ALK-positive locally advanced lung cancer in a patient who achieved long-term complete response with crizotinib: A case report

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Abstract. In the last two decades, the existence of key oncogenic alterations, such as activating mutations or chromosomal reorganization, has become crucial in the advanced stage non-small cell lung cancer (NSCLC) treatment paradigm. Among these, anaplastic lymphoma kinase (ALK) gene rearrangement is reported in 3-7% of NSCLC cases worldwide. In patients who respond to long-term ALK therapy, treatment duration is uncertain. The present study reported a case of variant type 1 ALK-rearranged stage 3B lung adenocarcinoma that maintained a complete response for >6 years under treatment with crizotinib. As first-line treatment, crizotinib was administered twice daily (250 mg) and a complete response was confirmed after 3 months. After a complete response to crizotinib for 6 years, the treatment was stopped and the patient was followed up. Multiple brain metastases were detected during the third month of follow-up.

Introduction

Lung cancer is the second most commonly diagnosed type of cancer and the most common cause of cancer-related death worldwide (1). Among all types of lung carcinoma, ~80% are non-small cell lung cancer (NSCLC) (2,3). Only 19% of patients who are diagnosed with NSCLC survive after 5 years (4). In the last two decades, as a result of the discovery of bioindicators with the aim of developing targeted treatments, survival rates have improved (5). Furthermore, the 5-year survival rate for metastatic conditions has improved to between 15 and 50% (6,7). Regarding anaplastic lymphoma kinase (ALK), which is among these cancer biomarkers, gene reorganization is reported in 3-7% of cases of NSCLC (8). As a result of phase two single-group studies in ALK-positive NSCLC cases, crizotinib was approved by the United States Food and Drug Administration as a treatment for this group of patients (9). In the phase three PROFILE 1014 study, progression-free survival (PFS) was found to be 10.9 months in the ALK-positive group, outperforming the rates resulting from chemotherapy (10). In the final analysis of the PROFILE 1014 study patients in both the crizotinib and chemotherapy arms had permanently discontinued treatment due to progression at the final overall survival (OS) analysis, with a median follow-up duration for OS of 45.7 months with crizotinib and 45.5 months with chemotherapy (11). In addition, in a previous study, the success of crizotinib compared with chemotherapy in first-line treatment inevitably disappeared with secondary ALK mutation-based crizotinib resistance, which was revealed to emerge in most cases within the first year in patients whose ALK rearrangement was positive (12). The present study reported the case of a 49-year-old woman with NSCLC for whom, after a complete response to crizotinib for 6 years, treatment was stopped due to the patient's own will, followed by the emergence of cranial metastasis and medical recurrence.

Case report

A 49-year-old, nonsmoking housewife, without occupational chemical exposure or family history of lung cancer, and complaining of a cough lasting for 2 months was admitted to the Sultan II.Abdulhamid Han Training and Research Hospital (Istanbul, Turkey) in November 2015 As a result of bronchoscopic biopsy, following the detection of a mass in the lung and mediastinal lymph node metastases on thoracic tomography, the patient was diagnosed with moderately differentiated invasive adenocarcinoma. On positron emission tomography-computed tomography (PET-CT) applied for staging, the pathological size and metabolic activity of the primary mass, mediastinal and scalene lymph nodes with were detected (Fig. 1Aa-c). The patient, whose cranial magnetic resonance did not show any metastatic lesions, and who was T2N3M0 stage 3B [according to the 7th edition of the tumor, node and metastasis classification (13)], was diagnosed with

