

Case Report

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# Response to a Combination of Full-Dose Osimertinib and Ceritinib in a Non-Small Cell Lung Cancer Patient with EML4-ALK Rearrangement and Epidermal Growth Factor Receptor Co-Mutation

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## Keywords

Osimertinib · Ceritinib · Tyrosine kinase inhibitors · Non-small cell lung cancer

## Abstract

Lung cancer has been the leading cause of cancer-related deaths in both developed and developing countries, with most primary lung cancers being non-small cell lung carcinomas. Treatment for this condition is sometimes individualized. With developments in modern treatment and phase III clinical trial results, epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) and ALK-TKI have proven their superior effectivity in comparison with the standard platinum-based doublet and are commonly approved as first-line indications in previously untreated advanced non-small cell lung cancer (NSCLC) patients with EGFR or ALK mutations. In the majority of cases, the presence of the ALK rearrangement mutation does not overlap with other mutations in NSCLC. Here, we report a patient with concomitant ALK rearrangement and EGFR mutation treated with a combination of TKIs: osimertinib and ceritinib.

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## Introduction

According to worldwide and Vietnam statistics, non-small cell lung cancer (NSCLC) accounts for approximately 75–80% of the total number of lung cancers. Currently, the treatment of this disease depends on many factors, such as stage, comorbidities, and associated pathology. For the advanced stage, the molecular characteristics of the tumour are very important in treatment and prognosis. Based on these characteristics, targeted therapies are expected to increase the effectiveness of the treatment compared to systemic chemotherapy. Recently, the results achieved in phase III clinical trials showed that NSCLC with epidermal growth factor receptor (EGFR) or ALK mutations have good results with tyrosine kinase inhibitors (TKIs) [1–4]. According to a study in Vietnam, EGFR and ALK mutations account for 32.3 and 5.4% of all mutations, respectively, and the rate of 2 mutations occurring simultaneously is 1.4% [5]. Treatment for this condition is sometimes individualized, with no standard treatment considered for this rare group of patients.

## Case Presentation

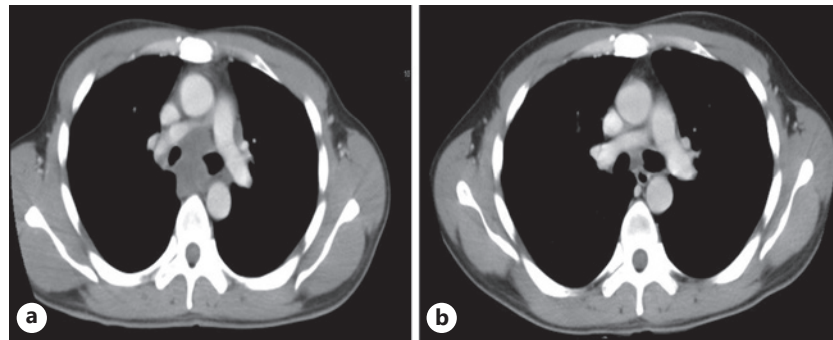
A 39-year-old male patient who was a non-smoker with no comorbidities arrived at our hospital in August 2019 and presented with dry cough for 6 months and a weight loss of 5 kg per month. The patient had no previous chest pain or dyspnoea. A physical examination was also performed. Computed tomography (CT) of the thorax revealed many bilateral lung lesions of approximately 4–9 mm with enlargement of the mediastinum, hilar and supra-vascular, and abdominal lymph nodes with the largest size of 28 × 31 mm. The brain MRI showed that the lesion in the frontal region located in the top left and right frontal lobe had the largest diameter of approximately 24 mm, causing oedema. Moreover, bone scintigraphy showed numerous bone metastases in the spine and bilateral pelvis. A CT-guided fine-needle biopsy of the lung tumour was also performed, and the histological identification illustrated lung invasive adenocarcinoma with both TTF1 and napsin A. The patient was diagnosed with stage IVC lung adenocarcinoma (brain, bone, and abdominal lymph nodes). Tissue samples were tested for next-generation sequencing. According to the results, the patient had both types of EGFR exon 19 deletion mutation mixed rearrangement ALK (ALK-EML4 fusion). In September 2019, we decided to use a second-generation ALK inhibitor, ceritinib (alectinib is not available in Vietnam), instead of EGFR-TKIs for the initial treatment of the patient. The patient's brain lesions were also closely monitored.

