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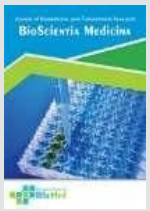

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Management of Resistance to Targeted Therapy in EGFR Mutational Lung Adenocarcinoma: A Case Report

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A B S T R A C T

Advances in diagnosis and treatment have enabled a targeted therapy approach to inhibit tumor progression and provide a favorable prognosis. One of the targeted therapies in non-small cell lung cancer (NSCLC) is tyrosine kinase inhibitor (TKI) in mutations epidermal growth factor receptor (EGFR). This study aimed to present a case with the management of resistance to targeted therapy in EGFR-mutated lung adenocarcinoma. Data shows median progression-free survival patients on TKI therapy at 10 to 14 months. Progressive caused by resistance to TKI and assessed using response evaluation criteria in solid tumors (RECIST) 1.1. and confirmed by repeat biopsy. Reported a male patient aged 66 years with adenocarcinoma of the right lung EGFR deletion exon 19 mutation and received afatinib therapy for 16 months. Patients experience oligo progressive in the 13th month of therapy and systemic progression 16th month.

1. Introduction

EGFR mutations occur in 33.7% of non-small cell lung cancer (NSCLC) patients.[1] EGFR mutations are found in 30-50% of patients with lung adenocarcinoma with a prevalence of 14-19% in European patients and 40-48% of Asian patients.[2,3] The most common mutations are deletions in exon 19 and substitutions in exon 21.[2] Other mutations that are rare are exons 18 and 20 mutations with a prevalence ranging from 10-18%.[4] Syahruddin E et al. reported the results of EGFR examination of 1,874 cytology samples of lung cancer patients in Indonesia in 2015–2016 obtained 44.5%, have mutations, mostly common mutation (exon 19 ins/dels and L858R) 57.1% were highly responsive to TKI EGFR therapy.[5] Inhibitor epidermal growth factor receptor –tyrosine kinase inhibitors (EGFR – TKIs) have developed in 3 generations. In Indonesia, the first-generation erlotinib and gefitinib, and second-generation afatinib have been covered by the national health insurance, while the second-generation dacomitinib and third-generation osimertinib have not.

Patients with EGFR mutation lung adenocarcinoma have an objective response rate (ORR) of 80% of TKI EGFR with progression-free survival (PFS) around 10-14 months.[6] The NEJ002 study reported that gefitinib's PFS (10.8 months) was superior to carboplatin + paclitaxel (5.4 months). The OPTIMAL study reported erlotinib's PFS (13.1 months) compared to carboplatin+ gemcitabine (4.6 months). The LUX-LUNG 3 study reported afatinib's PFS (11.1 months) versus cisplatin + pemetrexed (6.9 months).

In the study of FLAURA, first-line treatment with osimertinib compared to the previous generation EGFR-TKI group, osimertinib significantly increased PFS, i.e., 18.9 months.[7] Assessment of response to TKI EGFR therapy was based on subjective and semi-subjective responses based on clinical and objective responses based on RECIST. Category progressive on target therapy is divided into oligo progression and systemic progression, different from chemotherapy based on RECIST criteria progressive disease.[8] Frequency oligo progressive varies between 15-47% before finally becoming systemic progressive after the provision of TKI for an average of 1 year, depending on the generation of TKI used.[9] The cause of progress is the existence of resistance to TKI. TKI resistance is divided into resistance primary and secondary (acquired) resistance. Primary resistance occurs in 4-10% of adenocarcinoma patients with EGFR mutations.[10] Secondary resistance is obtained through modification of target genes such as T790M gene mutation (> 60%), MET amplification (4%), human EGFR type 2 (HER2) amplification 8-13%, PIK3CA mutation (2%), BRAF mutation (1%), the histological transformation from NSCLC to SCLC (6%), or epithelial-mesenchymal transition (1-2%).[11]

Rebiopsies are necessary to determine the cause of resistance. Another study reported that 59.6% underwent rebiopsies after experiencing resistance, and 53.3% found the T790M mutation. The suitability level of ctDNA in detecting the T790M mutation is 56.3% compared to tissue biopsy. Hong MH et al. reported patients who did not undergo rebiopsy 40.4% for various reasons, mostly caused because the T790M mutation was confirmed by ctDNA examination. Other reasons are tumors that are inaccessible for rebiopsies, patients refusing to undergo rebiopsies and cannot undergo rebiopsies procedures because of their poor status performance.[12] This study aims to present patients receiving TKI therapy who experience oligo progressive and systemic progressive, related to progressive assessment, resistance, and biopsy. This study aimed to present a case with the management of resistance to targeted therapy in EGFR-mutated lung adenocarcinoma.

