JMS2023;Vol 6 (2):140-146
UDC:616.24-006.66-085.277
DOI: 10.55302/JMS2362140i

EXCELLENT RESPONSE TO ALECTINIB IN ALK-POSITIVE NSLC ADENOCARCINOMA, CASE REPORT AND LITERATURE REVIEW

Irfan Ismaili,[1] Vesna Pachoska Stojchevska, [1] Olivera Gjeorgjieva Janev [2]
[1] University Clinic of Pulmonology and Allergology, Skopje, North Macedonia
[2] University Clinic of Rheumatology, Skopje, North Macedonia

Abstract

Non-small cell lung carcinoma (NSCLC) is a type of lung carcinoma that slowly grows within the lung tissue. Hence, it is often diagnosed late when the disease has already progressed and passed to other body organs and/or lymph nodes.

In most cases, this makes NSCL inoperable at the exact moment of diagnosing, which leads to the necessity of using chemotherapy that has the purpose of narrowing the extended masses in the lungs and/or any near/further metastases. Alectinib is a tyrosine-kinase inhibitor (TKI) that is currently being used as a first-line target therapy in treating the inoperable ALK rearranged NSCLC, but still the effectiveness of the treatment is not definitely known and examined.

Herein, we present the case of a 51-year-old male patient admitted to our hospital with hemoptysis for 2 weeks. Contrast-enhanced computerized tomography (CT) of the chest showed an approximately 28x23 mm soft tissue mass infiltrating the lumen of the right bronchus and causing obstruction.

On the same side at the base, a hypodense nodule of 19 mm with some surrounding pneumonic reaction and irregular contours was detected. Several significant lymph nodes were detected in the hilar and mediastinal regions. Bronchial biopsy of the mass showed pulmonary adenocarcinoma and the immunohistochemical testing results confirmed ALK rearrangements. TKI

Alectinib was given at a dosage of 600mg twice per day for 13 cycles, achieving a complete response of the disease with complete regression of the mass in the right bronchus, complete regression of the right nodule and hilar and mediastinal lymph nodes were not detected following the treatment.

The patient continued to receive Alectinib and did not report any specific discomfort at his 13th month follow-up.

Keywords: NSCLC, Lung adenocarcinoma, ALK rearrangement, TKIs, Alectinib.

Introduction

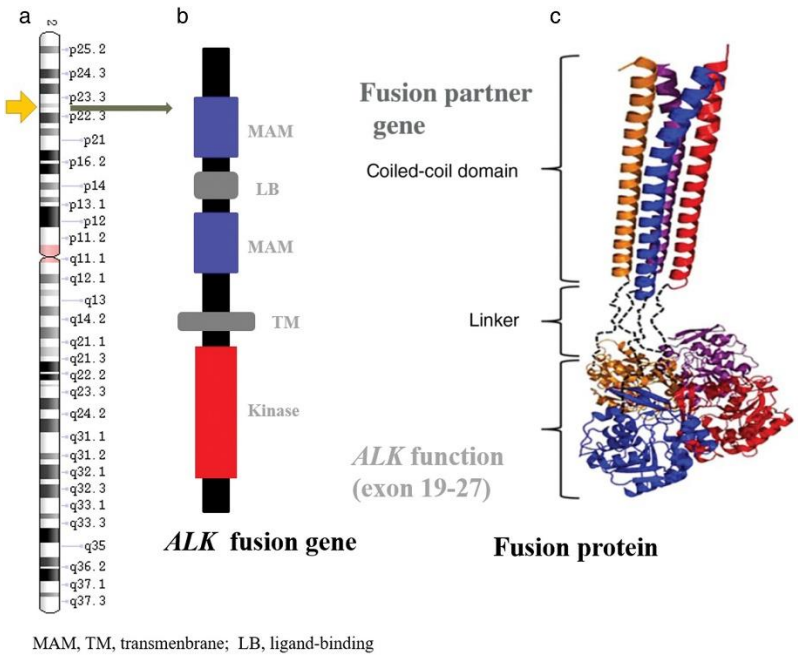
Lung cancer is one of the leading causes of death all around the world. Non-small cell lung cancer accounts for about 85% of all lung cancers, of which 30–40% are “resectable”, including most stage I-IIIA and a small proportion of stage IIIB lung cancers [1]. For the patients that have a later diagnosed lung cancer when the disease has already progressed to a higher stage, a resection is not an option.

