

Personalized Approach to Therapy Selection in a Patient with ALK-Positive Non-Small Cell Lung Cancer: A Clinical Case

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Abstract. Anaplastic lymphoma kinase-positive non-small cell lung cancer (ALK-positive NSCLC) is a molecularly defined subtype of lung cancer in which the optimal sequencing of systemic therapy is essential for achieving long-term disease control. Progression involving the central nervous system (CNS) represents a particular clinical challenge, as intracranial disease control becomes an independent and important treatment objective. The aim of this study was to demonstrate the potential of an individualized approach to treatment selection in a patient with ALK-positive NSCLC who received several consecutive lines of therapy with ALK inhibitors, including lorlatinib after CNS progression. The clinical case was described using data from the patient's medical history, computed tomography and magnetic resonance imaging, morphological, immunohistochemical, and molecular genetic examinations, multidisciplinary team decisions, and information on systemic and radiation therapy. A 40-year-old patient was diagnosed with ALK-positive NSCLC of the lower lobe of the right lung, stage IIIB (T4N2M0). Following disease progression after platinum-based chemotherapy, sequential targeted therapy with crizotinib and ceritinib was administered. When multiple brain metastases developed, the patient received symptomatic radiation therapy followed by chemotherapy. In February 2024, treatment with lorlatinib was initiated. This therapy resulted in clinical improvement, stabilization of the pulmonary lesions, and positive radiological dynamics according to follow-up brain MRI. The presented case highlights the importance of timely molecular profiling, regular assessment of CNS involvement, multidisciplinary decision-making, and personalized selection and sequencing of ALK inhibitors. Lorlatinib may provide effective systemic and intracranial disease control after progression during previous lines of treatment.

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Introduction

Non-small cell lung cancer (NSCLC) remains one of the leading causes of cancer morbidity and mortality. The identification of molecular subtypes of NSCLC has changed approaches to systemic treatment: tyrosine kinase inhibitors play a key role in the presence of driver rearrangements, including the rearrangement of the anaplastic lymphoma kinase (ALK) gene [1]. For patients with ALK-positive disease, it is especially important not only to control the systemic process, but also to prevent or treat metastatic CNS damage [2].

Brain damage in ALK-positive NSCLC is common and can determine a patient's prognosis, functional status, and quality of life [2]. Therefore, when choosing therapy after progression on early ALK inhibitors, it is necessary to take into account the activity of the drug against intracranial foci, previous therapy, tolerability and dynamics of the disease according to imaging data [3].

Lorlatinib is a next-generation ALK/ROS1 inhibitor designed to cross the blood-brain barrier [4]. The presented clinical example illustrates the practical importance of consistent use of ALK inhibitors and the transition to lorlatinib in a patient with confirmed progression in the central nervous system.

The aim of the study was to demonstrate the possibilities of an individualized approach to the choice of therapy in a patient with ALK-positive non-small cell lung cancer with the consistent use of ALK inhibitors, including the appointment of lorlatinib after the progression of the disease in the central nervous system.

Materials and methods

The material was prepared on the basis of a presentation clinical example containing information about the patient, examination data, decisions of a multidisciplinary group, conducted systemic and radiation therapy, as well as the results of control CT and MRI studies.

Patient information: Patient P, a 40-year-old male, non-smoker, has been observed since 2021. Diagnosis: malignant neoplasm of the lower lobe of the right lung, stage IIIB, T4N2M0; ALK-positive NSCLC. No metastatic brain damage was detected at the time of initial follow-up. The complaints included headaches, weakness, and periodic dizziness. In November 2020, the patient had a history of interstitial pneumonia on the right, associated with COVID-19.

Primary diagnosis: A CT scan of the chest organs from 05.01.2021 revealed signs of a malignant neoplasm of the right lung with multiple foci up to 35 mm, after which the patient was referred to an oncological center for further examination. Fibrobronchoscopy on 02.02.2021 showed no pathological changes. According to chest X-ray data from 02.02.2021, a focal formation in the right lung is described, requiring a differential diagnosis.

According to the decision of the multidisciplinary group dated 02/03/2021, surgical treatment is recommended. Diagnostic thoracotomy was performed on 04/15/2021. According to the data from an immunohistochemical study dated 04/23/2021, bronchiol-alveolar cancer, M8252/3, was established. A molecular genetic study dated 04/30/2021: no mutation of the epidermal growth factor receptor was detected; ALK 3+, PD-L1 expression was noted.