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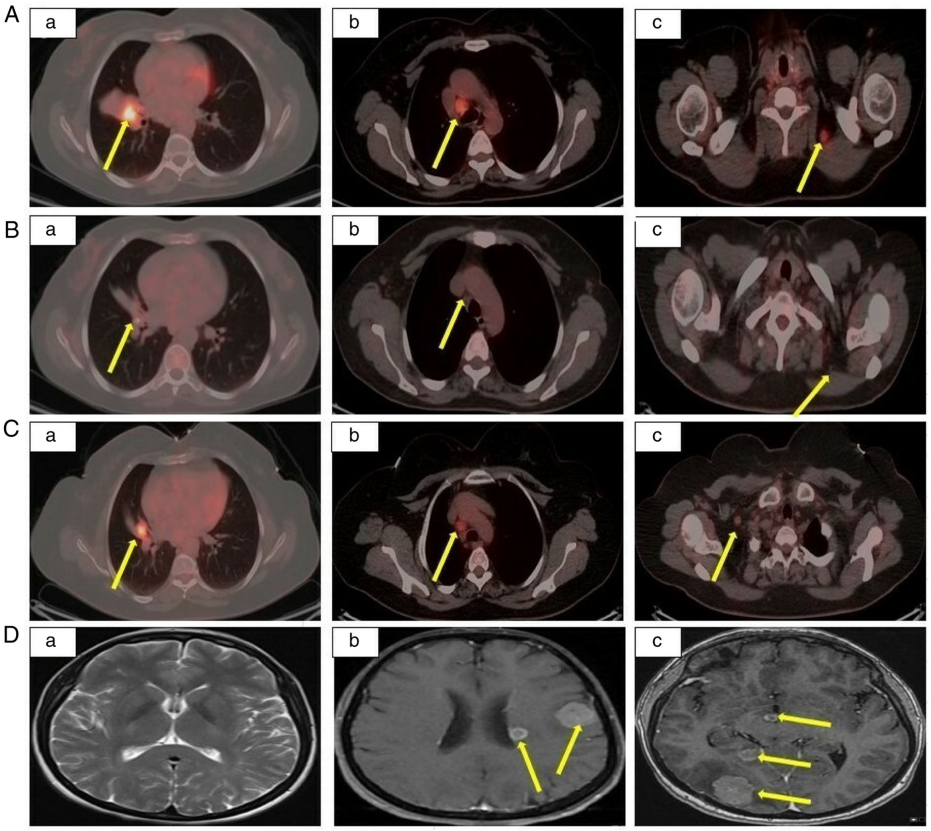

Figure 1. Radiological appearance at diagnosis, complete response and recurrence. PET-CT images of the diagnosis of (Aa) lung mass, (Ab) mediastinal lymph nodes and (Ac) scalene lymph nodes. PET-CT images showing complete response of (Ba) lung mass, (Bb) mediastinal lymph nodes and (Bc) scalene lymph nodes. PET-CT images of recurrent (Ca) lung mass, (Cb) mediastinal lymph nodes and (Cc) right supraclavicular lymph nodes. Brain magnetic resonance imaging at (Da) baseline and of (Db and Dc) multiple metastatic lesions on T1-weighted images. Yellow arrows indicate relevant radiological features. PET-CT, positron emission tomography-computed tomography.

unresectable lung carcinoma. Sanger sequencing method was used for EGFR detection, and fluorescence *in situ* hybridization method was used for ROS-1 and ALK detection (14,15). Following analysis of EGFR, ALK and ROS1, the patient was identified as ALK-rearranged variant type 1 (v1) positive. The patient started treatment with crizotinib in January 2016, at a daily dosage of 2x250 mg at the Sultan II.Abdulhamid Han Educational and Research Hospital (Istanbul, Turkey). After three courses, a complete response was obtained (Fig. 1Ba-c). Adverse events, such as grade 1-2 asthenia, transaminitis and nausea, were reported. Grade 3-4 side effects were not observed. The patient was followed up with a complete response to crizotinib treatment until February 2022. Upon the patient's request, the treatment was terminated in February 2022. In May 2022, at the hospital, the patient complained of headaches and multiple metastatic lesions accompanied by vasogenic edema were detected in the brain (Fig. 1Db-c). Furthermore, a primary lung mass, metastasis to mediastinal lymph nodes and suspected right supraclavicular lymph node metastasis were detected via PET-CT (Fig. 1Ca-c). The patient was initiated on Alectinib treatment, a second-line ALK inhibitor. The patient's follow-up and treatment continues.

Discussion

The present study reported the case of a patient with ALK-rearranged v1 lung adenocarcinoma that showed a complete response to crizotinib for 6 years and metastatic recurrence after cessation of treatment. In a phase III study in which crizotinib was compared with chemotherapy, PFS was revealed to be 10.9 months (10). In the final analysis of the PROFILE 1014 study, at the end of the fourth year, the survival rate in the crizotinib group was 56%, compared with 49% in the chemotherapy group (11). In the literature, PFS over 5 years with crizotinib treatment has rarely been reported (16). The 5-year estimated PFS rate with crizotinib treatment has previously been reported as 9% by Rangachari *et al* (17) in two cases in the metastatic stage. Kosaka *et al* (18) reported that in a patient who developed metastatic recurrence after surgery and adjuvant chemotherapy, complete response was confirmed after 4 months and was maintained over 5 years after the first administration of crizotinib. In addition, Gulmez (19) reported on a case of metastatic recurrence that received crizotinib treatment after postoperative adjuvant chemotherapy, in which 53-month PFS was obtained.

