ALECTINIB TREATMENT OF ALK POSITIVE NON SMALL CELL LUNG CANCER PATIENTS WITH BRAIN METASTASES: OUR CLINICAL EXPERIENCE

Simonida Crvenkova

University Clinic of Radiotherapy and Oncology, Faculty of Medicine, Skopje, Macedonia Skopje, R.N. Macedonia

ABSTRACT

Summary: 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 (TKIs) have revolutionized the management of this subset of lung cancer cases.

Purpose: This study aims to show alectinib (TKI) effectiveness and safety with focus on alectinib intracranial efficacy for ALK+ NSCLC patients.

Case presentation: Patient 1 was a 46-year-old woman diagnosed with non-small cell lung cancer with an echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase fusion gene (ALK+). She presented with intracranial and liver metastases and poor performance status of ECOG 3. Alectinib was initiated as a second line therapy, after whole brain irradiation and discontinuation of first line chemotherapy after two cycles, due to the central nervous system progression and liver metastases. Good response was consequently achieved, characterized with improved overall performance and without significant adverse events.

Patient 2 was a 53-year old man with left sided lung adenocarcinoma surgically treated in 2017. Post-operative pTNM stage was IIB with a positive resection margin- R1. He received adjuvant chemotherapy and radiotherapy. In 2019, after two and half years of being disease free, he presented with severe cerebral symptoms leading to poor performance status. CT scan of the brain showed multiple brain metastases. He was treated with first line alectinib after completion of whole brain radiotherapy. In 5 months period he got significantly better and able for work again.

Conclusions: We recommend alectinib as a first and second line treatment approach for ALK+ NSCLC patients, in particular the ones with brain metastases at the time of diagnosis and poor PS.

Keywords: brain metastasis, ALK+ NSCLC patients, alectinib

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]. NS-CLC histology accounts for more than 80% of all lung cancers and 60% to 70% of the NSCLC patients suffer from locally advanced and metastatic disease at diagnosis. 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 2%–7% of patients with NSCLC [2, 3]. The most common rearrangement in ALK is a combination of the N-terminal half of eml-4 and the intracellular kinase domain of ALK (EML4-ALK) [4, 5], leading to a novel active oncogene driver. There are many other differences in the ALK rearrangement. Additional ALK-related oncogenic drivers include point mutations in the kinase domain and ALK overexpression [6, 7]. ALK-positive NSCLC patients are typically of younger age and appear to be light or non-smokers [8]. The frequency of brain metastases (BMs) is greater in ALK-positive NSCLC patients and up to 50-60% of those patients will develop BMs during the course of their disease [8]. Alectinib is a potent second-generation ALK inhibitor and has been shown to be successful for a wide range of ALK rearrangements and ALK mutations. The aim of this study is to show alectinib efficacy and safety with focus on alectinib intracranial efficacy in ALK+ NSCLC patients treated at the University Clinic of Radiotherapy and Oncology in Skopje.

Fig. 1. Computed tomography scans of patient 1, depicting the tumor response at the inferior left lung lobe, 10 months after alectinib treatment (A pretreatment lung foci, B positive response to the alectinib after 10 months)

Fig. 2. Magnetic resonance imaging scans of patient 1, depicting the response of intracranial metastases after 10 months of alectinib treatment (A pretreatment metastatic foci, B positive response to the alectinib after 10 months)
CASE PRESENTATION

Patient 1

A woman aged 46, with light smoking history (15 years, 10 cigarettes per day) was admitted to our Clinic with cerebral symptoms, such as dizziness and headache which lasted for a period of at least 15 days. The patient had a poor performance status (PS) of 3. Chest X-ray and computed tomography (CT) scans displayed a tumor lesion in the inferior left pulmonary lobe. Bronchoscopic examination established a pathological adenocarcinoma with a signet ring cell component. CT scan of the abdomen and brain magnetic resonance imaging (MRI) revealed multiple liver and brain metastases. The patient was diagnosed with stage IV lung ade-