In recent years, chemotherapy has increasingly become a valuable but controversial treatment modality [2]. According to the NSCLC Meta-Analysis Collaborative Group [3], chemotherapy is effective in reducing tumor size and improving surgical resection rates, but has not shown any survival advantage.

Anaplastic lymphoma kinase (ALK) fusion is a well-defined biomarker for ALK tyrosine kinase inhibitors (TKIs) treatment in non-small cell lung cancer (NSCLC).

The ALK gene is located on the short arm of chromosome 2 (2p23), belongs to the insulin receptor superfamily, and encodes for the ALK protein (Figure 1a). ALK is a transmembrane tyrosine kinase receptor, and like the other receptor tyrosine kinases, it has an extracellular domain, a transmembrane segment, and a cytoplasmic receptor kinase segment (Figure 1a–c) [4-6].

ALK expression occurs in the nervous system during embryo genesis and decreases in postnatal life. Therefore, in human adults, low levels of ALK protein are produced only in rare, scattered neural and endothelial cells and in pericytes in the brain[7,8].



MAM, TM, transmenbrane; LB, ligand-binding

Figure 1

ALK inhibitors bind to the ATP-binding pocket of the intracellular tyrosine kinase domain, and regulate their downstream signals such as the RAS, PI3K-AKT, JAK/STAT signaling cascades which are involved in tumor progression; the attenuation of these cascades produces an antitumor effect [4-6].

At present, several ALK inhibitors, including crizotinib, alectinib, ceritinib, brigatinib, ensartinib, and lorlatinib, have been approved as a standard therapy for ALK-p NSCLC [7-9].

Alectinib, a second-generation ALK-TKI, has been shown to have significantly longer progression-free survival (PFS) compared to the first-generation ALK inhibitors in untreated ALK-rearranged NSCLC patients. However, its clinical efficacy on rare ALK fusions remains unclear [10].

Case presentation

We present a 51-year-old male patient with hemoptysis that had appeared two weeks before the examination. The patient does not smoke cigarettes and has never been a smoker.

A contrast-enhanced computerized tomography (CT) of the chest was performed, revealing a soft tissue heterodense substrate measuring 28x23 mm on the right side, infiltrating the lumen of the main bronchus and causing obstruction. On the same side at the base, a hypodense nodule of 19 mm with some surrounding pneumonic reaction and irregular contours was observed. Several significant lymph nodes were detected in the hilar and mediastinal regions (Figure 2).