Regarding the treatment of patients with ALK-positive NSCLC with crizotinib, two problems must be addressed. First, it is unclear what the duration of treatment in patients with locally advanced or metastatic NSCLC who have achieved a complete response with crizotinib therapy should be. In clinical practice and randomized controlled trials, in both first-line and post-treatment patients, the PFS with crizotinib was between 7 months and 1 year (20-22). In the long-term results of the ALEX study, in which alectinib was compared with crizotinib, in the fourth year,

Table I. Differences in crizotinib efficacy according to echinoderm microtubule-associated protein like 4-anaplastic lymphoma kinase variants.

First author, year	Total cases, n	Variant 1			Variant 2			Variant 3a/b			(Refs.)
		n	ORR	PFS	n	ORR	PFS	n	ORR	PFS	
Yoshida *et al*, 2016	35	19	74%	11 months	Non-variant						(26)
Woo *et al*, 2017	51	Non-variant 3a/b: n=24; ORR, 83%, 2-year PFSR, 76%			1: n=16; ORR, 63%; PFS, 4.2 months			20	75%	2 years	(27)
Lin *et al*, 2018	129	55	No data	9.2 months	Number of patients with non-v1 and non-v3a/b variants was too small			51	No data	7.5 months	(28)
Lei *et al*, 2016	61	22	73%	11 months	No data	No data	No data	18	No data	7.4 months	(29)
Cha *et al*, 2016	32	10	30%	No data	2	100%	No data	8	50%	No data	(30)
Li *et al*, 2018	60	14	46%	10.7 months	9	67%	18.5 months	20	65%	7.9 months	(31)

ORR, overall response rate; PFS, progression-free survival; PFSR, PFS rate.

PFS was 0% in the crizotinib group (23). As previously reported, to the best of our knowledge, there is no evidence-based information in the literature regarding the time required to continue treatment in patients with long-term and complete responses. The second issue is that the effect of the EML4-ALK variant on ALK inhibitor selection has not been clarified. It has been established that ~20 echinoderm microtubule-associated protein like 4 (EML4)-ALK fusion subtypes exist (24). Fusion variants are classified according to their breakpoints (24). The most common EML4-ALK variants are v1, v2 and v3a/b; the two EML4-ALK variants that together account for up to 70-80% of all EML4-ALK variants are v1 and v3a/b (25). Several studies have explored the potential association between EML4-ALK fusion and the therapeutic response to crizotinib, but the results are insufficient to draw a conclusion. These studies reported differential responses to crizotinib according to ALK variants in patients. Yoshida *et al* (26) reported longer responses to crizotinib with v1 than with non-v1, and the objective response rate (ORR) and disease control rate of crizotinib-responsive EML4-ALK v1 were 74 and 95%, respectively, whereas for other ALK fusions they were 63 and 63%, respectively. Woo *et al* (27) demonstrated that patients with non-v3 EML4-ALK had a longer response to crizotinib than those with the v3 EML4-ALK, thus suggesting that EML4-ALK v3a/b may be a major source of ALK inhibitor resistance in the clinical setting. In another similar study, no statistically significant difference in PFS was observed between patients with v1 and v3 EML4-ALK that were treated with crizotinib, although the median PFS was numerically shorter for v3 than for v1 in all contexts (28). Lei *et al* (29) did not observe any significant difference in the efficacy of crizotinib between patients with the EML4-ALK fusion v3, v1 and the less frequent v2. In a similar study, Cha *et al* (30) found no significant difference in survival between crizotinib-treated variants. Li *et al* (31) revealed that PFS in patients with v2 EML4-ALK was significantly higher than that in those with non-v2 EML4-ALK. Notably, although the present case was v1, a complete response was reached over 6 years. Previous studies have shown that ORR and PFS obtained with crizotinib treatment vary according to EML4-ALK variant subtypes (Table I).

As aforementioned, in previous studies, relatively long-term PFS was observed more frequently in EML4-ALK v1 and v2 subtypes with initial crizotinib treatment. However, it is unclear if these subtypes should be considered in treatment decisions due to insufficient evidence. Therefore, the efficacy of EML4-ALK variants in ALK-positive NSCLC remains an important question to be answered in the future.

To the best of our knowledge, this is the fifth case reported in the literature of NSCLC with a long-term complete response to crizotinib treatment. In addition, the present case is the first to achieve a complete response for >6 years with first-line crizotinib treatment in a locally advanced unresectable condition. Therefore, the present case seems to be valuable from a clinical standpoint.

In conclusion, prospective studies are needed to determine target-based agents according to variant subtype in first-line treatment and on the duration of treatment for patients with ALK-positive NSCLC.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

LE and OO contributed to the conceptualization and design of the study. OO collected clinical information and assisted with drafting the manuscript. LE searched the literature and wrote the manuscript. LE and OO confirmed the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written consent was obtained from the patient for publication of their data and images included in this case report.

Competing interests

The authors declare that they have no competing interests.

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