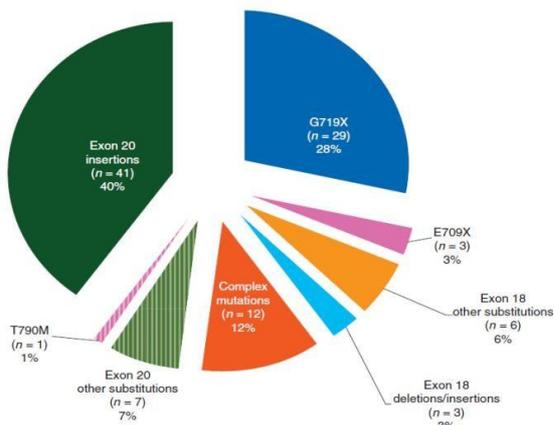


Figure 5. Distribution of the 102 rare EGFR mutations⁸

The clinical characteristic of patients with lung cancer is dominated by people aged 50-70 years old. The risk of developing lung cancer still has a higher incidence at the age of more than 40 years old, and then slowly begins to increase in the older age of over 70 years old in male. It rarely occurs in the age of 65 years old. The occurrence of lung cancer in young men and women is still low.¹⁶ In the Asia-Pacific region, around 60% of mutations occurs in women and only 37% in men.¹ Based on age, there was no statistically significant difference in the incidence of adenocarcinoma lung

cancer in exon 18 mutation (G719S) and exon 19.⁶ A study in Indonesia obtained the data on exon 18 (G719S) mutations in 7 cases occurring in women over 57 years old, but no more detailed information was provided whether they were in the form of single or complex mutations.¹⁷ Exon 18 + 21 double mutations occur in the age ranging 60-82 years old and are more common in women than men. There is no complete data of clinical characteristics provided in triple mutation cases so that the case report of a 65-year-old male patient with triple mutations of exon 18, 20 and 21 is a rare case.

A research in China found that complex mutations of EGFR exon 19, 20 and 21 and BRAF mutations tended to occur in non-smokers. The Asia-Pacific region recorded that 64% of EGFR mutations occurred in smokers and 33% in non-smokers.¹¹ In this case, the patient was a male and an active smoker for 20 years. A recent study by American Cancer Society in 2015 stated that this type of cancer could be found in smokers, but the frequency of its occurrence was not mentioned.²

The symptoms of cancer are almost the same in general, such as about 58% shortness of breath, 27-49% chest pain, and 75% coughing and massive pleural effusion.³ There were no differences in clinical description and symptoms between adenocarcinoma with EGFR triple mutations and other kinds of lung cancer. The complaints and symptoms of shortness of breath, chest pain, coughing and the presence of massive pleural effusion were found in this case.

Lung cancer is caused by the genetic damage. In theory, genetic damage that occurs can be caused by some external factors such as environment, virus, lifestyle, and also some internal factors such as genetic defects in various genes that play a role in the mechanism of repair and apoptosis. Scientific evidences have confirmed that cancer is a cumulative genetic damage that affects the uncontrolled cell growth, tissue invasion, and metastasis. The form of transformation from genetic abnormalities to cancer is called point mutation, gene amplification, or gene rearrangement (translocation or fusion gene), and coding sequence of a gene.^{18, 19} Based on this theory, it shows that there should be a relationship between cancer occurrence in the patient of this case report and some genetic factors, but he denied the presence of tumor or cancer in the history of his family. Various carcinogens in the environment, such as *benzo(a)pyrene*, found in cigarette smoke, pollutants, and food substances such as preserved foods, canned foods, salted fish, and others are thought to contain nitrosamine, a carcinogen, that has a high potential for cancer. The patient rarely ate canned and preservative foods, and never drank alcohol. He was an active smoker for 20 years and worked as a farmer. He was exposed to sunlight every day. According to the theory of ultraviolet light with a spectrum approaching 254 nm, it can damage DNA at 1,2 diprimidine.¹⁹

