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# Transformation of lung adenocarcinoma treated with afatinib into small-cell carcinoma — a case report

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Oncology in Clinical Practice  
2020, Vol. 16, No. 3: 140–142  
DOI: 10.5603/OCP.2020.0014  
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ISSN 2450–1654

## ABSTRACT

In patients with advanced lung adenocarcinoma harbouring *EGFR* mutations, the use of molecularly targeted therapy has significantly increased progression-free survival (PFS) and in some studies also overall survival (OS). Unfortunately, during therapy all patients develop resistance. In about half of the cases the cause of progression is the appearance of the T790M mutation of the *EGFR* gene. Other described resistance mechanisms are as follows: transformation into small-cell carcinoma (14%), *MET* amplification (5%), and *PIK3CA* mutations (5%). Herein we report the case of patient with disseminated lung adenocarcinoma treated with a tyrosine kinase inhibitor (afatinib), whose disease progressed after 13 months of treatment as a result of transformation into small-cell carcinoma. Despite palliative chemotherapy with cisplatin and etoposide, the patient died six months later.

**Key words:** lung cancer, EGFR inhibitors

Oncol Clin Pract 2020; 16, 3: 140–142

## Introduction

Lung cancer is the most common cancer in the world and the main cause of cancer-related deaths [1]. The distinction between non-small-cell (NSCLC) and small-cell lung cancer (SCLC) is of fundamental clinical importance. NSCLC is diagnosed in 85% of patients, which can be divided into adenocarcinoma, squamous-cell carcinoma, large-cell carcinoma, and other histological types. In patients with advanced lung adenocarcinoma, the presence of epidermal growth factor receptor (*EGFR*) gene mutations and *ALK* and *ROS1* gene rearrangements should be assessed. These molecular disorders are the gripping point for molecularly targeted drugs. The use of tyrosine kinase inhibitors (erlotinib, gefitinib, afatinib or osimertinib) in patients with an activating *EGFR* gene mutation has doubled the median progression-free survival (PFS) and has probably extended overall survival (OS). In phase III clinical studies in patients treated with afatinib, the median PFS reached 11 months and median OS 28 months [2]. Unfortunately, molecularly targeted

treatment induces resistance, the mechanism of which in some patients remains unexplained. Only patients with acquired T790M *EGFR* gene mutation may be treated with another targeted drug (osimertinib). Other patients in further treatment lines receive chemotherapy because immunotherapy seems to be ineffective.

Chemotherapy sometimes combined with immunotherapy (atezolizumab) is the main method of metastatic SCLC. Patients with objective benefit from systemic treatment should be offered elective radiation therapy to the central nervous system, and sometimes carefully selected patients also receive radiation therapy to the chest area, although the value of the latter procedure raises serious doubts [3].

## A case report

In May 2017, a woman aged 63 years was admitted to the Chemotherapy Department with the diagnosis of left lung adenocarcinoma with liver metastasis. The patient was in a very good condition and did not report

concomitant diseases, she was non-smoker, and the family history of cancer was negative. Molecular studies showed the presence of deletions in the 19<sup>th</sup> exon of the *EGFR* gene. In June 2017, the patient began treatment with afatinib within the Ministry of Health's drug program. Computed tomography performed after three months of treatment revealed partial remission of the disease according to the RECIST 1.1 criteria. Treatment with afatinib was continued, and a sustained response was observed in the subsequent imaging studies. The tolerance of EGFR inhibitor therapy was quite good and the side effects — acne-like rash, nail shaft inflammation and diarrhoea (all CTCAE grade 1) — resolved after supportive care. In July 2018, after 13 months of afatinib therapy, computed tomography revealed progressive disease in the chest and hepatic lesions as well as the appearance of bone metastases. The anti-EGFR treatment was discontinued.