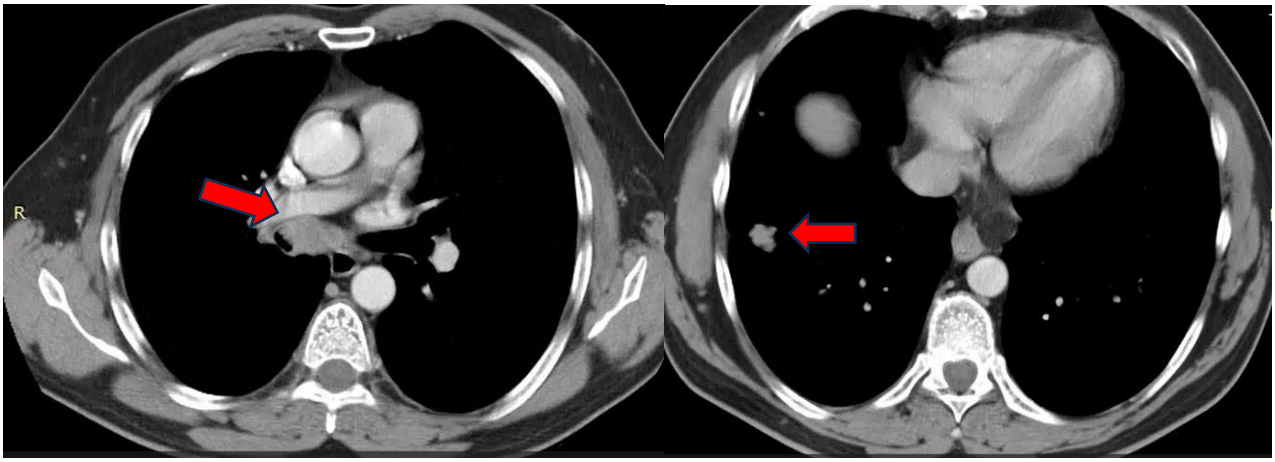


Figure 2 CT chest before treatment

The patient was scheduled for a bronchoscopy and less than 2 cm from the main carina, a fleshy tumor-like formation was seen, bleeding spontaneously and completely closing the start of the intermediate bronchus on the right (Figure 3).

A bronchial biopsy was taken, which provoked moderate bleeding controlled with saline and an ampoule of adrenaline. The biopsy showed neoplastic proliferate in a solid glandular arrangement, built from medium-large high cubic cells with a large nucleus and individual mitoses. There was abundant mucin production in the rich cytoplasm. Infiltrates were seen in the moderately expressed connective stroma and in the bronchial wall. The supplied biopsy material corresponded to a mucin-producing adenocarcinoma.

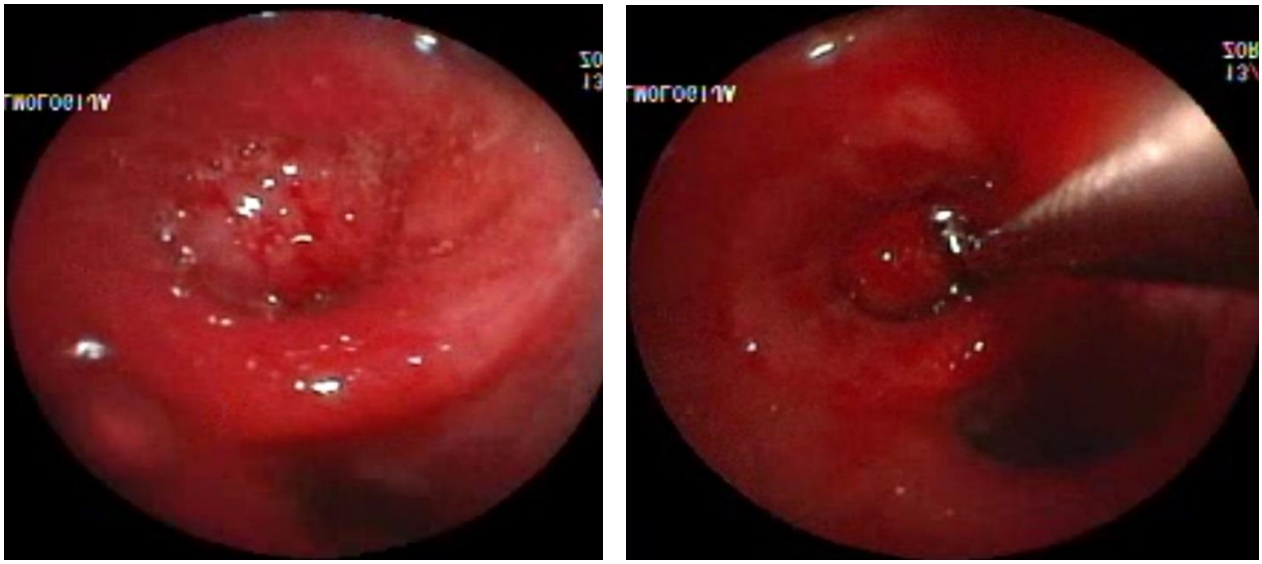


Figure 3 Bronchoscopic view

The patient was then referred to an oncologist where histopathological, radiological, and bronchoscopical evidence of primary adenocarcinoma was confirmed in the projection of the right main bronchus, with secondary changes in ipsilateral mediastinal lymph nodes and highly suspicious contralateral mediastinal lymph nodes.