A study in Italy reported that double mutations of exon 20 (T790M) and exon 21 (L858R) were found in 3 out of 14 biopsy specimens and also in 11 of 66 cytology samples examined by using the Sanger sequencing

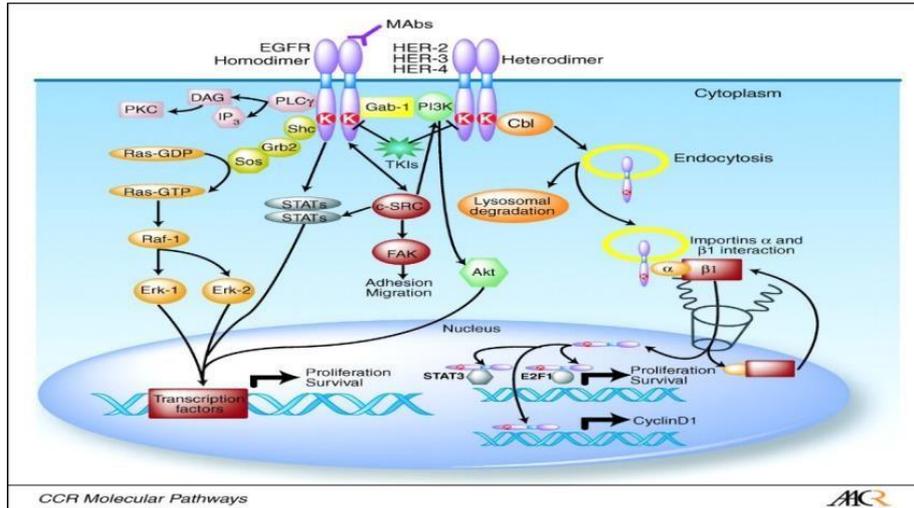


Figure 6. The Epidermal Growth Factor Receptor Pathway²⁰

	AA 688	728	729	761	762	823	824	875
	Exon 18		Exon 19		Exon 20		Exon 21	
Mutations (%)*	G719A (0.77)		All deletions (46%)		T790M (4.1)*		L858R (37.5)	
	G719S (0.47)		E746_A750 (39.4)		S768I (0.55)		L861Q (1.12)	
	G719C (0.26)		L747_P753>S (1.4)					
	All others (0.91)		L747_A750>P (0.81)		All insertions (1.45)			
			L747_T751 (.96)		V769_D770insASV	(.14)		
			E746_S752>V (.49)					
			L747_S752 (.44)		D770_N771insSVD	(.11)		
			E746_751 (.29)					
			All insertions (0.20)					

Figure 7. EGFR mutations and their frequency¹³

method with the result that mutations with various counts of neoplastic cell were detected.²¹ This cytology examination is a diagnostic procedure in accordance with the recommendation of NCCN Guidelines.¹⁶ Patients are diagnosed adenocarcinoma based on the anatomical pathology examination taken from the results of pleural fluid cytology, then examined by EGFR mutation test, and the result indicated a positive EGFR mutation on exon 18 (G719S), exon 20 (T790M), and exon 21 (L858R).^{3, 14}

EGFR has been identified as a target involved in regulating several important cellular functions in the proliferation and survival of cancer cells. In general, the increasing or exaggerating EGFR expression of various types of tumors is often associated with a poor prognosis of the disease,²² as in the case of the patient having triple mutations, or it can be said that excessive expression occurs in EGFR.

