



Efficacy of crizotinib therapy for a patient with non-small cell lung cancer with ALK gene rearrangement – case report and review of current therapeutic options

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Abstract

Introduction. Currently, nearly 23,000 cases of lung cancer are diagnosed in Poland annually, of which 5% are cases with rearrangements in the ALK gene. In recent years, tremendous progress has been made in understanding the genetic makeup of this type of cancer, which has enabled the use of new therapies, in particular, molecularly targeted drugs. Crizotinib is the first oral small molecule inhibitor of ALK, MET and ROS1 receptor tyrosine Kinases approved by the European Medicines Agency(EMA).

Case report. The paper presents the case of a 62-year-old patient diagnosed with non-small cell lung cancer with rearrangement in the ALK gene in stage IV of the disease. The patient was qualified for treatment with crizotinib under the B6 drug programme. Treatment started in May 2019. During treatment, assessment was made at 3 control points, where the first and second showed a partial response according to the RECIST 1.1 scale; in the next assessment, the response was maintained in the form of disease stabilization.

Key words

lung cancer, crizotinib, tyrosine kinase inhibitors, ALK gene rearrangement

INTRODUCTION

Lung cancer is responsible for as many as 1.6 million deaths annually [1]. It is the second most frequently diagnosed cancer and the leading cause of cancer deaths in 2020. One in ten cancers are diagnosed and one in five deaths are due to lung cancer. The five-year survival rate of lung cancer patients is only 10%-o 20% [2]. The high mortality rate is related to the fact that many tumours are already advanced at diagnosis. Studies have shown that at the time of diagnosis, 43.7% of patients had metastases to distant organs [3].

The most common histological subtype of lung cancer is non-small cell (NSCLC) (about 85%), in which the most common are lung adenocarcinoma and squamous cell carcinoma [4]. While the small-cell type (15%) is more aggressive, inoperable, even with a good response to treatment, in most cases the disease relapses rapidly. The non-small cell type often has a better prognosis [5].

The etiology of lung cancer is most often associated with smoking. This relationship is most strongly expressed in squamous and small cell carcinoma. Adenocarcinoma is more common among non-smokers [1, 4]. Significant links have been found between family history of lung cancer and its risk of developing [6]. Studies have shown that about 8% of all lung cancer cases result from genetic predisposition, and having a first-degree relative with confirmed lung cancer increases the risk of lung cancer development by 50% [7].

Interestingly, the picture of the lung cancer genome is clearly different between never-smokers and smokers. There is a much higher frequency of somatic mutations, mainly cytosine to adenine transversion and KRAS and TP53 mutations, in smokers. On the other hand, never-smokers usually have cytosine to adenine conversion resulting in more frequent EGFR mutations and translocations activating ROS1 and ALK. The identification of gene changes has significantly changed the management of lung cancer patients. Based on the results of tumour genotyping, individualized therapy with matched tyrosine kinase inhibitors can be adapted [4]. The study of disorders in the epidermal growth factor receptor gene and rearrangement of the anaplastic lymphoma kinase gene is now considered routine [8].

Treatment for lung cancer has changed significantly. Initially, it was limited to cytotoxic chemotherapy – platinum compounds related to the third-generation cytotoxic drugs paclitaxel, gemcitabine and pemetrexed [1]. Today, the action of chemotherapeutic agents is based on blocking the cell cycle. Recent advances in cancer treatment include the development of targeted therapies that block specific molecules whose over-expression or increased activity occurs only in neoplastic cells [1].

As many as 538 kinases are coded in the human genome. These are enzymes that regulate key cell functions by transferring γ -phosphate from the ATP cofactor to various substrates. In turn, the appropriate phosphatases reverse their action. Kinases play an important role in signaling pathways that regulate the processes taking place in neoplastic cells [9]. With their over-expression or increased

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activity, carcinogenesis occurs. Most protein kinases promote cell proliferation, survival and migration. Understanding these mechanisms has led to the use of kinase inhibitors as targeted therapeutic strategies in the treatment of human malignancies. Currently, there are approximately 35 drugs available, including 31 for anti-cancer therapy, approved by the US Food and Drug Administration (FDA) [10]. Development of new compounds is ongoing, many new molecules have entered clinical trials and others are at the pre-clinical stage. Kinase inhibitors represent a new and promising approach to cancer therapy that provides beneficial clinical effects [11].