Fig. 3. Computed tomography scans of patient 1, depicting the tumor response at the liver, 10 months after alectinib treatment (A pretreatment liver metastatic foci, B positive response to the alectinib after 10 months)

Fig. 4. Computed tomography scans of patient 2, depicting the tumor response in the brain, 3 months after alectinib treatment (A pretreatment brain metastatic expansive lesions with periedema, B tumor response after 3 months of alectinib, without tumors expansive lesions and persistent lesions like holes in the brain)
nocarcinoma, pTNM=T3N2M1b (LIV, BRA). The patient was initially treated with whole brain irradiation (WBI) to a total of 30 Gy with 300 cGy daily dose and two cycles of first-line chemotherapy with carboplatin/gemcitabine. Although chemotherapy yielded temporary lung tumor regression, progressive brain and liver metastases led to discontinuation of chemotherapy, after the two courses. The molecular analysis revealed ALK positivity determined by immunohistochemistry. Thereafter we started with alectinib 600 mg twice daily. Alectinib is covered by the national health insurance system in our country. She responded well to alectinib 600 mg twice daily. We evaluated tumor response after 10 months, from the initiation of the target therapy. Control CT of the lung, abdomen and MRI of the brain were performed and demonstrated lung and brain tumor disappearance and substantial tumor regression in the liver (Fig. 1, 2, 3). The patient remains on alectinib with no serious adverse events. The last follow-up visit, 12 months after commencing the alectinib treatment, showed there was no evidence of tumor progression or any remarkable toxicity. We noted mild musculoskeletal pain, alopecia and vision disorders as adverse effects.

Patient 2

A 53-year old man with left lung adenocarcinoma was treated with lung cancer surgery in 2017. Operative pTNM stage was IIB with R1 (positive resection margin). Post surgery, he was admitted to the Clinic of Radiotherapy and Oncology in Skopje, where he was treated with postoperative chemotherapy and radiotherapy. He was disease free on follow up, until October 2019 when he presented with severe cerebral symptoms. Brain CT showed multiple brain metastases. The patient presented with poor performance status of ECOG grade 3 and the brain was the only site of tumor progression. Upon disease progression we referred this patient, for biomarker analysis derived from the operative material. The molecular testing revealed EML4-ALK positivity. First we treated him with palliative whole brain radiotherapy and afterwards we put him on alectinib as a first line therapy. He demonstrated rapid symptom improved and after 3 months of therapy, he was well and able for work. We noted only mild obstipation as an adverse effect. In 3 months, control CT scan showed disappearance of expansive brain tumor lesions, instead it displayed multiple hole-like lesions in the brain tissue, in place of the tumors (Fig. 4, 5). At the last follow-up visit, 5 months after commencing the alectinib treatment, there were no signs of progression or any significant toxicity.

Fig. 5. Computed tomography scans of patient 2, depicting the tumor response in the brain, 3 months after alectinib treatment (A pretreatment brain metastatic expansive lesions and periedema, B positive response to the alectinib after 3 months, without tumors expansive lesions reduction, present with holes in the brain)
DISCUSSION

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. 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 which 50% were adenocarcinoma subtype, 40% were squamous cell carcinoma, 2% large cell carcinoma and 8% were NOS (non-specified). According to the International Staging System for Lung Cancer, out 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 all NSCLC patients for biomarker analysis. Eligible patients for this study included those with histological diagnosis of NSCLC and immunohistochemistry (ICH) proven ALK protein positivity. In our study there were 18 patients proven with ALK positivity. Gender wise 14 patients from this subset of patients, were men and 4 were women. As for the treatment strategy we treated 5 ALK positive patients with alectinib as a first line therapy, and 10 patients with alectinib as a second line therapy. Three patients from the ALK+ group, did not receive any ALKIs.

