

ВИПАДКИ З ПРАКТИКИDOI: 10.21802/artm.2024.2.30.140
UDC 616.24-006-07-085.277**ARE ALECTINIB-INDUCED MYALGIA AND ELEVATION CREATINE PHSPHOKINASE PREDICTORS OF HIGH RECURRECCE-FREE SURVIVAL? CASE REPORT.**O.I. Vynnychenko¹, R.A. Moskalenko²¹Sumy Regional Clinical Oncology Center, Sumy, Ukraine²Sumy State University, Department of Pathology, Sumy, Ukraine

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Abstract. Introduction. One in eight cases and one in five deaths are related to lung cancer. Due to high heterogeneity, lung cancer often has an unfavorable prognosis. Approximately 3–5% of patients with non-small cell lung cancer (NSCLC) have an anaplastic lymphoma kinase (ALK) gene rearrangement.

Patients with stage I, II, or III lung cancer are undergoing surgery and adjuvant platinum-based chemotherapy. However, the five-year risk of recurrence and death ranges from 45% for patients with stage IB to 76% for patients with stage III. In addition, during adjuvant chemotherapy, 66% of patients experience grade 3 and 4 adverse events.

Research rationale. ALK-positive patients require targeted alectinib therapy. Alectinib is a highly selective second-generation TKI approved by the FDA for treating locally advanced and metastatic NSCLC. Several clinical trials have compared the efficacy and safety of alectinib with other TKIs (crizotinib, ceritinib) and platinum-based chemotherapy. The survival of patients taking alectinib is significantly higher than chemotherapy. In this case report, we would like to describe the development of alectinib-induced myalgia and creatine phosphokinase (CPK) elevation and evaluate their association with recurrence-free survival.

Materials and methods. We collected laboratory results and clinical data of a patient with stage IIIA of ALK-positive NSCLC who received adjuvant therapy with alectinib at 600 mg daily for 24 months.

The results. Four weeks after alectinib treatment, a biochemistry test showed a grade 1 CPK. After 12 weeks of alectinib treatment, the patient complained of severe muscle pain and weakness. The level of CPK increased three times and corresponded to 2 grades of severity. Targeted therapy was temporarily discontinued. The patient did not take alectinib for ten days. Myalgia symptoms were improved, so the patient continued the alectinib in the previous dose. Moderate myalgia continued for four months. Long-term follow-up after completion of treatment continues for five years and four months. No recurrence of the disease was registered.

Discussion. According to the scientific literature data, the mechanism of increasing CPK and the development of myalgia remains unknown. There are assumptions that the cause of myalgia may be inflammation in the muscles. In the ALEX clinical trial, myalgia was a reasonably common side effect of alectinib. 17.1% of patients reported pain, tenderness, or muscle weakness. However, in most cases, the symptoms were moderate, and only 3.3% of patients corresponded to 2 grades of severity. 76% of patients with stage III have a recurrence of the disease within a five-year period. The recurrence-free period of our patient lasts five years and four months. It can be assumed that the treatment results of this patient are satisfactory. Grade 2 myalgia and grade 2 CPK are potential predictors of good response to treatment and high recurrence-free survival. Patients taking alectinib should be warned about the possible appearance of myalgia already within the first month after the start of targeted therapy. Biochemistry test must include CPK. In most cases, there is a direct relationship between the level of CPK and the manifestations of myalgia.

Conclusions. Severe myalgia and grade 2 elevation of CPK are likely predictors of five-year recurrence-free survival in patients with completely resected NSCLC treated with adjuvant alectinib therapy.

Keywords: alectinib, targeted therapy, lung cancer, recurrence-free survival, ALK mutation, tyrosine kinase inhibitors, creatine phosphokinase, myalgia.

Introduction. Every eighth case of morbidity and every fifth case of death is related to lung cancer [1]. The most common histological variant is adenocarcinoma. It is diagnosed in 39% of men and 57% of women. Due to high heterogeneity, lung cancer often has an unfavorable prognosis [2].

Approximately 3–5% of patients with non-small cell lung cancer (NSCLC) have an anaplastic lymphoma kinase (ALK) gene rearrangement. ALK-positive patients are primarily under 50 years old, never smokers with adenocarcinoma tumor histology. At the time of diagnosis, they often have advanced stages [3].

Patients with stage I, II, or III lung cancer are undergoing surgery and adjuvant platinum-based chemotherapy. However, the five-year risk of recurrence and death ranges from 45% for patients with stage IB to 76% for patients with stage III. In addition, during adjuvant chemotherapy, 66% of patients experience grade 3 and 4 adverse events [4].

Rationale of study. Patients with ALK rearrangements require targeted tyrosine kinase inhibitors (TKIs) therapy. Alectinib is a highly selective second-generation TKI approved by the FDA for treating locally advanced and metastatic NSCLC. Several clinical trials have compared the efficacy and safety of alectinib with other

TKIs (crizotinib, ceritinib) and platinum-based chemotherapy. The survival of patients taking alectinib is significantly higher than chemotherapy [5, 6, 7]. This is probably related to the ability to penetrate the blood-brain barrier and affect brain metastases, diagnosed in about 60% of ALK-positive patients [8]. Long-term patient follow-up suggests that alectinib has a high safety profile. Most of the side effects can be eliminated by reducing the dose or temporarily withdrawing the drug [9].