2. Case Presentation

A male patient, aged 66 years, was diagnosed with right lung cancer with exon 19 mutation adenocarcinoma stage IV in April 2021. The patient has had a chest photo examination, chest CT scan, and bronchoscopy. Initially, the chest X-ray did not show a mass, but the patient complained of a dry cough, chest pain, and shortness of breath which had not improved since 8 months ago.

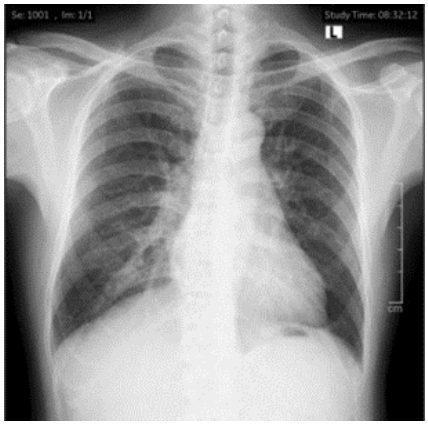

Figure 1. Chest X-ray before administering TKI therapy.

The patient underwent a thoracic to suprarenal CT scan baseline on March 26th, 2021, in contrast to the results showing an inhomogeneous enlarged mass in the right paracardial with indistinct boundaries, irregular edges, size 3.2x4.6x4.9 cm. There were multiple lymph node enlargements in the subcarinal and left perihilar. Minimal left pleural effusion was seen. There is a well-defined mass with regular

nodular edges in the right hepatic lobe measuring 8.5x5.7x4.5 cm.

The conclusion from the CT scan is suggestive of a right lung tumor with multiple subcarinal and perihilar lymphadenopathy accompanied by minimal right pleural effusion + liver lesion, suspected metastatic DD liver hemangioma.

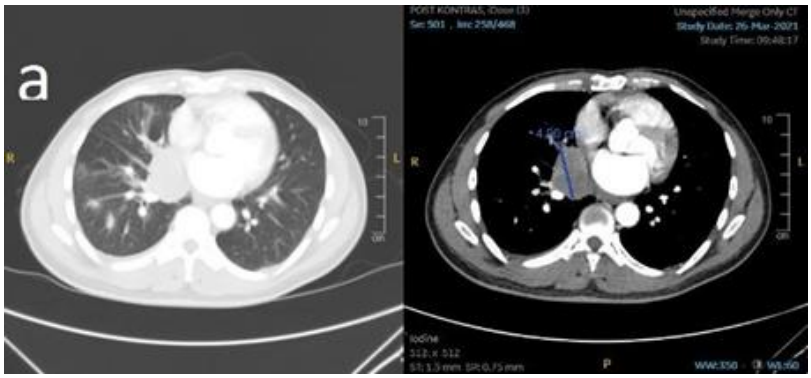

Figure 2. Thoracic CT scan before administration of Afatinib on March 26th, 2021.

There was one target lesion in the lung with the longest diameter of 4.9 cm and multiple enlarged lymph node non-target lesions in the subcarinal and perihilar left, and effusion minimal left pleura. The lesion in the liver after an abdominal CT scan was concluded as a hemangioma of the liver, and action was taken by the vascular surgery department.

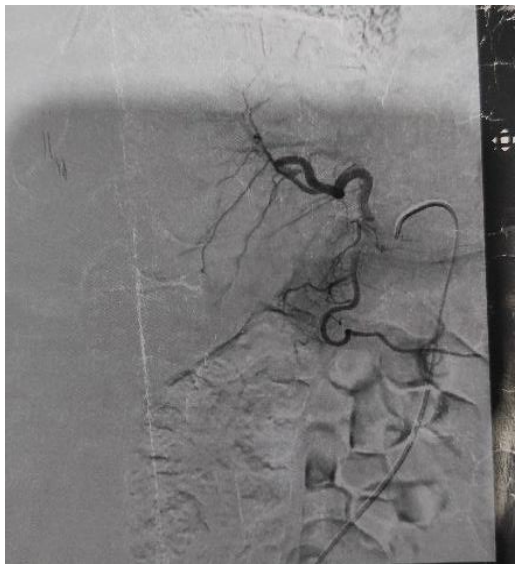

Figure 3. Hemangioma of the liver in a patient.