The activation of EGFR can lead to homodimer and heterodimer. Phospholipase Cy and STAT transcription factor bind directly to the receptor while Ras needs several molecules. PI3K can bind directly to one of EGFR heterodimers and then the receptors are activated simultaneously to undergo endocytosis to reach the nucleus. EGFR in the nucleus acts as an appropriate

transcription factor or as a co-regulator of other gene trans activators. The pathway results in gene activation associated with cell proliferation, survival, invasion, and metastasis. This can be hampered by EGFR TKI (figure 6).²⁰

EGFR mutations usually occur in the first four exons that have a code for Tyrosine Kinase (TK), such as deletion (usually five amino acids) in exon 19 and leucine-to-arginine missens mutations in codon 858 of exon 21 (L858R).⁷

Based on several studies, most of mutated EGFR genes appear as a heterozygote. Point mutations occur in G719, L585R, and L861Q (figure 7) and the three deletions are delE746-A750, delL747-T751inS, and delL747-P753inS. As many as 90% of point mutations is in exon 21 and deletion in exon 19 del746-750.^{13, 17} In this case, the point mutations most likely occurred in exon 21 (L858R), resulting in a combination of other mutations.

The molecular test for EGFR mutations of exon 18 to 21 has been recommended by NCCN Guidelines. A case report by Lammers, *et al.* revealed that mutational testing is one of the important components or the initial stages of managing patients with NSCLC. One mutation test can be done to confirm the existence of mutations in

the next offspring and to find out the point mutations, and reveal the resistance of the first generation of EGFR TKI. The patients in the case report of Lammers experienced progressive disease during the administration of the therapy of EGFR TKI and the biopsy was repeated and the additional examination of molecular profiling tumors by PCR was carried out.¹² A year of gefitinib treatment led to drug resistance in most patients, and it occurred in about 60% of cases on exon 20 (T790M).²³ In this case, the patient had an exon 20 mutation type (T790M). The mutation test was carried out to find that the resistance was not done, so that it was difficult to know whether there was a drug resistance in the patient or not. The patient experienced progressive disease and it could be seen in the evaluation of thoracic CT scan with contrast. Repeating the procedures of biopsy and molecular testing were not carried out during EGFR TKI therapy.

The management of lung cancer includes surgery, chemotherapy, and radiation. EGFR TKI as a targeted therapy can be administered in patients with NSCLC type of Adenocarcinoma EGFR positive mutation. EGFR TKI works by inhibiting the activity of enzyme tyrosine kinase in EGFR gene which plays a role in cell proliferation. It is very significant because most of the incidences of adenocarcinoma lung cancer are related to the activation of tyrosine 3 kinase due to the mutation of EGFR gene.^{17, 22} Currently, the targeted therapies aimed to treat adenocarcinoma are gefitinib and erlotinib with the doses of 250 mg every 24 hours per oral. The therapy starts immediately after the results of EGFR test are confirmed.

Types of EGFR TKI include gefitinib and erlotinib as the first-generation of EGFR TKIs that inhibit the growth of several lines of derived cancer cells and xenografts tumor, although the effect of this drug does not correlate with either EGFR expression levels or associated members of ErbB receptor family. The second generation of EGFR TKI, such as afatinib, dacomitinib, and neratinib, showed promising activity against T790M in preclinical models, but the drug failed to overcome T790M resistance in patients because of the dose-limiting toxicity resulted from the selective inhibition of wild-type EGFR. The discovery of a new drug as a the third generation EGFR inhibitor (osimertinib) to overcome the problem has been developed and proven to be effective against T790M mutations while wild-type sparing.^{23, 24} The drug could be administered in the patient of the case report because he had an exon T790M mutation, but the access to this drug was not available.

In this case, the subjective response of gefitinib provides some benefits, but the objective response does not. It is related to the result of a chest CT scan with contrast indicating the progressive disease. The response of gefitinib can be very good in the subgroup of patients who are sensitive to gefitinib, resulting in the approval of this medication as a single drug treatment

for lung cancer.⁴ Gefitinib therapy in the patient of this case was continued, even though the progressive disease was detected after 2 evaluations of chest CT scan with contrast. The objective response in the seventh month, based on the result of CT scan, found that the disease was stable. So far, in some studies, the incidence of patients with triple mutations experiencing the stable disease after previously having progressive disease, like the patient in this case report, has not been recorded yet.

