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Research Article

Confirmation of the Tumor Response by PET/CT for Lung Cancer Patients Treated with Alectinib: Our Clinical Experience

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Abstract

Background: Anaplastic lymphoma kinase (ALK) rearrangement is identified in approximately 3-7% of all metastatic non-small cell lung cancer (NSCLC) patients, and ALK tyrosine kinase inhibitors (ALKIs) have revolutionized the management of these patients.

Purpose: The aim of this study is to present treatment strategy with Alectinib and complete tumor response confirmed by PET/CT for metastatic NSCLC patients at the University Clinic of Radiotherapy and Oncology in Skopje.

Material: The primary and point of our institutional study was assessed tumor response, duration of response DoR and CNS efficacy. Tumor response evaluation we performed initial CT of the lung and abdomen or PET/CT (not able to perform for all patients in our country), CT/MRI of the brain and then control previous images including if it possible PET/CT on 3 - 6 mounts, during follow-up visits.

Results: We treated nine ALK positive patients with alectinib. We were presented complete tumor response in two of our patents confirmed by PET/CT.

Introduction

Lung cancer is the most common cause of cancer-related death worldwide. About 1.2 million people die every year from lung cancer [1]. The molecular profile of the tumor currently determines the therapeutic strategy for advanced lung cancer. Distinctive chromosomal rearrangements in the ALK gene (ALK-positive) were first identified in 2007 and occur in nearly 3% - 7% of patients with NSCLC [2,3]. Patients with ALK-positive NSCLC benefit from treatment with ALK-targeted therapies. The randomized, phase 3, global ALEX study has established alectinib as the first-line treatment strategy for ALK-positive NSCLC [4]. ALK-positive NSCLC patients are typically of younger age and appear to be light or non-smokers [5]. Positron emission tomography coupled with computed tomography (PET/CT) has been widely used in clinical practice for the evaluation of tumor response to the therapies in patients with lung cancer [6-8]. Standard uptake value (SUV) between baseline and follow-up studies is one of the most common parameters tested; however, it is affected by various factors, such as technical, physical and biological factors [9]. In order to facilitate the reproducibility of PET/CT results, in 1999, the European Organization for Research and Treatment of Cancer (EORTG) criteria were developed. Those criteria were based on the SUV normalized to body surface area (SUVba) to reduce the influence of the body weight of (SUV) [10]. Later in 2009 the American researches introduced an alternative protocol for the assessment of response to therapy in oncological patients, the Positron Emission Tomography Response Criteria in Solid tumors (PERCIST 1,0). PERCIST 1,0 recommends using SUV corrected for lean body mass (SUL) to falsely avoid high organ SUV in obese patients between baseline and follow-up studies is one of the most common parameters tested [11]. According the literature metabolic tumor volume (MTV) and total lesion glycolysis (TLG) as a tumor metabolic index can be used to assess the tumor response and prognosis of patients [12].

The aim of this study is to present treatment strategy for metastatic NSCLC patients with ALK positivity and to presented complete tumor response conformed by PET/CT at the University Clinic of Radiotherapy and Oncology in Skopje.

Material and Methods

Patients included the study were ages greater than or equal to 18 years, with Eastern Cooperative Oncology Group performance status of 0-3, with measurable tumor lesion according (RECIST criteria 1,0), previously treated with first line chemotherapy or previously untreated patients with metastatic ALK immunohistochemistry (IHC) positive NSCLC. Patients with brain metastases were eligible; previously Whole Brain Irradiation (WBI) was allowed if it was completed greater than or equal 15 days before enrollment. Previous first line therapy was chemotherapy platina based and thoracic conformal radiotherapy. All eligible patients were received twice-daily 600 mg alectinib until progressive disease (PD), unacceptable toxicity, or death. All patients provide written informed consent. At the time of enrollment, ALK IHC-positive status was determined in patient samples using the Ventana ALK Assay, which were performed in University central laboratories in Skopje. The samples were scored as IHC-positive or negative according to the manufacturers scoring algorithm. The primary and point of our institutional study was assessed complete response (CR), partial response (PR) and stabile disease (SD), duration of response DoR and CNS efficacy. Overall response (OR) was defined as the sum of CR and PR. DoR was defined as the time from CR and PR to the first met occurrence of progression event. CNS end points were analyzed in patients with baseline CNS disease. Tumor response evaluation we performed initial CT of the lung and abdomen or PET/CT (not able to perform for all patients in our country), CT/MRI of the brain and then control previous images including if it possible PET/CT on 3 - 6 mounts, during follow-up visits.