The patient underwent a bronchoscopy examination cryobiopsy on March 29th, 2022. The results of the patient's bronchoscopy examination showed a narrowing of the lumen of the right middle lobe with irregular mucosa and bleeding easily (Figure 4).

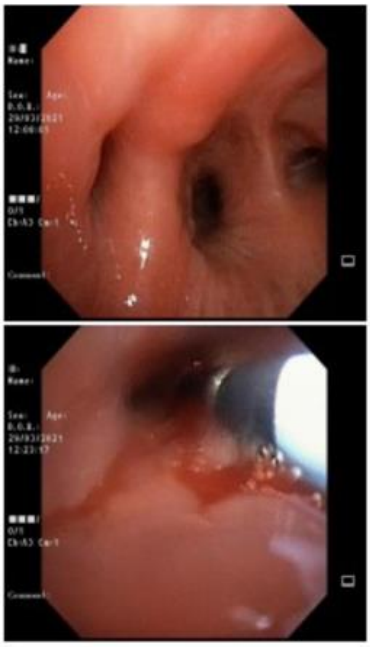

Figure 4. Bronchoscopy and cryobiopsy on March 29th, 2021. There was a narrowing of the lumen of the right middle lobe with an irregular mucosa and bleeding easily.

Anatomical pathology examination results cryobiopsy demonstrated invasive adenocarcinoma. The results of the mutation EGFR examination on April 22nd, 2021, showed a positive EGFR mutation in exon 19.

The patient was diagnosed with adenocarcinoma of the right lung exon 19 T2bN2M1b mutation (pleura, liver) stage IVa PS ECOG 1 and given afatinib target therapy 1x40 mg per day.

During the 3 days of consuming afatinib, the patient experienced side effects of the drug in the form of blisters and canker sores in the mouth. This complaint made the patient treated for 5 days because he could not eat and drink. The patient also complained of diarrhea after 2 months of afatinib administration. Ingrown toenail and reddish spots all over the body since 3 months of afatinib administration. Afatinib was stopped for 1 week until the side effects of the drug decreased to grade 2 and then continued with the patient's tolerance dose to 1x30 mg.

TKI's response assessment was delayed by 1 month in the moon the fourth TKI due to drug side effects at the beginning of therapy. Chest CT scan examination on September 6th, 2021, showed a 56% reduction in tumor mass baseline, RECIST effect partial response.

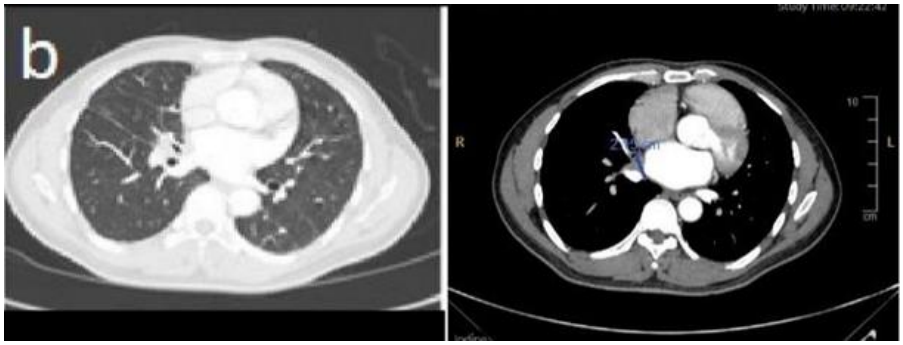

Figure 5. thoracic CT scan examination on September 6th, 2021, first RECIST.

The size of the target lesion decreased to 2.15 cm in longest diameter. The non-target lesion disappeared completely. Subjective response to improvement, now the patient is not complaining of coughing, shortness of breath, and chest pain. The semi-subjective response was improved, and there was an increase in body weight of 4 kg while receiving TKI therapy. CT scan of the chest on January 13th, 2022, showed a reduction in tumor mass with the longest diameter of 2.56 cm, 47.8% of the baseline, suggesting a partial response.