The types of mutations that are sensitive to gefitinib are exon 19 and exon 21. It occurs because they have different biochemical signaling activities against receptors. Both types of mutations increase EGFR activation through auto phosphorylation which results in the malignant transformation. Exon 19 and 21 mutations can change pocket configuration to be more appropriate with TKI.^{5, 14} A meta-analysis study by Zhang, *et.al.* in 2014 found that patients with EGFR exon 19 mutations experienced a significant reduction in the disease after EGFR TKI administration compared to exon 21. The three currently developing hypotheses include: The first is exon 19. It has a greater affinity for EGF receptor than that of exon 21. The second is exon 20 (T790M). It is a secondary mutation that is resistant to TKI and it appears more frequently with exon 21 L858R which is the point mutation. The third is exon 18 (G719S). It appears more frequently with exon 21 (L858R).^{23, 25} In this case, it was reported that the patient did not have an exon 19 mutation form which has been reported that, based on various studies, the EGFR TKI response to exon 19 was very sensitive. The patient had a triple mutation consisting of exon 18, 20, and 21 and the gefitinib response was good.

In this case report, the response to mutation therapy of exon 18 (G719S) is based on the result of a study in France indicating that EGFR TKI was better for patients with exon 18 mutations, and the survival rate was 22 months while exon 20 mutations had only 9.5 months. Another study found a different thing. Exon 18 (G719S) showed a poor result on the administration of TKI due to the heterogeneity of the intratumoral tissue of the type of exon 18 (G719S). These tumors contain mutation cells with lower sensitivity when they were treated with EGFR TKI. That is why EGFR TKIs are unlikely to provide success.^{9, 23}

The therapeutic response of multiple mutations of exon 18 (G719S) + 21 (L858R) was reported in this study. Two of 21 patients had progressive disease and 1 patient had a stable disease.⁸ The data and results of researches regarding the same form of the triple mutations as it occurred in the patient of this case report are not available. The therapeutic response in the triple cases of other forms of exon mutations (unwritten mutations) was reported to be less responsive to EGFR TKI therapy. In this case, the patient had triple mutations of exon 18, 20, and 21 simultaneously and he could stand with the condition for 11 months. After two evaluations with the identification of progressive

disease, the stable disease occurred. The performance scores of the patient also remained stable and it was a score of 1.

Kobayashi, *et al.* indicated that EGFR with a multiple mutation of 21 (L858R) + 20 (T790M) was resistant to gefitinib and erlotinib with a maximum, tolerated dose. Multiple mutations such as L858R + E709A, L858R + E709G and L858R + L838V indicate that exon L858R mutation is sensitive to gefitinib. It shows that EGFR TKI responds well to exon 21 (L858R) + 20 (T790M) mutations, and even exon 18 (G719S) mutations that occur in the patient.

The form of mutations L858R + L747V and L858R + R776H has a partial response for erlotinib.¹⁵ The substitution information related to each exon is presented in figure 10.¹³ The result of a study in Japan indicated that the efficacy of gefitinib in patients with complex mutations was similar to those with a single mutation. From 12 patients with complex mutations under gefitinib treatment, it was found that one patient showed complete response (CR), seven had partial response (PR), two had a stable disease, and two indicated progressive disease.⁹

The case of triple mutation in this patient included exon 18, 20, and 21 mutations, although one of the exons (exon 18) was considered insensitive to gefitinib, but the drug was still administered due to its benefits and success which could be seen from the patient's positive response and his 11 months of PFS.

SUMMARY

A 65-year-old man with the history of 20 years smoking habit was diagnosed stage IV D of lung cancer type adenocarcinoma with a positive mutation of EGFR exon 18 G719S + 20 T790M + 21 L858R. The frequency of triple EGFR mutations is rare. This type of mutation is an EGFR complex mutation with an incidence of 12% of mutated EGFR. The therapeutic response was good based on the survival rate of more than 11 months, even though initially he had a progressive disease and become a stable disease. Time to progress in the patient was 8 months and his survival rate was more than 11 months.

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