In our study we describe two cases of ALK-positive NSCLC patients with BMs, severe cerebral symptoms and poor PS. 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 months [9] in comparison with alectinib treatment, where median overall survival will not be reached in 5-years follow-up [10]. 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. As a result, ALK inhibitors have been developed, which demonstrated a systemic effectiveness and greatly improved results in comparison to the chemotherapy in patients with ALK-positive advanced NSCLC. Median progression-free survival with crizotinib as a first line therapy was longer compared with chemotherapy (10.9 versus 7 months). However, the intracranial efficacy of crizotinib is poor, due to the poor blood-brain barrier (BBB) penetration [11, 12]. Furthermore, ALK inhibitors with time, needed to be improved to enable intracranial disease control and expand the spectrum of ALK mutations targeted. As a result, the second generation ALK inhibitors like ceritinib, alectinib and brigatinib as well as the third-generation ALK inhibitor lorlatinib were developed [13]. 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 [14]. 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 [15]. Alectinib efficacy in patients with BMs was also assessed in phase III clinical trials. In the ALUR study [16], 24 alectinib-arm patients and 16 chemotherapy-arm patients had baseline brain metastases. The icORR was significantly higher with alectinib treatment 54.2% versus chemotherapy treatment 0% (p <0 .001). Various real-life retrospective cases with alectinib confirmed high efficacy in regard to the brain and leptomeningeal metastases [17, 18]. In addition, Ou and colleagues reported two cases of ALK-positive NSCLC patients with BMs who had undergone stereotactic radiosurgery (SRS) to the brain prior to treatment with alectinib. Both patients had radiation necrosis which was confirmed by neurosurgery and pathological examination showed pseudo-progression [19]. This particular brain development following SRS and alectinib, has to be recognized as such, in order to prevent incorrect classification into progressive disease and discontinuation of alectinib. In the context of brain radiotherapy studies have shown that the progression of BBB damage can be explained by complex interactions involving endothelial cell death, altered gene expression and micro-environmental changes [20]. Data showed that endothelial cells suffer from two waves of radiation-induced cell death after exposure to radiation: early ceramide-mediated apoptosis within < 24 hours and delayed, DNA-induced mitotic death > 72 hours, recorded up to 1 month after RT. Finally, this BBB disruption after focal RT or whole brain radiotherapy is pre-
sumed to lead to an increase in drug permeability [21, 22]. The reason for combining brain RT and targeted therapies in BMs patients is also based on the radiosensitizing properties of these drugs, which allow for better intracranial control (23). As a result we chose alectinib in our study patients. 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 (24,25).

Alectinib is metabolized by cytochrome. Results from J-ALEX and ALEX studies provided additional proof of the systemic and CNS efficacy of alectinib, with maximum 38 percent CNS response rates in patients with detectable CNS lesions at baseline. The cumulative incidence rate (CIR) of CNS progression in the ALEX ITT population, given the daunting risks of non-CNS progression and death, was 9.4 percent with alectinib versus 41.4 percent with crizotinib (26, 27). Median OS was NR (Non Reachable) with alectinib and 57.4 months with crizotinib (95% CI 34.6–NR) (10). 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+ NSCLC patients. Our data confirm that alectinib demonstrates superior efficacy for CNS disease in both of our study patients. Brain metastases are an adverse prognostic factor in ALK+ advanced NSCLC.

Our first patient with ALK-positive NSCLC, who was previously treated with chemotherapy and radiotherapy, is still on alectinib with good response including the brain mets. There was no proof of disease progression or exceptional toxicity at the last follow-up, after 12 months of alectinib treatment.

Our second patient at the last follow-up visit, 5 months after starting of alectinib treatment was well and without any cerebral symptoms.

**CONCLUSION**

Considering its efficacy and tolerability based on these two cases, we recommend alectinib as a best treatment approach for ALK+ NSCLC patients in first line.