The phase 3 ALINA study investigated the safety and efficacy of alectinib compared with adjuvant chemotherapy in patients with completely resected ALK-positive NSCLC. After two years of follow-up, 93.8% of patients from the alectinib group and 63% from the chemotherapy group had no disease recurrence [10]. Increasing levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin were the most common hematological adverse events of TKI. An increase in alkaline phosphatase and signs of renal failure were occasionally recorded [11]. Myalgia and elevation of creatine phosphokinase (CPK) are considered rare side effects of alectinib.

In this case report, we would like to describe the development of alectinib-induced myalgia and CPK elevation and evaluate their association with recurrence-free survival.

Materials and methods. We collected laboratory results and clinical data of a patient with ALK-positive NSCLC. A 46-year-old female patient visited the Sumy Regional Clinical Oncology Center in November 2018 due to a dry cough and shortness of breath within two months. Computed tomography revealed a tumor of the upper lobe of the right lung with a size of 15 mm, multiple mediastinal lymph nodes on the side of the lesion, and bifurcation lymph nodes. Bronchoscopy was not informative. Mediastinoscopy with biopsy confirmed that the histological variant of the tumor is adenocarcinoma. The patient was

diagnosed with IIIA stage of lung cancer (T1bN2Mo). An extended upper lobectomy on the right was performed in December 2018.

The patient was younger than 50 years old and had never smoked. Therefore, the presence of a genetic mutation was suspected. Tumor tissue as a paraffin block was sent to the CSD laboratory (Kyiv) to detect EGFR and ALK mutations. As a result, the presence of ALK rearrangement was confirmed. The patient had stage IIIA lung cancer and a poor prognosis. She was offered targeted therapy with alectinib.

The results. In January 2019, the patient started taking alectinib orally at a dose of 600 mg per day. No clinically significant deviations in laboratory indicators were registered on the baseline. The general condition of the patient was satisfactory. The level of CPK was within normal ranges. However, four weeks after alectinib treatment, a biochemistry test showed a grade 1 CPK. This condition required dynamic monitoring. Eight weeks after the treatment started, the level of CPK did not change, and no clinical symptoms were observed. After 12 weeks of alectinib treatment, the patient complained of severe muscle pain and weakness. Serum levels of AST, alkaline phosphatase, and uric acid increased to grade 1. The level of CPK increased three times and corresponded to 2 grades of severity. Targeted therapy was temporarily discontinued. No medication therapy was performed. An intensive drinking regime and restriction of physical activity were recommended. The patient did not take alectinib for ten days, after which a biochemistry test was repeated. All laboratory indicators were within normal ranges. Myalgia symptoms were improved, so the patient continued the alectinib in the previous doses. Moderate myalgia continued for four months. The levels of CPK during treatment with alectinib are presented in Figure 1.

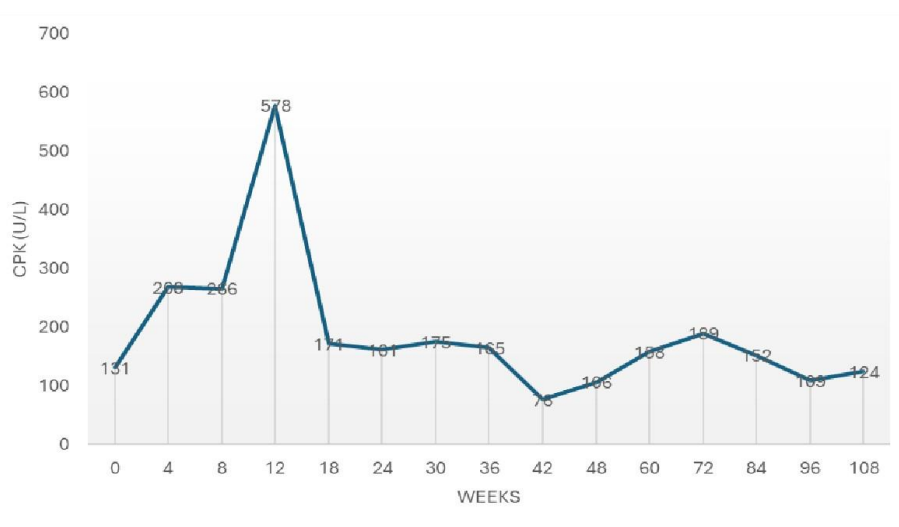


Figure 1. Changes of CPK during alectinib treatment. The normal range is 26–192 U/L.

The patient used alectinib targeted therapy for 108 weeks (24 months). During the entire period of treatment, dose modification was not performed. CPK remained within normal ranges. Long-term follow-up after completion of treatment continues for five years and four months. No recurrence of the disease was registered.

Discussion. We have described a rare clinical case of the development of grade 2 myalgia and grade 2 elevation of CPK. This condition was associated with alectinib treatment. According to the scientific literature data, the mechanism of increasing CPK and the development of myalgia remains unknown. There are assumptions that the cause of myalgia may be inflammation in the muscles [12].