It was proposed that the patient undergo a liquid biopsy or collect histopathological material from the metastatic liver tumour in order to determine the T790M mutation. The patient chose a coarse needle liver biopsy. Small-cell lung carcinoma was found in the liver specimen. Genetic testing confirmed the presence of deletions in the 19<sup>th</sup> exon of the *EGFR* gene, and T790M mutation was excluded. Therefore, chemotherapy with cisplatin with etoposide was initiated (first cycle in August 2018). Computed tomography after three cycles of chemotherapy showed partial remission according to RECIST 1.1 criteria and features of asymptomatic pulmonary embolism. Treatment with therapeutic dose of low-molecular weight heparin was initiated, and chemotherapy was postponed for a month. Then another two cycles of systemic treatment were given, during which deterioration of performance status and worsening of tolerability of therapy were observed. After the fifth cycle, the patient was diagnosed with neutropenic fever. Due to the appearance of pain, skeletal scintigraphy was performed, which revealed the progression of bone metastases. Palliative chemotherapy was discontinued. The patient underwent palliative radiotherapy of the right hip and pubic area to alleviate pain. Computed tomography performed in January 2019 revealed multiple metastatic changes in the brain, lungs, and liver. Due to deterioration of the patient's general condition, palliative radiotherapy to the central nervous system was abandoned. Symptomatic treatment was applied. The patient died in January 2019.

## Discussion

Patients receiving EGFR inhibitors (reimbursed in Poland in the first line of treatment — erlotinib, gefitinib, afatinib) develop resistance over time. In about half of the patients (49–54%), the cause of disease

progression is the appearance of a secondary T790M mutation [4, 5]. In these patients, the use of osimertinib, a third-generation EGFR inhibitor, significantly improves the prognosis compared to chemotherapy. Further resistance mechanisms described comprise: transformation into small-cell carcinoma (14%), *MET* amplification (5%), and *PIK3CA* mutation (5%) [4]. According to the literature, the frequency of transformation in SCLC ranges from 3% to 14% [4, 6]. The described phenomenon can be explained by the formation of secondary mutations leading to a change in the phenotype of the tumour or the primary coexistence of small- and non-small-cell carcinoma cells in the tumour, followed by the selection of SCLC cells during molecularly targeted treatment. In most cases, after transformation in SCLC, the same *EGFR* mutation is still found, suggesting a direct evolution from NSCLC into SCLC, rather than an independent SCLC component [7]. The predisposing factor for the transformation of the lung adenocarcinoma into SCLC is probably the inactivation of the *RB1* and *TP53* genes [8].

In 2018, Marcoux et al. published a retrospective analysis of 67 patients with SCLC with *EGFR* mutation [9]. Eighty-seven per cent of patients were diagnosed with NSCLC and then transformed into SCLC during treatment (93% during *EGFR* inhibitor therapy). Other patients were originally diagnosed with SCLC and underwent *EGFR* mutation. In the NSCLC group, the median time from the initiation of molecularly targeted therapy to transformation into SCLC was 15.8 months, and the median time from the diagnosis of advanced NSCLC to the diagnosis of SCLC was 17.8 months. In this population, the median OS from the first diagnosis of malignancy and survival time from the transformation to SCLC were 31.5 and 10.9 months, respectively. After diagnosis of SCLC, chemotherapy with cisplatin and etoposide was most commonly used, with clinical response in 54% of patients. CNS metastases often appeared in the analysed group.

Ferrer et al. analysed survival parameters in 61 patients previously diagnosed with NSCLC, who were diagnosed with SCLC during treatment [10]. In the group of patients with the *EGFR* mutation (48 patients), the median time to transformation in SCLC was 16 months. Median OS and survival after diagnosis of SCLC were also similar to those obtained by Marcoux, and were 28 and 10 months, respectively. In 45% of patients with SCLC, partial response to cisplatin-etoposide chemotherapy was achieved. Data obtained by Ferrer et al. show that primary SCLC and SCLC induced by molecularly targeted treatment have similar clinical features.

Our patient had slightly worse survival parameters than those presented in the above-mentioned papers. Survival time from the initiation of afatinib

treatment to diagnosis of SCLC was 13.9 months. The patient lived 20.4 months from the diagnosis of NSCLC and 6.1 months after the diagnosis of SCLC.

## Conclusion

Transformation of lung adenocarcinoma treated with afatinib into SCLC is an example of a rare, but described in the literature, mechanism of resistance to treatment with EGFR inhibitors. In the presented patient, the collection of tissue material to determine the T790M mutation, followed by repeated histopathological examination, enabled the diagnosis of SCLC and administration of appropriate systemic treatment. The liquid biopsy, because it has a lower sensitivity in detecting the T790M mutation than a tissue biopsy, would not allow the transformation into another histological type to be found.

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