Treatment and dynamics of the disease: Palliative chemotherapy followed by a CT scan of the chest organs was recommended at the meeting of the multidisciplinary group on 05.27.2021. The patient received 4 courses of chemotherapy according to the pemetrexed + platinum drug

scheme. CT scan of the brain from 10/19/2021 revealed no pathological changes, but CT scan of the chest organs from 10/19/2021 showed the progression of the tumor process (Figure 1A).

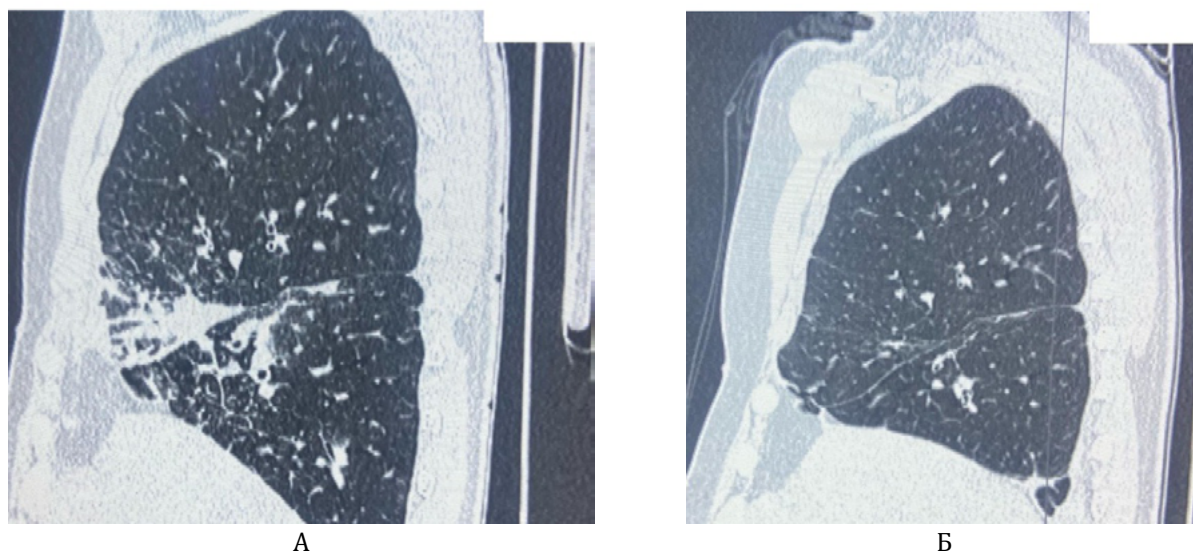


Figure 1. Patient P, a 40-year-old man, diagnosed with malignant neoplasm of the lower lobe of the right lung, stage IIIB, T4N2M0; ALK-positive NSCLC: A - baseline study (2021); B - control study (2024).

Source: photo of the authors

After the progression to platinum-containing chemotherapy on 10/27/2021, it was decided to prescribe targeted therapy with crizotinib. After the first courses of treatment, according to CT scans of the chest organs from 03/24/2022, signs of a malignant process of the lower lobe of the right lung and carcinomatosis of the right lung persisted without obvious negative dynamics; MRI of the brain from 03/26/2022 revealed no pathological changes. At the meeting of the MDG dated 04/05/2022, the condition was assessed as stabilization, and it was recommended to continue crizotinib.

After 5 courses of crizotinib, according to CT scans of the chest organs from 06/07/2022, progression of the process was recorded. At the meeting of the MDG dated 06/20/2022, a change of targeted therapy to ceritinib was recommended. After 3 courses of ceritinib, CT scan from 09/29/2022 showed positive dynamics in relation to malignant neoplasm of the lower lobe of the right lung, CT signs of right-sided hydrothorax were also described. The follow-up course was completed on 10/26/2022; the patient was subsequently treated inpatient for duodenal ulcer.

Progression with damage to the central nervous system. In April 2023, there were complaints of headaches. CT scan of the brain from 04/20/2023 revealed multiple pathological formations in the brain substance on both sides, more than 10 foci, with a maximum size of up to 21x22 mm in the left temporal region, peripheral contrast enhancement and zones of perifocal edema. The conclusion corresponded to a secondary metastatic brain lesion.

According to the decision of the MDG dated 04/20/2023, the patient was recommended a symptomatic course of remote gamma therapy/radiation therapy; the patient was hospitalized in the radiation therapy department, where a symptomatic course of treatment was carried out. In the future, according to the decision of the MDG dated 06.06.2023, platinum-containing chemotherapy with a follow-up examination is recommended. The patient received 7 courses

of chemotherapy. The CT scan from 08/14/2023 was regarded as without dynamics, and the CT scan of the brain from 08/10/2023 showed a partial response to treatment.