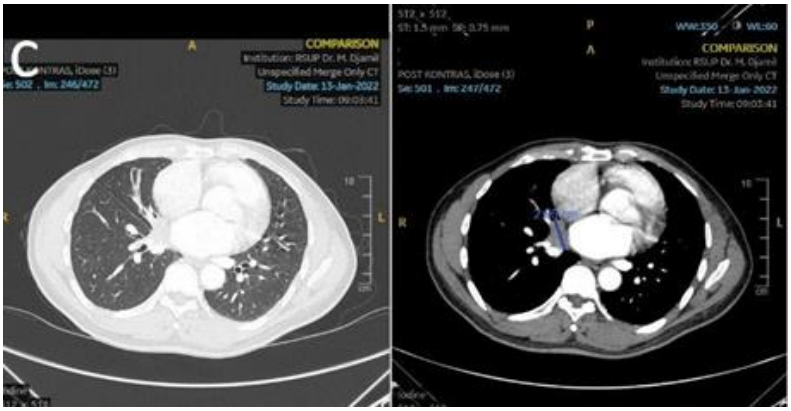

Figure 6. CT scan of the chest January 13th, 2022, second RECIST.

Target lesion size increased from CT scan nadir 19.1%, but still reduced in comparison base*line* with the longest diameter of 2.56 cm, no non-target lesions. The subjective response is persistent, the patient has no complaints, and the patient is able to carry out the patient's hobby, namely badminton. Semi-subjective response to improvement, there was an increase in body weight of 6 kg while receiving TKI therapy, partial impression response.

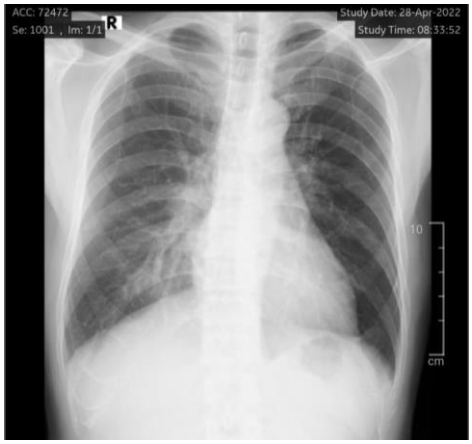

Figure 7. Photograph of the chest on April 28th, 2022, it appears that the right hilum is thicker than the chest photo baseline.

A repeat chest photo on April 28th, 2022, shows that the right hilum is thicker than the chest photo baseline. CT scan chest evaluation May 9th, 2022 The longest diameter of the target lesion increased to 2.85 cm 32.6% compared to the CT scan nadir with progressive disease impression.

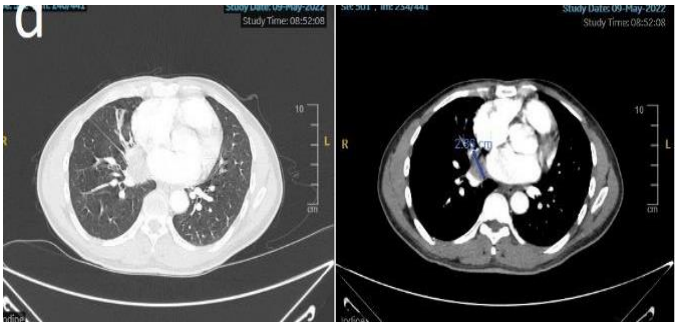

Figure 8. Thoracic CT scan evaluation on May 9th, 2022, third RECIST.

The size of the target lesion increased from the CT scan nadir by 32.6%. The non-target lesion reappeared in the right perihilar lymph nodes. The subjective response persists, and the patient has no complaints. Sedentary semi-subjective response, no weight loss, impression oligo progressive in the 13th month of TKI. TKI therapy is continued.

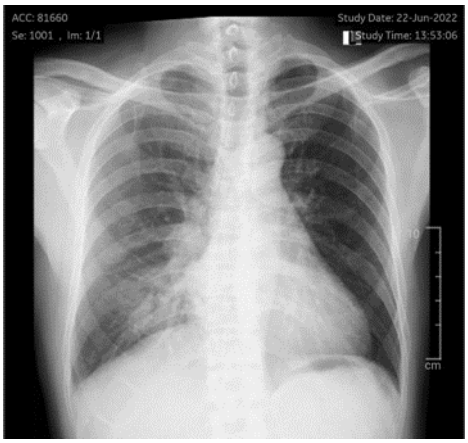

Figure 9. Thoracic photo June 22nd, 2022, visible mass on the right perihilar.