**Consent**

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

**REFERENCES**

1. WHO Statistics. http://www.who.int/mediacentre/factsheets/fs297/en/ (accessed 21 December 2017).
2. Salomon B, Varella-Garcia M and Camidge DR. ALK gene rearrangements a new therapeutic target in a molecularly defined subset of non-smal cell lung cancer. J Thorac Oncol 2009; 4: 1450–1454.
3. Soda M, Choi YL, Enomoto M. et al. Identification of the transforming EML4-ALK fusion gene in NSCLC. Nature 2007; 448: 561–566.
4. Rikova K, Guo A, Zeng Q, et al. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. Cell 2007; 131: 1190–1203.
5. Kris M, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA 2014; 311: 1998–2006.
6. Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with NSCLC who harbor EMLA-4-ALK. J Clin Oncol 2009; 27: 4247–4253.
7. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in NSCLC. N Engl J Med 2010; 363: 1693–1703.
8. Passaro K, Lazzari C, Karachaliou N et al. Personalized treatment in advanced ALK-positive NSCLC; from bench to clinical practice. Onco Targets Ther.2016; 9: 6361–6376.
9. Costa DR, Kobayashi S, Pandya SS, et al. CSF concentration of anaplastic lymphoma kinase inhibitor crizotinib. J Clin Oncol 2011; 29: c443-c445.
10. Mok T, Camidge D. R., Gadgeel S. M.et al. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung can-
cer in the Annals of Oncology ALEX study 2020 doi: https://doi.org/10.1016/j.annonc.2020.
11. Metro G, Lunardi G, Floridi P, et al. CSF concentration of crizotinib in two ALK-positive NSCLC patients with CNS metastases deriving clinical benefit from treatment. J Thorac Oncol 2015;10:e26-e27.
12. Ricciuti B, De Gioglio A, Mecca C, et al. Precision medicine against ALK positive NSCLC: beyond crizotinib. Med Oncol 2018; 35: 72.
13. Rossi A, Alectinib for ALK-positive NSCLC. Exp Rev Clin Pharmacol 2016; 9: 1005–1013.
14. Vavalia T, Novello S. Alectinib in the treatment of ALK-positive non-small cell lung cancer: an update on its properties, efficacy, safety and place in therapy. Ther Adv Med Oncol 2018, Vol. 10: 1–12.
15. Kodama T, Hasegawa M, Takanashi K, et al. Antitumor activity of selective ALK inhibitor alectinib in models of intracranial metástasis. Cancer Chemother Pharmacol 2014; 74: 1023–1028.
16. Katayama R, Sakashita T, Yanagitani N, et al. P-glycoprotein mediates ceritinib resistance in anaplastic lymphoma kinase-rearranged NSCLC. Bio Medicine 2016; 3: 54–66.
17. Novello S, Mazieres J, Oh IJ, et al. Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive NSCLC: results from the phase III ALUR study. Ann Oncol 2018; 29: 1409–1416.
18. Metro G, Lunardi G, Bennati C, et al Alectinib’s activity against CNS metastases from ALK-positive NSCLC a single institution case series. J Neuro Oncol 2016; 129: 355–361.
19. Gainor JF, Sherman CA, Willoughby K, et al. Alectinib salvages CNS relapses in ALK-positive lung cancer patients previously treated with crizotinib and ceritinib. J Thorac Oncol 2015; 10: 232–236.
20. Ou SH, Klempner SJ, Azada MC, et al. Radiation necrosis presenting as pseudoprogression (PsP) during alectinib treatment of previously radiated brain metastases in ALK-positive NSCLC implications for disease assessment and management Lung cancer 2015; 88: 355–359.
21. Nordsal RA, Wong CS. Molecular targets in radiation-induced blood-brain barrier disruption Int J Radiat Oncol Biol Phs 2005; 52: 279–287.
22. Qin DX, Zheng R, Tang J et al Influence of radiation on the blood-brain barrier permeability changes and optimum time of chemotherapy. Int J Radiat Oncol Biol Phs 1990; 19: 1507–1510.
23. Khalifa J, Amini A, Popat S et al Brain metastases from NSCLC: radiation therapy in the era of targeted therapies Jour of Thorac Oncol 2016; 10: 1627–1643.
24. Tran PN and Klempner SJ. Focus on alectinib and competitor compounds for second line therapy in ALK-rearranged NSCLC. Front Med (Lausanne) 2016; 3: 65.
25. Gadgeel SM, Shaw AT, Barlesi F, et al. Cumulative incidence rates for CNS and non CNS progression in two phase II studies of alectinib in ALK-positive NSCLC Br J Cancer 2018; 118: 38–42.
26. Chuan YC, Huang BY, Chang HW, Yang CN. Molecular modeling of ALK L1198F and/or G1202R mutations to determine differential crizotinib sensitivity. Sci Rep. 2019; 9: 11390.
27. Camidge DR, Dziadziuszko R, Peters S, et al. Updated efficacy and safety data and impact of EML4-ALK fusion variant on the efficacy of alectinib in untreated ALK positive advanced non–small cell lung cancer in the global phase III ALEX study. J Thorac Oncol. 2019; 14: 1233–1243.
28. Dagogo-Jack I, Rooney M, Lin JJ, et al. Treatment with next-generation ALK inhibitors fuels plasma ALK mutation diversity. Clin Cancer Res. 2019; 25: 6662–6670.
29. Shaw AT, Solomon BJ, Besse B, et al. ALK resistance mutations and efficacy of lorlatinib in advanced anaplastic lymphoma kinase-positive non–small-cell lung cancer. J Clin Oncol. 2019; 37: 1370–1379.
Резиме