Lorlatinib therapy. Targeted therapy with lorlatinib has been launched since February 2024. The treatment was well tolerated. According to CT scans of the chest organs from 10/23/2024, in comparison with the study from 03/18/2024, stabilization of the malignant process in the lower lobe of the right lung was noted (Figure 1B). An MRI scan of the brain from 02.10.2024 showed a positive trend in the form of a decrease in the size of foci.

A CT scan of the brain from 06/21/2024 described a secondary lesion of the temporal lobe of the left hemisphere of the brain of a metastatic nature without visible dynamic changes compared to CT scans from 12/01/2023; previously described formations in other departments were not contoured during contrast-free examination. Collectively, the data from the control studies corresponded to the stabilization of the process and positive dynamics against the background of continued therapy with lorlatinib.

Safety and laboratory monitoring. Against the background of lorlatinib therapy, the presented material indicates the absence of clinically significant adverse reactions in the lipid profile. The total cholesterol level was: October 2024 — 4.2 mmol/L; November 2024 — 5.4 mmol/L; December 2024 — 3.6 mmol/L; January 2025 — 5.3 mmol/L.

Biochemical blood test from 02/17/2025: total protein — 65 g/l, urea — 3.56 mmol/L, creatinine — 93 mmol/L, total bilirubin — 9.2 mmol/l, ALT — 15.45 units/l, AST — 8.75 units/l, glucose — 5.00 mmol/L. The obtained indicators did not require discontinuation of therapy according to the data presented.

Results

As a result of consistent application of systemic approaches — platinum-containing chemotherapy, early—generation ALK inhibitors, radiation therapy for CNS progression, repeated chemotherapy and subsequent administration of lorlatinib - clinical improvement, stabilization of the process in the lungs, and positive dynamics from the side of metastatic foci of the brain were achieved. According to the patient's profile, a total of 4 courses of primary chemotherapy, 5 courses of crizotinib, 5 courses of ceritinib, 7 courses of subsequent chemotherapy, and 15 courses of lorlatinib were performed. The full timeline of the clinical case is shown in Table 1.

Table 1

Timeline of a clinical case

Date/period	Key event
November 2020	Interstitial pneumonia on the right associated with COVID-19.05.01.2021
05.01.2021	chest CT: signs of malignant tumor of the right lung, multiple foci up to 35 mm
15.04.2021	Diagnostic thoracotomy.
23-30.04.2021	IHC: bronchiol-alveolar cancer; MGI: epidermal growth factor receptor negative, ALK3+, PD-L1 expression.
May-October 2021	4 courses of chemotherapy пеметрекседwith pemetrexed + platinum; further progression by CT OGK.

October 2021- June 2022	Targeted crizotinib therapy; initial stabilization, then progression after 5 courses.
June-October 2022	Change of therapy to ceritinib; after 3 courses - positive dynamics on CT.
20. 04.2023	brain CT: multiple brain metastases; a symptomatic course of radiation therapy was performed.
June-August 2023	Platinum-containing chemotherapy; partial brain CT response.
February 2024	Lorlatinib therapy has been initiated.
21.06.2024	CT: metastatic focus with no visible negative dynamics; some of the previously described foci are not contoured.
02.10.2024	Brain MRI: positive dynamics, reduction in the size of foci.
23.10.2024	Chest CT: stabilization of the process in the lower lobe of the right lung.
17.02.2025.	Biochemical control without significant deviations that require discontinuation of therapy according to the presented data.

Discussion

This clinical example highlights the need for early molecular genetic testing in patients with NSCLC. In this case, it was the identification of the ALK-positive status that determined the possibility of switching from standard chemotherapy to consistent targeted therapy.

The initial use of crizotinib provided a period of stabilization, but further systemic progression was noted. The change of therapy to ceritinib was accompanied by positive dynamics, reflecting the importance of consistent use of ALK inhibitors while maintaining the dependence of the tumor on the ALK signaling pathway. However, the subsequent progression with multiple brain damage required a review of treatment tactics.

CNS damage is one of the key clinical problems in ALK-positive NSCLC. In this case, the development of multiple brain metastases was accompanied by clinical symptoms and required radiation therapy. After that, the patient received additional chemotherapy with a partial response according to the CT scan of the brain.