The disease stage according to the TNM classification is T4N3M0 Stage IIIC. The oncologist indicated initiation of chemotherapy according to the T/P (paclitaxel plus cisplatin) protocol. In the meantime, the biopsy material was sent for molecular diagnostics so as to detect any specific genetic mutations.

The patient received two cycles of chemotherapy according to the T/P protocol with adequate premedication and hydration while waiting for the results of the molecular diagnostics.

The provided molecular profile of the disease was positive for ALK rearrangements.

The rearrangements were detected with immunohistochemical testing of the expression of ALK protein with Ventana anti-ALK Rabbit Monoclonal Primary Antibody clone DF53- Ventana BechMark ULTRA automated stainer (Ventana Medical system). A strong granular cytoplasmic positivity was present in over 40% of the tumor cells. It was indicated to start first-line anti-ALK inhibition with Alectinib 150 mg capsules, four in the morning and four in the evening (600 mg twice daily). After one month of regular control, a slight elevation of creatinine above the upper limit and a slight elevation of total bilirubin above the upper limit were noted.

The therapy continued with a reduction in dosage (three tablets in the morning and three in the evening). After three months, a control CT of the chest was performed showing regression of the soft tissue substrate in the right hilar, which was not detected at all, and a reduction in the irregular nodule right basally from 19 mm to 10 mm with presence of surrounding fibrotic densities. There was no hilar or mediastinal lymphadenopathy.

A control CT of the abdomen was performed as well, where no secondary deposits were detected. The patient underwent a three-week control with a complete laboratory analysis, and due to the normalization of laboratory parameters, the dose of 4+4 capsules of Alectinib 150 mg (total 1200 mg- twice 600 mg) was resumed. Six months after the initiation of the Alectinib therapy, a second control CT of the chest was performed with further regression of the previously described residual change in the right lung.

The patient underwent a control CT of the chest and abdomen every three months with further regression. After 13 months from the start of anti-ALK inhibition with Alectinib, the control CT of the lungs showed complete regression of the tumor, with the disappearance of the irregular nodule right posterobasal, which initially was 19 mm, with the existence of a flat fibrotic change with traction of the local bronchi and the interlobium at the same place (Figure 4).

The patient's therapy with anti-ALK inhibition with Alectinib continues with regular controls every three weeks and a control CT of the chest every three months.

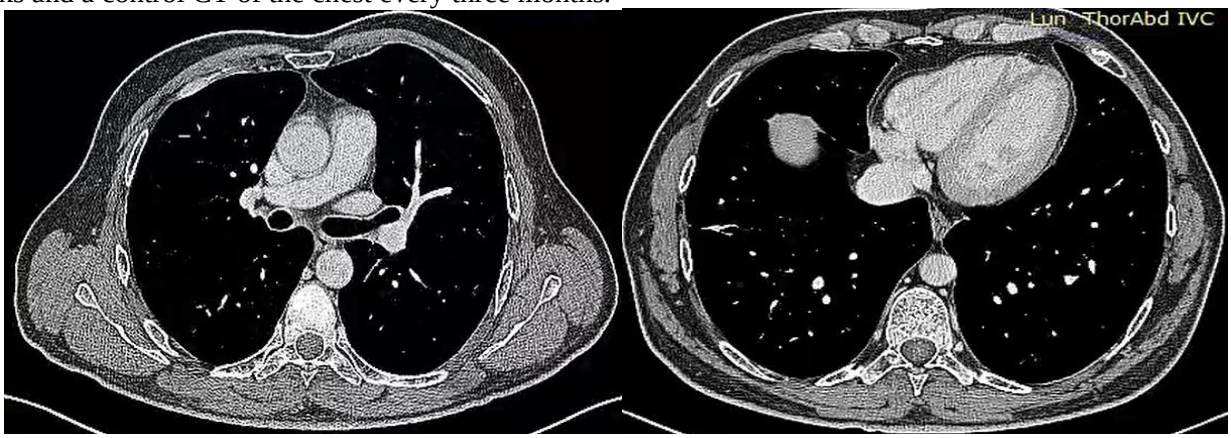


Figure 4 After treatment

Discussion

Lung cancer is the cause of 1.5 million deaths every year with <20% of 5-year-prognosis for newly diagnosed patients [16]. In 50% of those diagnosed, the disease is in an advanced stage. Medical overall survival is less than 1 year and a five-years-survival rate is approximately 4-5%. In recent years, medical overall survival has increased dramatically, especially in the developed countries primarily due to early diagnosis and specific treatment with a targeted therapy or immunotherapy.