Within 3 months of treatment, the patient's clinical symptoms markedly improved. The patient did not experience cough or chest pain. The CT scan indicated that lesions of the bilateral lungs, as well as the mediastinal and abdominal lymph nodes were greatly reduced and exhibited partial response (Fig. 1).

Nevertheless, brain MRI showed that metastatic tumours responded poorly to treatment. Thus, the patient underwent stereotactic radiosurgery with one fraction at a dose of 18 Gy on the brain lesion for local control, whilst continuing with ceritinib.

However, the patient's condition started to worsen at 4 months. He began to experience chest tightness and coughing with increasing breathing difficulty. The CT showed massive bilateral pleural effusion and a low degree of pericardial effusion (Fig. 2).

We identified progressive disease and decided to choose erlotinib, a first-generation EGFR-TKI, for the second-line treatment. Three months after the therapy, the patient's respiratory symptoms clinically improved, such as cough relief, chest pain relief. Moreover, the chest CT exhibited partial response, but the patient had 2 seizures in the right half of the body. Brain MRI indicated metastatic damage to the frontal lobe; the left apex increased in size to



**Fig. 1.** Chest CT images before (a) and after 3 months of treatment with ceritinib (b). Before treatment with second-generation ALK-KI, CT showed that numerous mediastinal lymph nodes exhibited heterogeneous drug absorption after injection. Figure b was taken after 3 months of treatment with ceritinib and shows no abnormal mediastinal lymph nodes. CT, computed tomography.



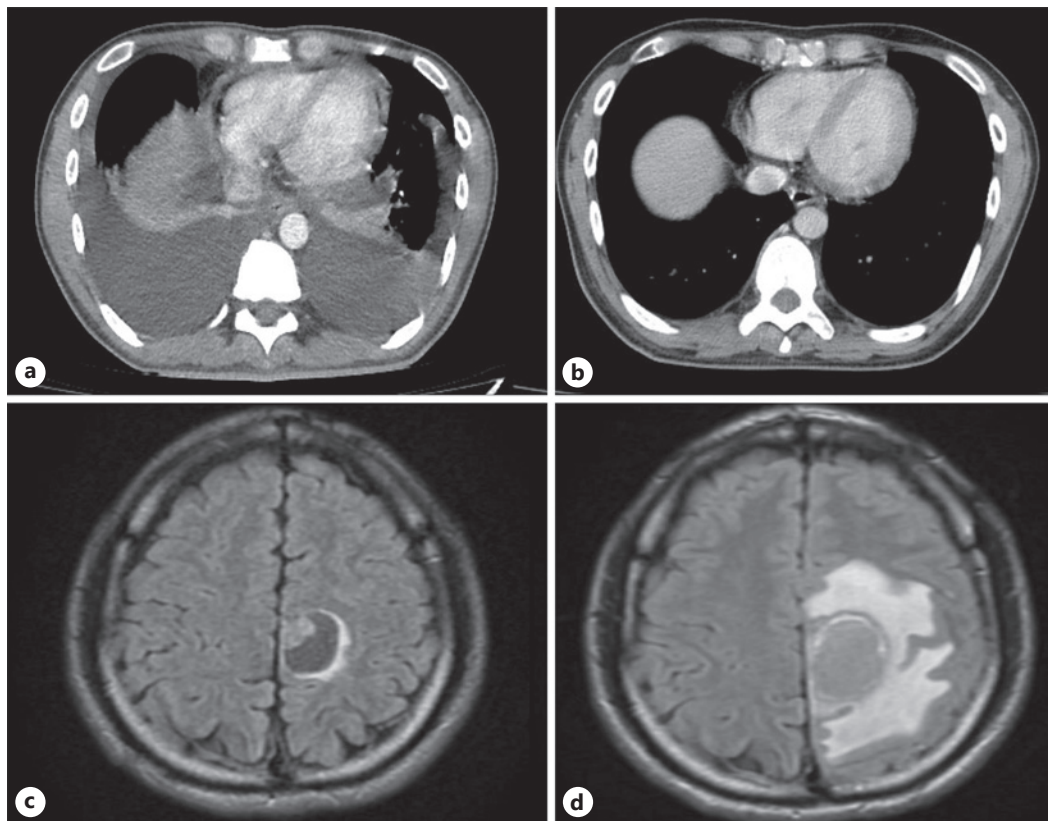
**Fig. 2.** Chest CT images were taken 4 months after ceritinib treatment. At this time, the patient developed difficulty breathing due to massive bilateral pleural effusion and pericardial effusion. CT, computed tomography.

approximately  $27 \times 40$  mm, causing increased oedema with at least 5 lesions with less peripheral drug absorption (Fig. 3).