One of the tyrosine kinase inhibitors (TKI) is crizotinib, which targets ALK, ROS1 and MET receptor kinases [12]. It was first approved by the FDA in 2011 for the standard treatment of ALK-positive NSCLC [13]. Crizotinib is more effective than standard chemotherapy in patients with previously treated advanced non-small cell lung cancer with ALK rearrangement. Anaplastic lymphoma kinase (ALK) is a tyrosine kinase target also in other cancers, including anaplastic large cell lymphoma and neuroblastoma. Compared to standard chemotherapy, crizotinib therapy results in a longer progression-free survival, a significantly higher response rate, reduction in symptoms, and a significant improvement in the overall quality of life [14].

Several randomized studies have shown that therapy with the second-generation ALK inhibitors, alectinib, brigatinib and ensartinib, results in better clinical effects compared to crizotinib [15–19].

The use of tyrosine kinase inhibitors has obtained unprecedented benefits in terms of survival in selected patients. However, overall cure rates for survival in NSCLC remain low, particularly in metastatic disease. Therefore, further research into new drugs and combination therapies is necessary, to prolong survival and increase the possibility of cure in a number of patients [4].

This study describes the case of a patient treated with crizotinib in connection with the diagnosis of non-small cell lung cancer with ALK gene rearrangement.

CASE REPORT

A 61-year-old mlen was admitted to the Pulmonology Clinic in 2019 due to a persistent cough that had lasted for two months. Advanced diagnostics were started with a bronchofiberscopy in which balloting granulation tissue was observed in the bronchus to the lower left lobe of the left lung, 7 × 5.5 cm in size. A slice was taken from the lesion for histopathological evaluation, which showed the presence of non-small cell glandular carcinoma of the left lung with ALK gene rearrangement. Computed tomography revealed an osteosclerotic remodeling of Th10 and the left sacrum, most likely of a metastatic nature. The image of the brain and abdominal cavity in computed tomography did not raise any concerns. Stage IV was established. The general condition of the patient, determined on the basis of the 6-point Eastern Cooperative Oncology Group (ECOG) scale, was satisfactory and remained at the level of 1. The patient did not report any pain. Treated comorbidities (hypertension, type 2 diabetes, obesity), was stable and did not present any contraindications for treatment initiation.

From 2016, a programme for the treatment of non-small cell lung cancer with crizotinib, refunded by the National

Table 1. Criteria for patient inclusion in the refunded Xalkori treatment programme [31]

CRITERIA FOR PATIENT INCLUSION IN THE REFUNDED XALKORI TREATMENT PROGRAM	
1	histological or cytological diagnosis of lung adenocarcinoma or non-small cell lung cancer with predominance of adenocarcinoma
2	diagnosis of said neoplasm at the stage of local advancement or generalization
3	presence of rearrangement in the ALK gene based on fluorescent in situ hybridization (FISH) or next generation sequencing (NGS) using a validated test
4	progression after first-line chemotherapy after previous systemic treatment (multi-drug chemotherapy with platinum or monotherapy)
5	presence of measurable changes to objectively assess the response in imaging tests using the RECIST 1.1 evaluation criteria or the presence of quantifiable changes that are not measurable
6	no metastases in the central nervous system or signs of progression of metastases in the central nervous system in patients after previous local treatment (surgery or radiotherapy) and no clinically significant neurological symptoms and the need to increase the dose of glucocorticosteroids in the last month prior to enrollment in the program
7	resolution or reduction to grade 1 of adverse reactions related to previous treatment (exception – hair loss)
8	age over 18
9	0–2 degree efficiency according to the Zubrod-WHO or ECOG classification
10	exclusion of coexistence of clinically significant diseases (uncontrolled arterial hypertension, unstable coronary artery disease, myocardial infarction in the last year, ventricular arrhythmias requiring treatment)
11	the activity of the hematopoietic system enabling treatment in accordance with the current Summary of Product Characteristics
12	treatable kidney function (creatinine levels up to 1.5 times upper limit of normal)
13	hepatic function enabling treatment (bilirubin levels not exceeding 1.5 times the upper limit of normal and the activity of transaminases and alkaline phosphatase not exceeding 5 times the upper limit of normal)
14	absence of contraindications to the use of crizotinib specified in the Summary of Product Characteristics
15	exclusion of the simultaneous use of chemotherapy and other molecularly targeted drugs