Based upon the microscopic appearance of tumor cells, lung cancers are classified into two main types: small cell lung cancer (15– 20%) and non-small cell lung cancer (80–85%). [18] NSCLC are further subdivided into three main types: adenocarcinoma (40%), squamous cell carcinomas (30%) and large cell carcinomas.

This classification is based upon the types of cells found in the tumor [19].

Molecular and biological targets involved in cancer growth and survival (gene mutations, proteins and signaling pathways) have been identified and progress has been made in the understanding of tumor biology [20].

Gene mutations like EGFR gene mutation (10–15% nsclc), KRAS mutations (10–15% nsclc) and ALK gene rearrangement (5% NSCLC); Proteins like Epidermal growth factor receptor (EGFR), abnormal ALK protein; are some of the targets in NSCLC that have modernized the concept of personalized medicine [21].

These newer developments have essentially led to modern molecular classification of NSCLC particularly in the case of the histology cell type adenocarcinoma. Lung adenocarcinoma (LUAD) is the most common histologic subtype of lung cancer and accounts for approximately 40% of lung cancer incidence worldwide [22].

Adenocarcinoma of the lung usually evolves from the mucosal glands and represents about 40% of all lung cancers. It is the most common subtype to be diagnosed in people who have never smoked. Lung adenocarcinoma usually occurs in the lung periphery, and in many cases, it may be found in scars or areas of chronic inflammation [23].

Anaplastic lymphoma kinase (ALK*)* gene rearrangements occur in a small portion of patients with non-small cell lung cancer (NSCLC). These gene rearrangements lead to constitutive activation of the ALK kinase and subsequent ALK-driven tumor formation. Patients with tumors harboring such rearrangements are highly sensitive to ALK inhibitors such as crizotinib, ceritinib, and alectinib [24].

ALK rearrangements occur in approximately 5% of patients with NSCLC. While initially identified as EML4-ALK,[25,26]· fusions with a variety of other genes have been reported, all leading to dysregulated over-expression of ALK. Patients with ALK positive tumors tend to be younger and more likely to be never-smokers or light smoker [25] with ALK rearrangements occurring in 12% of never-smokers compared to only 2% of former or current smokers [24].

Alectinib is a potent and highly selective anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor. Oral alectinib monotherapy is approved in the EU as first-line treatment for adults with advanced ALK-positive non-small cell lung cancer (NSCLC) and for the treatment of adults with advanced ALK-positive NSCLC previously treated with crizotinib[27].

In some studies comparing alectinib to crizotinib, alectinib was associated with longer progression-free survival and lower toxicity than crizotinib and showed activity against CNS disease in patients with ALK-positive NSCLC. [27].

Current evidence indicates that alectinib is an important treatment option for patients with advanced ALK-positive NSCLC who were previously untreated or those previously treated with crizotinib. Given its efficacy and tolerability, current guidelines include alectinib as a treatment option in these settings, and the NCCN guidelines recommending it as a preferred option for first-line therapy[28].

Conclusion

In the presented case we can observe the benefit of molecular diagnostics on biopsied tissue, the detection of ALK rearrangements, and the selection of appropriate treatment.

ALK rearrangements should be considered and investigated in all younger non-smoking patients with histopathologic proven lung adenocarcinoma given the good response to specific targeted therapy in these patients.

The patient is still on the first line of anti-ALK inhibition with Alectinib and will continue to be monitored. However, we have observed excellent results in the patient from the presented case and complete regression of the disease after only 13 months of therapy with Alectinib.

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