In the ALEX clinical trial, myalgia was a reasonably common side effect of alectinib. 17.1% of patients reported pain, tenderness, or muscle weakness. However, in most cases, the symptoms were moderate, and only 3.3% of patients corresponded to 2 grades of severity. The first manifestations of myalgia appeared on average 1.1 months after the start of targeted therapy and disappeared 8.1 months after its completion. Myalgia relapse occurred in 11.5% of cases [9].

Shalata et al. [13], on the example of two cases from practice, suggested evaluating myalgia and CPK as predictors of a good response to alectinib therapy. However, in both cases, the patients had advanced ALK-positive tumors. In our case, the patient had stage IIIA and surgically resected NSCLC; therefore, the effectiveness of alectinib can be evaluated only by considering the impact on recurrence-free and overall survival. The recurrence-free period of our patient lasts five years and four months. 76% of patients with stage III have a recurrence of the disease within a five-year period [4]. It can be assumed that the treatment results of this patient are satisfactory. Grade 2 myalgia and grade 2 CPK are potential predictors of good response to treatment and high recurrence-free survival.

Patients taking alectinib should be warned about the possible appearance of myalgia already within the first month after the start of targeted therapy. Biochemistry test must include CPK. In most cases, there is a direct relationship between the level of CPK and the manifestations of myalgia. With an increase in CPK of more than 2.5 times and the presence of severe muscle pain, temporary withdrawal of alectinib is recommended. The drug is continued in the same doses with the normalization of laboratory indicators and muscle pain relief. If CPK increases by more than five times and after the withdrawal of the drug does not decrease to the initial level, the dose of alectinib is reduced. Repeated increases in CPK by more than five times or the first increase by more than ten times are indications for temporary withdrawal of the drug and subsequent dose reduction [14].

Conclusions. Severe myalgia and grade 2 elevation of CPK are likely predictors of five-year recurrence-free survival in patients with surgically resected NSCLC treated with adjuvant alectinib therapy.

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Conflict of interest. The authors declare no conflict of interest.

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ЧИ Є ІНДУКОВАНА АЛЕКТИНІБОМ МІАЛГІЯ ТА ПІДВИЩЕННЯ РІВНЯ КРЕАТИНФОСФОКІНАЗИ ПРОГНОСТИЧ- НИМИ ФАКТОРАМИ ВИСОКОГО БЕЗРЕЦИДИВНОГО ВИЖИВАННЯ? ВИПАДОК З ПРАКТИКИ

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Вступ. Кожен восьмий випадок захворюваності та кожен п'ятий випадок смерті пов'язаний з раком легень.

Обґрунтування дослідження. Приблизно у 3–5% пацієнтів, хворих на недрібноклітинний рак

легень (НДКРЛ), виявляють перебудову гена кінази анапластичної лімфоми (ALK). Такі пацієнти потребують таргетної терапії алектинібом. У даному випадку з практики ми хочемо повідомити про розвиток алектиніб-індукованої міалгії та підвищення креатин фосфокінази (КФК) та оцінити їх зв'язок з безрецидивною виживаністю.

Матеріали та методи. Ми збрали дані лабораторних та інструментальних досліджень пацієнтки з IIIA стадією ALK-позитивного раку легень, що отримувала ад'ювантну терапію алектинібом у дозі 600 мг на день протягом 24 місяців.

Результати. Через 4 тижні від початку терапії зареєстровано підвищення КФК 1 ступеня. Через 12 тижнів від початку терапії з'явилася важка міалгія, рівень КФК підвищився до 2 ступеня тяжкості. Алектиніб відмінили на 10 днів. Після нормалізації рівня КФК та полегшення симптомів міалгії відновили прийом препарату у тих же дозах. Безрецидивний період у пацієнтки триває 5 років та 4 місяці.

Обговорення. У 76% пацієнтів з III стадією рецидив захворювання реєструють протягом перших п'яти років після радикальної операції. ALK-позитивні пацієнти потребують ад'ювантної таргетної терапії препаратом алектиніб. За даними наукової літератури алектиніб-індуковане підвищення КФК вважається предиктором гарної відповіді у пацієнтів із метастатичним раком легень. Зокрема, на прикладі двох випадків із практики автори запропонували оцінювати міалгію та КФК як предиктори гарного прогнозу. Проте, в обох випадках пацієнти мали занедбані ALK-позитивні пухлини. У нашому випадку пацієнтка мала IIIA стадію та повністю резектований НДКРЛ, тому можна оцінювати ефективність алектинібу лише в аспекті впливу на безрецидивну та загальну виживаність.

Висновки. Важка міалгія та підвищення КФК більш ніж у 3 рази, ймовірно, можуть вважатися предикторами п'ятирічної безрецидивної виживаності у пацієнтів з повністю резектованим НДКРЛ, що отримували ад'ювантну терапію алектинібом.

Ключові слова: алектиніб, таргетна терапія, рак легень, безрецидивна виживаність, мутація ALK, інгібітори тирозинкінази, креатинфосфокіназа, міалгія.

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