Health Fund, has been approved for use, for which the patient must meet all the criteria listed in Table 1. After assessing the patient's condition, it was found that he patient met the above-mentioned requirements; therefore, in May 2019, therapy with a molecularly targeted drug was started – crizotinib (Xalkori 2x250 mg per day). Additionally, due to the identified osteolytic changes in the skeletal system, bisphosphonate therapy was started.

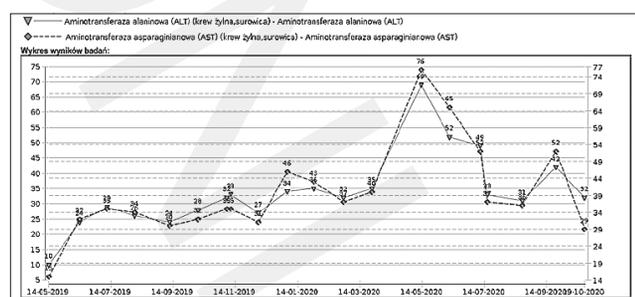
At the first check-up in August 2019, a chest CT scan showed a reduction in tumour volume, showing a partial response to treatment (Fig. 1). RECEIST 1.1 was used to objectively assess the patient's response to Xalkori. (CR –



Figure 1. Comparison of CT images of the chest in which remission of neoplastic lesions is observed (from the left, May 2019, August 2019, August 2020 own study)

complete response, PD – disease progression, PR – partial response, SD – disease stabilization) [20]. The patient's fitness level was 1 on the ECOG scale. Subsequent imaging studies confirmed the persistence of partial regression. No new metastatic lesions were detected. During treatment, after about two weeks of taking the drug, swelling of the lower limbs appeared, which is a common side-effect of crizotinib. Low doses of diuretics were used; however, trace swelling persisted during treatment.

Due to the previously mentioned side-effects of the biological drug therapy, and in particular the high risk of hepatotoxicity, the level of the liver enzymes AST and ALT was strictly monitored in the patient for fear of liver damage. Measurements were performed systematically (every 2 months), which allowed for quick detection of the elevation of transaminase values one year after the initiation of crizotinib therapy. Protective treatment was implemented, noting an improvement in liver parameters. Currently, the level of liver enzymes is satisfactory, remaining within reference standards (Fig. 2).



In the current study, there was a statistically significant prolongation of the median PFS in patients treated with ceritinib, compared to the group treated with chemotherapy (5.4 vs. 1.6 months; HR = 0.49; 95% CI: 0.36–0.67; $p < 0.0001$). The ORR was 39.1 and 6.9%, respectively, for the above groups [30]. No randomized trial has been conducted so far to directly compare the results of treatment with ceritinib and crizotinib. However, the ASCEND 4 study showed that ceritinib was more effective than first-line chemotherapy. The study showed that the use of ceritinib reduces the risk of progression or death by 45% (HR = 0.55; 95% CI: 0.42–0.73; $p < 0.00001$). The median PFS for patients treated with ceritinib was 16.6 months, and 8.1 months for patients receiving chemotherapy. Patients treated with ceritinib had a significantly higher ORR compared to patients receiving chemotherapy (72.5 vs. 26.7%) [30].

Currently, molecularly targeted drugs represent a great potential in the therapy of many disease entities. Particular progress has been made in terms of prolonged survival in patients with NSCLC; hence, it is important to identify its genetic makeup when determining the histopathological affiliation of a tumour. This action will allow careful selection of a specific inhibitor of a given receptor, thus increasing the chances of successful treatment.

In summary, patients diagnosed with non-small cell lung cancer with ALK gene rearrangement can benefit from the use of a biological drug. It has been shown that molecular targeting has advantages in terms of progression-free survival and overall survival. When ALK has been treated with other systemic treatments, such as chemotherapy, it is acceptable to complete the treatment. It is important that a patient with known ALK rearrangement receives an ALK inhibitor at some point during treatment, and that the most effective treatment should be given first.

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