We were presented our patients with CR, documented on PET/CT. We assessed subjective improvements and alectinib adverse effects, every mounts on follow-up visits.

Results

Our study population consisted of 725 patients (562 men and 163 women) with lung cancer, diagnosed between March 2019 and the end of February 2020 at the Lung Cancer Department, at the University Clinic of Radiotherapy and Oncology in Skopje. Study cut-off for tumor response evaluation was December 2021. According the age, 358 patients were between 50 - 60 years of age, 184 patients between 50 - 60 years, 142 above 70 years old, and only 41 patients were under 50. All histological and biomarker analysis were performed in Skopje. NSCLC tumors appeared in 544 patients of whom 50% were adenocarcinoma subtype, 40% were squamous cell carcinoma, and 2% large cell carcinoma and 8% were NOS (non-specified). According to the International Staging System for Lung Cancer, of 544 NSCLC patients, 429 patients presented with stage III and IV (locally advanced and metastatic disease) and 115 patients with stage I and II (early stage disease). We referred 181 patients (25%) from stage IV NSCLC patients for biomarker analysis. Eligible patients for this study were 12 with histological diagnosis of NSCLC and immunohistochemistry (ICH) proven ALK positivity. Three patients from the ALK positive group did not receive any ALKIs and were not analyzed. We treated nine of patients with alectinib therapy which was covered by the national health insurance system. According treatment strategy and current drag availability et our Clinic, 4 of the ALK positive patients were treated with alectinib as a first line therapy, and 5 patients with alectinib as a second line therapy. Patient characteristics were presented on table 1. There were two of patients with baseline CNS lesions. We presented tumor response, duration of tumor response, subjective improvements and adverse effects for 9 patients on table 2. We were conformed CR in 5 of our patients by imaging methods including PET/CT or CT, brain MRI or brain CT, PR in two of them and SD in three.

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Age (years)	36	46	53	56	57	65	59	39	50
sex	female	female	male	male	male	male	female	female	female
Histological subtypes	Large cell NSCLC	Adeno NSCLC	Adeno NSCLC	Adeno NSCLC	Adeno NSCLC	Adeno NSCLC	Adeno NSCLC	Adeno NSCLC	Adeno NSCLC
Smoking status	Non smoker	Light smoker	Light smoker	Light smoker	Light smoker	Heavy smoker	Non smoker	Non smoker	Light smoker
Alectinib line of treatment	I	II	I	I	I	II	II	I	II
ECOG PS	1	3	1	3	3	3	1	2	2
Baseline CNS	no	yes	yes	no	no	no	no	no	no

Table 1: *Lung cancer patient's characteristics treating with alectinib.*

Tumor response	CR	PR	SD	DoR months	Dead from lung cancer	Dead from other reasons	Subjective improvements	Most common adverse events
Patient 1	yes			24	live		yes	myalgia
Patient 2	yes			35	live		yes	Myalgia and vision disorders
Patient 3	yes			23	live		yes	fatigue
Patient 4	yes			16		COVID- 19	yes	No adverse
Patient 5			yes	3	dead		no	No adverse
Patient 6			yes	3	dead		no	Fatigue, myalgia
Patient 7		yes		19	live		yes	No adverse
Patient 8	yes			16	live		yes	No adverse
Patient 9		yes		15	dead		yes	Constipation, increased weight, fatal lung hemorrhage

Table 2: *Tumor response, duration of response, subjective improves and adverse event in ALK positive patients treated with alectinib.*

We were presented complete tumor response in one of our patents confirmed by PET/CT (Figure 1 to 3). Patient was 36-year-old woman with no smoking history. She was admitted at our Clinic in Skopje presented with bone pain and dyspnea. PET/CT scan showed a tumor lesion of the inferior left lung lobe, N3 mediastinal disease and multiple bone metastases. Bronchoscopy established a PHD Large Cell Carcinoma with Ctnm = T2N3M1b (Bones). We referred material for molecular testing and molecular profile was: ALK positive (immunohistochemistry analysis); EGFR -; PD-L1-. She is very young and we started with alectinib as a first line treatment. She has immediate subjective response to alectinib 600 mg bid with rapid pain relief. After 3 months, control PET-CT showed complete tumor

response in mediastinal lymphadenopathy, lung tumor lesion and bone lesions. Tumor markers: CEA, CEA 15-3, CEA 125 and CYFRA 21-1 after 3 months were normalized. We confirmed the complete tumor response 15 months after treatment with alectinib, by control PET/CT, too. Duration of subjective response was 24 months, expressed on the final follow up visit, December 2021. Our patient continues to be treated with alectinib without serious adverse events, only myalgia grade 1-2 was occurred.