ТРЕТМАН СО ALECTINIB КАЈ БОЛНИТЕ
СО ALK ПОЗИТИВЕН НЕМИКРОЦЕЛУЛАРЕН БЕЛОДРОБЕН КАРЦИНОМ
И МОЗОЧНИ МЕТАСТАЗИ: НАШЕ КЛИНИЧКО ИСКУСТВО

Симонида Црвенкова
Универзитетска клиника за радиотерапија и онкологија Скопје, РС Македонија

Целта на студијата е да ја прикаже ефикасноста и безбедносниот профил на alectinib, со посебен фокус на неговата интракранијална ефикасност кај ALK+ NSCLC пациенти.

Приказ на случај: Пациентот 1 е 46-годишна жена со дијагноза на немикроцелуларен белодробен карцином, која има фузија на microtubule-associated protein-like 4-anaplastic lymphoma kinase генот. Кај неа се детектирани интракранијални и хепатални метастази и има лош performance status степен 3. Болната ја лекувавме со alectinib, по претходно спроведената ирадијација на целиот мозок и по прекин на хемотерапијата по спроведени два циклуси, поради настанатата прогресија на церебралната и хепаталната симптоматологија. Кај болната се постигна добар одговор на туморот со подобрување на performance статусот и немаше изразени несакани ефекти на лекот. Пациентот 2 е 53-годишен маж со опериран аденокарцином на левото белодробие пред три години (2017). Оперативниот рTNM-стадиум на болеста беше IIВ, но со Р1 (позитивна ресекциска маргина). По две и пол годишно преживување без болест, во 2019 година ненадејно кај болниот се појавиле церебрални симптоми и имал лош performance статус. На направениот CT на мозокот видени се бројни мозочни метастази. Болното е третиран со alectinib и по 5 месеци е добар и способен за работа.

Заклучок: Ние го препорачуваме alectinib како прволиниски третмански пристап кај ALK+ NSCLC болни, посебно кај оние што имаат мозочни метастази во моментот на поставување на дијагнозата и се со лош PS.

Ключни зборови: мозочни метастази, ALK+ NSCLC болни, alectinib