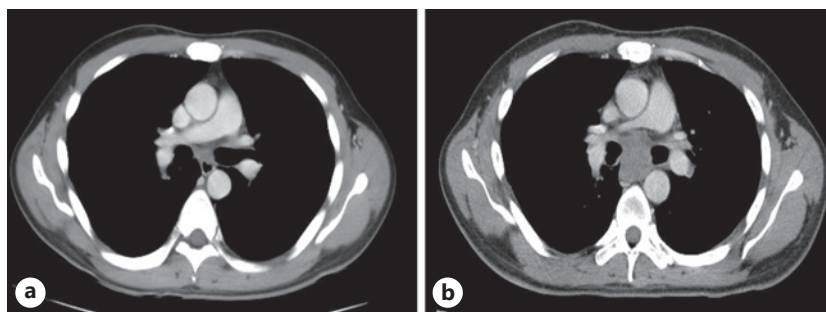
At this time, second gamma-knife surgery was considered, and at the same time, the patient was administered the third-generation TKI osimertinib, with the hope that the brain damage would be better controlled. After a month of treatment with osimertinib, we evaluated the patient with a total examination; the brain lesion was stable, and the mediastinal lymph nodes had increased in size (Fig. 4).

The patient's condition at that time was also very poor, with an Eastern Cooperative Oncology Group performance status index of 3. The patient felt exhausted and had difficulties tolerating chemotherapy. Therefore, we decided to incorporate ceritinib and osimertinib (starting in April 2020). The disease was assessed as exhibiting partial response 2 months after treatment when the mediastinal lymph nodes exhibited a decrease on the CT chest scan and the brain metastasis exhibited stability on the cranial MRI (Fig. 5).

To date, the patient has undergone 11 months of treatment with this regimen. Clinically, the patient's respiratory symptoms have significantly improved. The patient ceased coughing and exhibited improvements in chest pain and the mild paralysis in the right half of the body, as well as an improved quality of life. The pulmonary and lymph node lesions on chest CT tended to decrease, brain metastases were stable, and brain oedema decreased compared to the period before treatment. In terms of tolerance, the following adverse events were observed: grade I skin rash, mild fatigue, and grade I passing twice daily, which was well-controlled with loperamide.



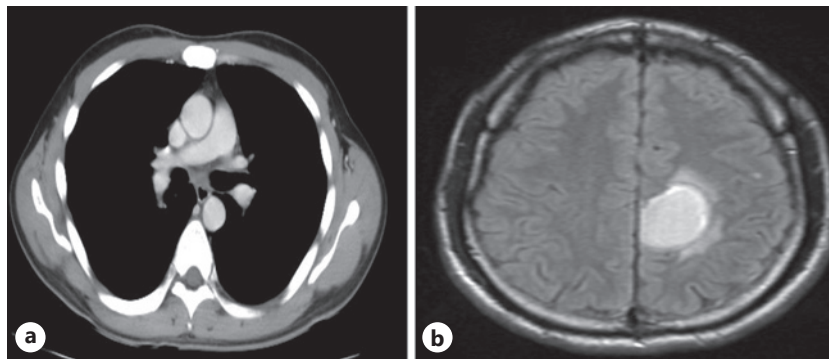
**Fig. 3.** Chest CT, cranial magnetic resonance imaging before (a, c) and after 3 months of treatment with erlotinib (b, d). The lung nodules, mediastinal lymph nodes, pleural fluid, and pericardial fluid have decreased compared to the untreated time; however, the brain lesions tended to progress in terms of size, and a number of brain metastases were accompanied by oedema. CT, computed tomography.



**Fig. 4.** CT scan images before (a) and after (b) administration of osimertinib. This time, the mediastinal lymph nodes returned and enlarged the bronchi and the mediastinal vessels. CT, computed tomography.

### Discussion

Detecting the molecular profile of tumours, particularly the identification of activating mutations of EGFR and ALK genes, is becoming very important in finding effective treatments for NSCLC. According to the literature, these 2 types of mutations are often found independently [6]. However, in reality, a number of authors have reported cases of concurrence of these 2 mutations.



**Fig. 5.** CT scans of the chest (**a**) and cranial MRI (**b**) were recorded 2 months after treatment with the TKI combination of osimertinib and ceritinib. Mediastinal lymph nodes rapidly decreased and brain metastases stabilized, with a decrease in size and oedema of the surrounding brain. TKI, tyrosine kinase inhibitor; CT, computed tomography.