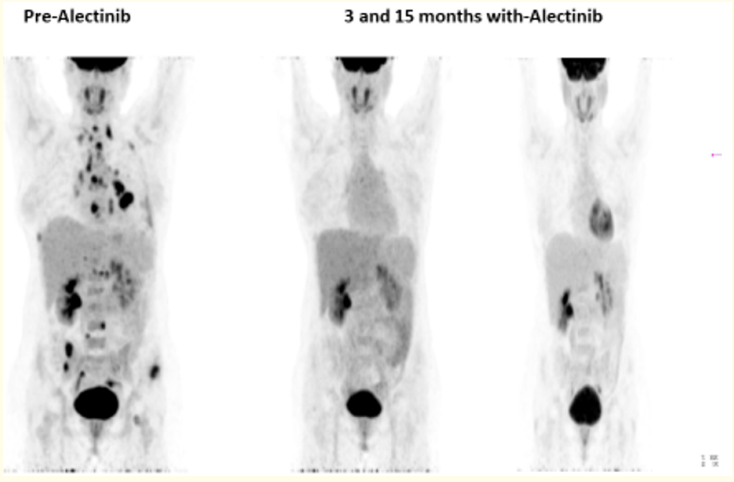

Figure 1: *Complete tumor response et the 36 years old women after 3 an 15 months of treatment with alectinib-PET/CT longitudinal view.*

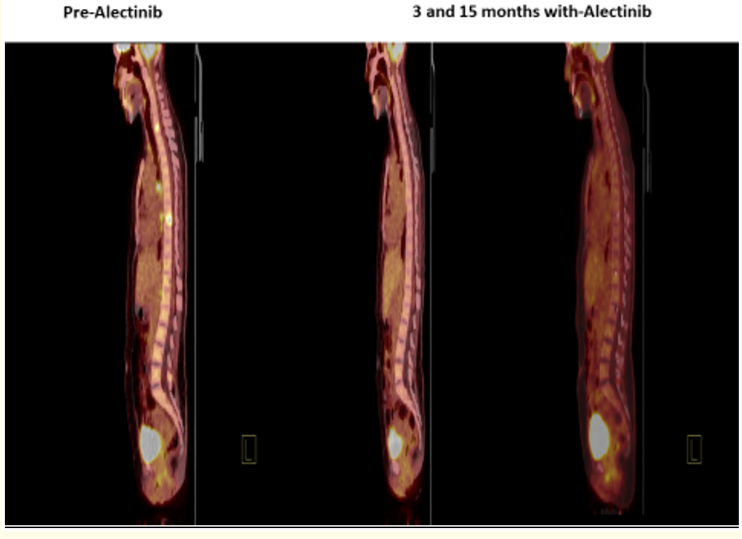

Figure 2: *Complete tumor response et the 36 years old women after 3 and 15 months treatment with alectinib-PET/CT sagital view.*

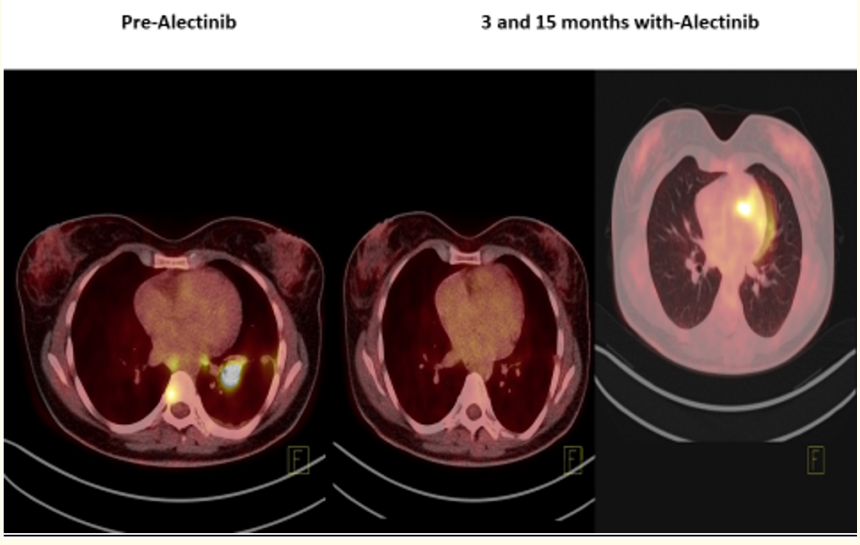

Figure 3: *Complete tumor response et the 36 years old women after 3 and after 15 months of treatment with alectinib-PET/CT transversal view.*