The appointment of lorlatinib in February 2024 has led to stabilization of the systemic process and positive dynamics according to brain MRI data. This is especially important given the previous therapy with two ALK inhibitors and the confirmed damage to the central nervous system. The clinical example demonstrates that when choosing the next line of therapy, it is necessary to take into account not only the fact of systemic progression, but also the localization of progression, primarily intracranial foci.

Security monitoring is of particular importance. Lorlatinib is characterized by potential adverse reactions from the lipid profile, nervous system, body weight and peripheral edema. There was no clinically significant hypercholesterolemia in the presented material; biochemical parameters from 02/17/2025 remained without significant deviations. Nevertheless, in real practice, patients on lorlatinib require regular assessment of their lipid profile, neurological and cognitive status, body weight, edematous syndrome, and the need for dose adjustment.

Our results are consistent with data from international studies, which also show that lorlatinib controls brain tumors well in patients who have already received first- and second-generation

ALK inhibitors [5, 6]. For example, Bauer et al. It was noted that the drug gives a noticeable and long-lasting effect even with metastases in the central nervous system. This is explained by the fact that it penetrates well through the blood-brain barrier [5]. Compared with ceritinib and crizotinib, lorlatinib provides at least no worse, and often more pronounced, control of intracranial manifestations. This is confirmed by both clinical data and meta-analyses [7, 8]. However, due to the nature of the undesirable effects of lorlatinib, including possible cognitive impairment, the work of a team of specialists is especially important. This approach should include regular monitoring of lipids and cognitive state in order to adjust treatment in time, if necessary, and maintain a good quality of life for the patient [5, 6].

The evidence base for targeted treatment of ALK-positive NSCLC developed from the identification of the EML4-ALK fusion and the initial demonstration of clinical activity with crizotinib [9, 10], followed by randomized trials that established crizotinib as an effective systemic treatment [11, 12] and studies confirming the efficacy of ceritinib [13, 14]. Subsequent phase III trials demonstrated improved systemic and intracranial disease control with alectinib [15, 16], brigatinib [17, 18], and ensartinib [19], while the global phase II study of lorlatinib confirmed clinically meaningful activity after previous ALK inhibitors, including in patients with CNS metastases [20]. Molecular studies have shown that resistance may arise through secondary ALK mutations, compound mutations, and bypass signaling mechanisms [21-23], and clinical observations emphasize the prognostic importance of brain metastases in this population [24]. Additional studies support the systemic and intracranial activity of brigatinib [25, 26] and alectinib [27-29] after crizotinib failure. Current molecular-testing recommendations and international clinical guidelines therefore support timely biomarker testing and biomarker-directed treatment selection for advanced NSCLC [30-32].

Conclusion

This clinical example well demonstrates how important an individual approach is in the treatment of ALK-positive NSCLC. Step-by-step systemic therapy, timely detection of progression, control of CNS damage, and the transition to lorlatinib made it possible to improve the patient's condition, keep the disease in the lungs under control, and achieve positive changes in brain metastases.

To successfully manage such patients, molecular testing, regular CT and MRI monitoring, discussion of therapeutic tactics in a team of specialists, and careful monitoring of the undesirable effects of targeted therapy are especially needed.

Author contributions:

A.M., R.Zh. - conceptualization; **A.B., U.K.** - project administration.; **R.Zh., A.K.** – investigation; **R.Zh., A.B.** - interpretation of results; **R.Zh., D.B., A.M.** - manuscript preparation.

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Compliance with ethical standards. All procedures performed in this study involving a human participant were in accordance with the ethical standards of the national research ethics committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed voluntary consent was obtained from the patient for participation

and for the publication of clinical data and accompanying diagnostic images. All patient data were anonymized to ensure confidentiality and protect the patient's privacy.

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ALK - позитивті кіші жасушалы емес өкпе обыры бар науқаста терапияны таңдаудағы жеке тәсіл: клиникалық жағдай

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Аңдатпа. ALK-позитивті ұсақ жасушалы емес өкпе обыры (ӨҰЖЕО) — өкпе обырының молекулалық тұрғыдан анықталған қосалқы түрі. Бұл жағдайда ауруды ұзақ мерзімді бақылауға қол жеткізу үшін жүйелік терапияның оңтайлы реттілігін таңдау аса маңызды. Орталық жүйке жүйесінің (ОЖЖ) зақымдануымен жүретін аурудың үдеуі ерекше клиникалық қиындық туғызады, өйткені интракраниалдық ошақтарды бақылау емдеудің дербес әрі маңызды мақсатына айналады. Зерттеудің мақсаты — ОЖЖ-де ауру үдегеннен кейін лорлатинибті қолдануды қоса алғанда, ALK тежегіштерімен бірнеше дәйекті терапия желісін алған ALK-позитивті ӨҰЖЕО бар пациентте емді жеке таңдаудың мүмкіндіктерін көрсету.