Recent data show that between 1.3 and 1.6% of patients with NSCLC have both EGFR mutations and ALK translocations [7, 8]. To date, there have been no optimal treatment protocols for these patients. In patients with driver mutations, numerous phase III clinical trials have demonstrated the superior efficacy of targeted therapy compared with chemotherapy containing platinum, in terms of improved response rates and progression-free survival [1–4]. The remarkable point of this treatment over chemotherapy is the ability of the TKIs to cross the blood-brain barrier, making the drug effective in patients with CNS metastases [9].

At present, there are insufficient data to decide whether to choose an anti-EGFR or ALK as primary therapy in patients with concurrent EGFR and ALK mutations. A 100-case review found that ALK-TKIs seem to elicit a higher response rate than EGFR-TKIs [10]. By contrast, as reported by Schmid et al. [11] EGFR inhibition may be more effective than ALK-TKI in patients with concomitant EGFR-ALK mutations.

In our patient, we decided to use the selective ALK-TKI ceritinib for first-line treatment because the patient had brain metastases and because osimertinib is not approved for use in Vietnam. However, despite a rapid clinical response, the patient's disease progressed only after 4 months. When the treatment was switched from an ALK-TKI to an EGFR-TKI (erlotinib), the patient experienced a partial response. However, the response time was only a few months. According to Schmid et al. [11], their patient was initially treated with ALK-TKI and exhibited progression after 1.3, 5.7, and 7.3 months. According to them, an initial treatment with EGFR-TKI achieves an mPFS of 5.8 months, which is lower than the results of previous phase III trials [1, 3, 4]. In contrast, Yang et al. [8] reported an mPFS of 11.2 months amongst patients on first-line treatment with EGFR-TKI. Thus, the hypothesis of rapid progression with TKI treatment is also inconsistent in the previous studies; nevertheless, according to a review of 100 cases with this concomitant mutation, many cases rapidly progress after TKI treatment [10].

After failure with monotherapy, the combination of both EGFR and ALK-TKIs, osimertinib and ceritinib, continued to elicit a response. In terms of drug tolerance, our patient experienced well-controlled adverse effects, and the patient's quality of life also significantly improved. After 10 months of treatment, the disease remains stable.

From this case, we would like to raise a few points for discussion. First is the choice of sequential treatment with TKIs or an initial combination of 2 types of TKIs. In our patient, after failing with ALK-TKI, the EGFR treatment elicited a good response; however, the response time of ALK-TKI and EGFR-TKI is only 3–4 months. It appears that the remaining mutant cell lines of ALK or EGFR continue to grow if we use only one of the 2 types of TKIs.

Moreover, in our patient, the response and tolerance to the two-target combination was good and had been more likely to be more effective in prolonging the response time than sequential treatment. To date, the problem of combination treatment with 2 targets, ALK and EGFR, has not been fully addressed in terms of efficacy and toxicity.

The last point is with regard to CNS Response. In this patient's case, both ALK-TKI and EGFR-TKI treatment did not achieve a substantial intracranial response; nevertheless, the extracerebral response was excellent. Therefore, stereotactic radiosurgery has been performed to control the size and symptoms of the brain metastases, which are very common in patients with ALK and EGFR mutations. New-generation TKIs have also been shown to elicit a high response rate to CNS metastases [12, 13]. However, with the unexpected brain response results in our patient, we have reviewed the literature; unfortunately, the CNS response in patients with these 2 mutations remains unclear.

## Conclusions

Concurrent EGFR mutation with ALK reassortment is a relatively uncommon case amongst patients with advanced NSCLC, therefore, understanding the molecular characterisation of genes via gene profiles is necessary. Currently, there have been some reports on the use of EGFR-TKI or ALK antagonists in monotherapies as lines of treatment. However, there is no clinical evidence proving the efficacy or safety of the combination of EGFR and ALK inhibitors or multi-targeted TKIs. Furthermore, the response of the central nervous system remains unclear, and which TKI generation should be used for highest efficiency still needs follow-up assessment.

## Statement of Ethics

The written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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There is no funding source or sponsor to report.

## Author Contributions

T.H.T.N. and X.D.P. contributed substantially to the conception and design of the case report, as well as to the acquisition, analysis, and interpretation of the patient data. T.H.T.N. drafted the manuscript. X.D.P., K.L.D., and T.T.V. critically reviewed and revised the manuscript for important intellectual content and gave their final approval.

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