Another patient who had a complete response was female 46 years old, with baseline brain metastases treated with second line alectinib, after progression on two cycles' chemotherapy (C/G) and whole brain radiotherapy. Four of baseline brain metastases had been identified on brain MRI, the largest of which were in the right occipital region and on 10 months' control MRI, confirmed CR. This remission, was further documented by a head CT with contrast, demonstrated duration of complete tumor response for 21 months of alectinib (Figure 4). This remission was further documented by PET/CT scan 25 months after initial start of alectinib (Figure 5). The duration of tumor response for this patient is 35 months without any proof of disease progression or exceptional treatment toxicity on follow-up visit.

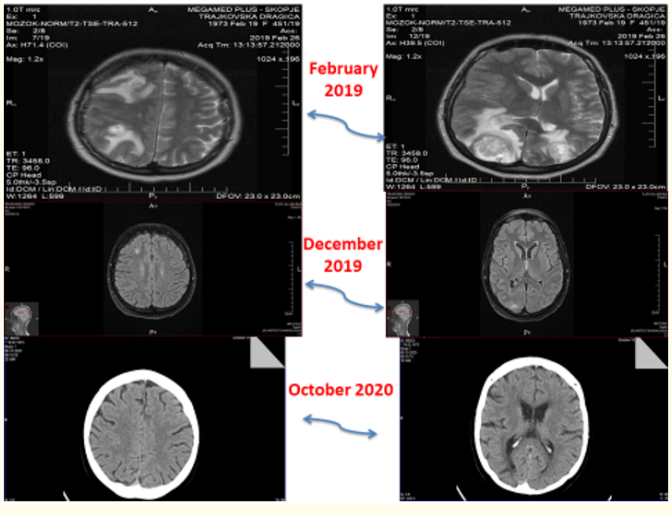

Figure 4: *MRI et baseline for 46 years old women performed 10 months later, on December 2019 depicting the CR of all brain metastases. We hadconformation of this response 21 months later, October 2020 with brain CT.*

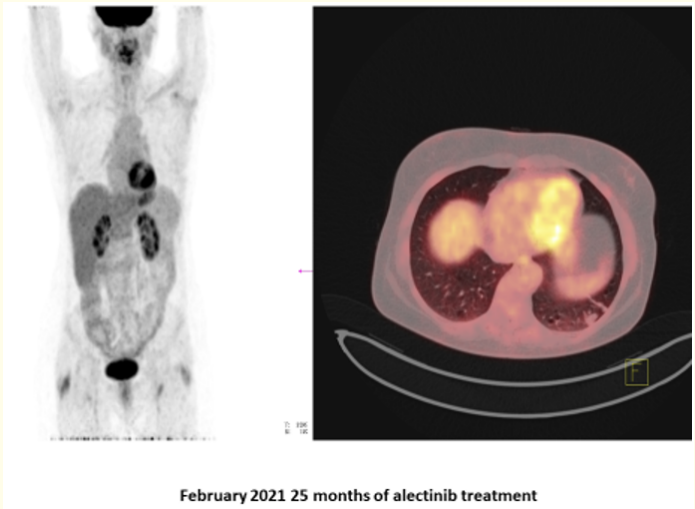

Figure 5: *CR et the same patient after 25 months of treatment with alectinib-PET/CT.*

Discussion

Indication for molecular based therapy for patients with NSCLC harboring corresponding target genes therefore should be determined separately from that for cytotoxic chemotherapy for non-selected population [13]. As a result, ALK inhibitors have been developed, which demonstrated a systemic effectiveness and greatly improved survival results in comparison to chemotherapy in patients with ALK positive advanced NSCLC [14]. Recently, Kodama and colleagues showed alectinib to have a stronger antitumor activity than crizotinib in intracranial tumors in mouse model of EML4-ALK-positive NSCLC due a significantly better penetration of BBB [15]. Alectinib is not a P-glycoprotein substrate and this can play a role in the higher penetration of BBB. P-glycoprotein itself has indeed proved to be a resistance mechanism to ALK inhibitors, especially in the brain [16]. Alectinib efficacy in patients with BMs was also assessed in phase III clinical trials in the ALUR study [17]. Alectinib is available and covered by the state insurance in our country.