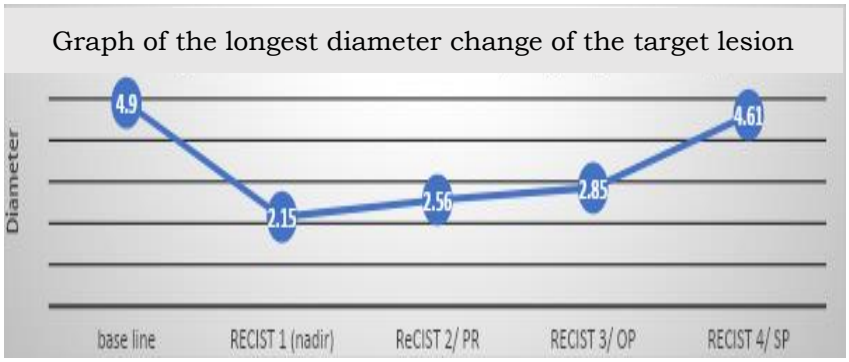

Figure 10. Graph of the longest diameter change of the target lesion. Nadir: smallest size ever achieved during treatment PR: partial response, OP: Oligoprogression, SP: Systemic progression.

The thoracic photo of June 22nd, 2022, shows the mass in the right perihilar. CT scan examination after 16 months of afatinib administration showed an increase in the size of the longest diameter of the target lesion to 4.61 cm 114% compared to Nadir CT scan. There is an enlargement of the lymph nodes in the right perihilar with the shortest axis of 1.8 cm.

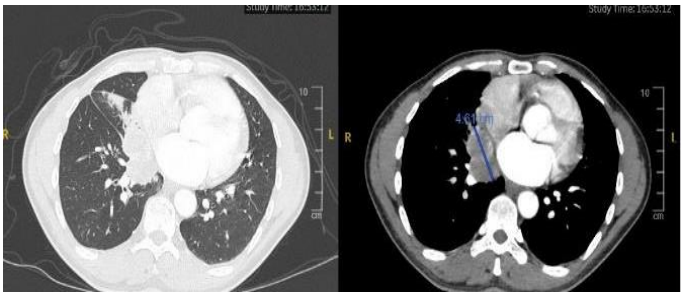

Figure 11. Thoracic CT scan examination August 3rd, 2022, fourth RECIST.

The size of the target lesion increased from a Nadir CT scan to 4.61 cm 114%, and the non-target lesion size of the lymph nodes increased with a short axis diameter of > 1.5 cm. The subjective response is worsening. The patient complains of increasing dry cough and disturbing the patient's sleep. Worse semi-subjective response, weight loss of 4 kg in this 1 month, Systemic impression progression in the 16th month of TKI. TKI therapy was discontinued. A repeat biopsy in this patient was not performed because the patient refused. The patient was given first-line compensation chemotherapy with a carboplatin + paclitaxel regimen. The patient is currently undergoing a second cycle of chemotherapy.

3. Discussion

A 66-year-old male patient with stage IV mutated EGFR adenocarcinoma of exon 19. In contrast to several studies, it was reported that EGFR mutations were more common in women, the East Asian race, and non-smokers. Mitsudomi et al. reported that EGFR mutations occur in 44-55% of adenocarcinoma patients, 51%-68% of non-smokers, 42-62% of women, and 30-50% of Asians.[7] EGFR mutations with smaller numbers were also found in 10% of smokers, 14% of men, and 8% of adenocarcinomas of the European race. Shigematsu et al. also reported a higher frequency of lung cancer from East Asia than from non-Asia (30% versus 8%, P<0,001), women compared to men (59% versus 26%, P<0,001), non-smokers compared to smokers (66% compared to 22%, P<0,001), and in adenocarcinoma compared to other NSCLC histologies (49% versus 2%).[8]