Клиникалық жағдай пациенттің анамнезі, компьютерлік және магниттік-резонанстық томография нәтижелері, морфологиялық, иммуногистохимиялық және молекулалық-генетикалық зерттеулер, мультидисциплинарлық топтың шешімдері, сондай-ақ жүргізілген жүйелік және сәулелік терапия туралы мәліметтер негізінде сипатталды. 40 жастағы пациентке оң өкпенің төменгі бөлігінің ALK-позитивті ӨҰЖЕО диагнозы қойылды: IIIB сатысы (T4N2M0). Құрамында платина бар химиотерапия аяқталғаннан кейін ауру үдегендіктен, кризотинибпен және церитинибпен дәйекті таргеттік терапия жүргізілді. Мида көптеген метастаздар пайда болған кезде пациент симптоматикалық сәулелік терапиядан, кейіннен химиотерапиядан өтті. 2024 жылғы ақпанда лорлатинибпен емдеу басталды. Ем нәтижесінде клиникалық жақсару, өкпедегі ошақтардың тұрақтануы және мидың бақылау MPT деректері бойынша оң рентгенологиялық динамика байқалды. Ұсынылған жағдай уақтылы молекулалық профильдеудің, ОЖЖ зақымдануын жүйелі бағалаудың, мультидисциплинарлық шешім қабылдаудың, сондай-ақ ALK тежегіштерін жеке таңдау мен дәйекті қолданудың маңыздылығын көрсетеді. Лорлатиниб алдыңғы терапия желілерінде ауру үдегеннен кейін тиімді жүйелік және интракраниалдық бақылауды қамтамасыз етуі мүмкін.

Түйін сөздер: ALK-позитивті NSCLC, өкпенің ұсақ жасушалы емес қатерлі ісігі, лорлатиниб, кризотиниб, церитиниб, ми метастаздары, мақсатты терапия.

Индивидуальный подход в выборе терапии у пациента с ALK-позитивным немелкоклеточным раком лёгкого: клинический случай

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Аннотация. ALK-положительный немелкоклеточный рак лёгкого (НМРЛ) представляет собой молекулярно определённый подтип рака лёгкого, при котором оптимальная последовательность системной терапии имеет важное значение для достижения длительного контроля заболевания. Особую клиническую сложность представляет прогрессирование с поражением центральной нервной системы (ЦНС), поскольку контроль внутричерепных очагов становится самостоятельной и важной целью лечения. Цель исследования — продемонстрировать возможности индивидуализированного подхода к выбору терапии у пациента с ALK-положительным НМРЛ, последовательно получавшего несколько линий терапии ALK-ингибиторами, включая лорлатиниб после прогрессирования заболевания в ЦНС. Описание клинического случая основано на данных анамнеза пациента, результатах компьютерной и магнитно-резонансной томографии, морфологического, иммуногистохимического и молекулярно-генетического исследований, решениях мультидисциплинарной команды, а также сведениях о проведённой системной и лучевой терапии. У пациента в возрасте 40 лет был диагностирован ALK-положительный НМРЛ нижней доли правого лёгкого, стадия IIIB (T4N2M0). После прогрессирования заболевания по завершении платиносодержащей химиотерапии была последовательно проведена таргетная терапия кризотинибом и церитинибом. При развитии множественных метастазов в головном мозге пациент получил симптоматическую лучевую терапию с последующей химиотерапией. В феврале 2024 года была начата терапия лорлатинибом, которая привела к клиническому улучшению, стабилизации очагов в лёгких и положительной рентгенологической динамике по данным контрольной МРТ головного мозга. Представленный случай подчёркивает важность своевременного молекулярного профилирования, регулярной оценки поражения ЦНС, мультидисциплинарного принятия решений, а также персонализированного выбора и последовательного применения ALK-ингибиторов. Лорлатиниб может обеспечивать эффективный системный и внутричерепной контроль заболевания после прогрессирования на предшествующих линиях терапии.

Ключевые слова: ALK-позитивный НМРЛ, немелкоклеточный рак лёгкого, лорлатиниб, кризотиниб, церитиниб, метастазы в головной мозг, таргетная терапия.

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