Alectinib (RO5424802/CH5424802) is a second generation, ATP-competitive, orally and highly selective inhibitor of ALK, specifically designed to overcome crizotinib resistance. Unlike crizotinib, alectinib does not inhibit MET or ROS1 kinase activity, but it inhibits RET with comparable potency of ALK. Alectinib is effective, *in vitro*, in treating numerous crizotinib-resistant ALK mutations. It also showed *in vitro* efficacy against ceritinib resistant ALK-mutant L1198F and moderate potency against the composite mutation D1203N+F1174C [18-20]. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study results OS data remain immature with 37% of events recorded (stratified HR 0.67, 95% CI 0.46e0.98). Median OS was NR (Non Reachable) with alectinib and was 57.4 months with crizotinib (95% CI 34.6eNR was 57.4 months with crizotinib (95% CI 34.6eNR). The 5-year OS rate was 62.5% (95% CI 54.3e70.8) with alectinib and 45.5% (95% CI 33.6e 57.4) with crizotinib. The OS benefit of alectinib was evident across a number of patient subgroups, including those with CNS metastases at baseline [HR 0.58 (95% CI 0.34e1.00); 50.0% of events] and those without [HR 0.76] [21]. Our data confirm that alectinib demonstrates superior efficacy for CNS disease in two of our study patients presented with baseline brain metastases and poor performance status. Also we were assessing duration of tumor response in all of our patients. The longest duration of response was 35 months in one of our patient and the

short was 3 months recorded in two of our patients. Based on the ALEX data, the National Comprehensive Cancer Network guidelines were updated to include alectinib as a category 1 recommendation for first-line treatment of ALK positive NSCLC patients.

PET/CT is not only a reference imagining tool for the diagnosis and staging of tumors, but can also reflect the metabolic status of the tumor, to be used for evaluation of efficacy and prognosis [22]. Once PET/CT was used to evaluate the effects of a patient with multiple metastases, clinicians can comprehensively assess patient's condition changes. In ALK inhibitors like alectinib, PET/CT can reflect the metabolic abilities of the cells to predict the curative effect early and adjust the treatment plan on time. At present MTV is considered a prognostic indicator of tumor survival, being a volumetric and metabolic biomarker of the tumor [23,24]. Thus, unlike SUV max, MTV can quantify the overall tumor burden. In some studies, higher MTV and TLG were significantly associated with shorter progression-free survival (PFS) [25-27]. In this study case we could detect complete tumor response within 3 months of treatment in first of our patients. This remission was further documented by PET/CT scans 15 months after initial start of treatment. Identifying resistance to treatment at an early moment in individual patients is important, because in solitary or oligometastases localized treatment options such as stereotactic radiotherapy, video-assisted resections or radiofrequency ablation can be applied [28,29]. Response assessment with ^{18}F-FDG PET/CT could represent a method with the ability to identify early resistance to treatment and to identify patients with solitary, oligo or "systemic" metastases. Future research should focus on whether such strategy will improve survival, quality of life and cost-effectiveness [30,31]. To overcome alectinib resistance, different therapeutic strategies have been developed like starting treatment with next-generation ALK inhibitors [32,33].

Our second presented patient, who was previously treated with chemotherapy and palliative whole brain radiotherapy, have complete remission further documented by PET/CT scan 25 months after initial start of alectinib. There was no proof of disease progression or exceptional toxicity at the last follow-up visit, after 35 months of alectinib treatment. Whole brain irradiation (WBI) and chemotherapy as a standard treatment in NSCLC patients with poor PS and BMs is of little clinical value. It offers median OS (overall survival) of approximately 3-5 months [34] in comparison with alectinib treatment, where median overall survival will not be reached in 5-years follow-up [21].

Conclusion

Considering its efficacy and tolerability based on these nine cases, we recommend alectinib as a treatment approach for ALK positive NSCLC patients with advanced tumor and multiple metastases. Follow up with PET/CT increases early detection of metastases.

Consent

Written informed consent for the publication of this study and accompanying photographs were obtained from our patients.

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