Two mutations in the EGFR exon 19 and a single amino acid substitution, L858R in exon 21, are referred to as common mutation EGFR, together account for 85% of the mutations EGFR on NSCLC and provide good sensitivity to TKI. The remaining 15% of rare mutations are mutations EGFR of exons 18-20.[13,14] Patients were given afatinib targeted therapy at a dose of 1x40 mg. Guide of National Comprehensive Cancer Network (NCCN) 2022 for lung cancer patients with the adenocarcinoma type with EGFR mutations in exon 19 receiving therapy in the form of EGFR-TKI target therapy. The therapy that can be given can be seen in Figure 13.[15] The Lux-Lung 7 study reported that afatinib's PFS was superior to the first generation TKI's EGFR, namely 11.0 months. Afatinib is a potent, selective, irreversible inhibitor of the family ErbB tyrosine kinase. Afatinib covalently binds to all homodimers and heterodimers formed by EGFR, HER2, ErbB3, and ErbB4, thereby inhibiting tyrosine kinase autophosphorylation and downregulating ErbB signaling.[16] The patient experienced drug side effects after 3 days of receiving afatinib with symptoms of sores on the lips and mouth accompanied by profuse stomatitis according to WHOtoxicity grade 4. Side effects of afatinib are skin rashes, paronychia, and stomatitis. The incidence of these side effects can occur even to the point of requiring discontinuation of treatment. The Lux-Lung 3 study demonstrated that a 70% incidence of mucositis was reported in patients treated with afatinib.[17]

Afatinib preparations consist of 20 mg, 30 mg and 40 mg. Dosage reduction may be given if side effects occur. Afatinib therapy is discontinued if side effects are grade 2 (prolonged/intolerable) or ≥ grade 3. Afatinib administration can be continued after side effects decrease to grade 1. Afatinib is administered by reducing the afatinib dose to 10 mg/day from the initial dose. The management of the patient, in this

case, was in accordance with the existing guidelines. The dose of afatinib that this patient tolerated was 30 mg/day.[18] The patient showed a good response during afatinib treatment. The patient had no complaints of shortness of breath, cough, and chest pain. There was a weight gain of 6 kg while receiving afatinib therapy. The longest diameter size of the target lesion was reduced by 56% in the first RECIST of the 4th month TKI and 47.8% in the second RECIST of the 9th month TKI compared to the baseline. Currently, the patient's objective response is a partial response. AND evaluation of response to complementary chemotherapy and targeted therapy RECIST 1.1 It has become the reference standard in assessing response to solid tumors. RECIST terminology characterizes the lesion as measurable or non-measurable and target or non-target. Measurable lesions are lesions that can be assessed quantitatively. The target lesion is selected from the measured lesions. Once a lesion is targeted, it is always targeted in subsequent evaluations, even if the lesion falls below the measurable lesion size limit.[19,20] Radiological examination baseline performed no later than one month before the start of treatment. The subsequent response to treatment was evaluated radiologically baseline or the next scan showing the lowest target disease count (nadir).[19,20] The target lesion is determined on the radiology baseline and provided that the longest diameter is not less than 10 mm or 15 mm on the short axis if the lesion is a lymph node. A lesion that can be measured on a chest X-ray is greater than or equal to 20 mm, provided the lesion is well-defined and surrounded by an aerated lung.[19,20] A maximum of 5 lesions can be selected as target lesions, with a maximum of 2 lesions per organ. The sum of all long-axis measurements and or short-axis measurements is calculated. Following response assessment, the same lesion is measured, and the number of target lesions is recalculated. The measurement does not have to be on the same axis (as measured at the start), but it must always be the longest axis of the lesion at that time and not necessarily on the same slice position, provided the measurements are on the same lesion. If the initial measurement is made in the axial plane, all further measurements of the lesion must remain in the axial plane.[19,20] Bone lesions with a soft tissue component of 10 mm can be designated as target lesions. Sclerotic bone lesions cannot be used.[19,20] If the lesion disappears, it should clearly be 0 mm in size, but if the lesion persists but is too small to measure accurately, a standard size of 5 mm should be given. If the lymph node size is reduced to <10 mm, it does not need to be counted but remains a target lesion. If lesions merge, the long axis of the resulting lesions is measured as a single lesion. If the lesion is split, the long axis of each lesion is added.[19,20]

Assessment of response to treatment at month 13 subjective response persisted, with no weight gain. Target lesion size increased from CT scan nadir 32.6%, non-target lesions reappeared right perihilar lymph nodes compared to CT scan nadir, the patient experienced oligo progression, and TKI therapy was continued. Progressive assessment of TKI therapy is divided into oligo progression and systemic progression. The IASTO and PDPI algorithms explain simply the definition of oligo progression and systemic progression. Oligo progression was in patients who were clinically good but experienced an increase in target lesion size > 20% and no new lesions. Systemic progression is clinically deteriorating or improving, and new target lesions are increasing. For patients who experience oligo progression, TKI therapy can be continued.[8] The patient experienced clinical deterioration after 16 months of receiving afatinib therapy. The size of the target lesion increased from a Nadir CT scan to 4.61 cm 114%, and the non-target lesion size of the lymph nodes increased with a short axis diameter of > 1.5 cm. The subjective response is worsening. The patient complains of increasing dry cough and disturbing the patient's sleep. Worse semi-subjective response, weight loss of 4 kg in this 1 month. The patient has systemic progression in the 16th month of TKI. Based on an evaluation algorithm for TKI EGFR target therapy, treatment of TKI patients experiencing systemic progression was discontinued and continued with a repeat biopsy examination to determine the cause of TKI resistance. Afatinib therapy was discontinued, and the patient was given the education to undergo a repeat biopsy, but the patient refused due to the risks of the procedure. Hong MH et al. reported that 40.4% of patients did not undergo rebiopsies for various reasons, including the

doctor decided not to perform rebiopsies in 37 cases, 20 cases did not undergo rebiopsies because plasma samples had been detected to contain the T790M mutation, 28 patients showed tumors that were inaccessible for rebiopsies, 5 patients refused to undergo rebiopsy, and another 5 were unable to undergo rebiopsy procedure due to poor status performance.[12] NCCN 2020 guidelines, adenocarcinoma patients who have the progressive disease are tested for T790M mutation. Cytology and histology samples are needed to identify mutations in the EGFR gene. Obtaining repeat biopsy tumor specimens is challenging because of the potential risks of invasive diagnostic procedures. Prospective studies show that the success rate for repeat biopsies is 75-95%, and serious complications are detected in approximately 1% of cases.[22]

The presence of intra-tumor heterogeneity influences tumor evolution, metastasis, and resistance mechanisms in different ways, including somatic mutations, epigenetic changes, and post-transcriptional modifications. Selection bias may occur because a single biopsy specimen is not sufficient to accurately represent all the different resistance mechanisms.[6] Liquid biopsies can provide a source of information about resistance mutations from across the tumor landscape, compared to single sites sampled using tissue biopsies. Circulating cell-free tumor DNA (ctDNA) was adopted for the exploration of noninvasive resistance mechanisms and tumor genetic alterations. Mutation EGFRT790M can be detected in plasma samples by highly sensitive genotyping methods, including sequencing, digital droplet polymerase chain reaction (ddPCR), emulsion, amplification, and magnetics (BEAMing) assays. Using ctDNA to detect mutations can yield a high positive predictive value. However, not all tumors release ctDNA to the same degree due to differences in tumor size, stage, location, vascularity, site of metastatic disease, and treatment history. Darusman Y et al. reported the sensitivity, specificity, positive value (NNP), and negative predictive value (NPN) of ctDNA examination in detecting EGFR predictions, namely 66.7%, 100%, 100%, and 80% based on tissue cytology examination as the gold standard.[23,24] Some studies have found that up to 35% of patients withEGFRT790M have a false negative plasma level, compared to tissue biopsies. This condition is the reason for tissue biopsies to be carried out to confirm if the liquid biopsy shows a mutationEGFRT790M negative.[6]

The patient did not undergo ctDNA examination because if a T790M mutation is found, the next treatment is with 3rd generation TKI osimertinib, which is currently not included in the national health insurance catalog. The cause of resistance in this patient could not be determined because a repeat biopsy was not performed. Resistance to TKI is divided into primary resistance and secondary (acquired) resistance. Primary resistance occurs in 4-10% of patients with newly diagnosed adenocarcinoma with EGFR mutations. The clinical picture of primary resistance is the appearance of progressivity at the beginning of TKI therapy. The mechanism of primary resistance is still not clearly understood.[10] Secondary or acquired resistance through modification of target genes, such as mutase of the T790M gene, is the most common mechanism (> 60%) where mutations occur in gene 790 in exon 20 of the EGFR gene. Other mechanisms include MET amplification (4%), human EGFR type 2 (HER2) amplification 8-13%, PIK3CA mutation (2%), BRAF mutation (1%), the histological transformation from NSCLC to SCLC (6%), or transition epithelial mesenchyme (1-2%).[10]

4. Conclusion

Oligo progression in this patient occurred in the 13th month of treatment, and systemic progression occurred in the 16th month of afatinib treatment. Assessment of the cause of resistance in this patient could not be determined because a re-biopsy was not performed.

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