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Case Report

Treatment of a ROS1-Positive Non-Small Cell Lung Cancer Patient with Leptomeningeal Metastasis using Lorlatinib and Whole Brain Radiotherapy: A Case Report

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Abstract

Background: The first-line treatment for patients with advanced NSCLC with ROS-1 rearrangement is targeted therapy with first-generation ALK inhibitor. When leptomeningeal metastasis occurs, the treatment regimen for ROS-1-positive NSCLC patients is relatively limited. This study aimed to report the efficacy of lorlatinib combined with whole brain radiotherapy in an advanced NSCLC patient with leptomeningeal metastasis.

Case presentation: A 34-year-old male patient was diagnosed with stage IV non-small-cell lung Adenocarcinoma with pleural and bone metastases in August 2017. After 18 months of treatment with crizotinib, the patient experienced disease progression with leptomeningeal metastasis. After failure of treatment with ceritinib, the patient achieved PFS for 11 months with the third-generation ALK inhibitor lorlatinib combined with whole brain radiotherapy. On April, 2020, the patient experienced disease progression, which was mainly abdominal metastasis, and the CNS remained stable.

Conclusion: For ROS1-positive NSCLC patients with leptomeningeal metastasis who do not respond to first-generation and second-generation ALK inhibitor treatment, lorlatinib combined with whole brain radiotherapy may be a potential treatment option.

Keywords: Lorlatinib; ROS-1; Whole brain radiotherapy; Leptomeningeal metastasis; NSCLC

Introduction

ROS proto-oncogene 1 (ROS1)-positive Non-small Cell Lung Cancer (NSCLC) is very rare, accounting for approximately 1% - 2% of all NSCLC cases. The rate of ROS1 positivity in Chinese NSCLC patients is 2.59% [1,2]. According to the National Comprehensive Cancer Network (NCCN) guidelines, the first-line treatment for patients with advanced NSCLC with ROS-1 rearrangement is targeted therapy with crizotinib or ceritinib. Based on results from the PROFILE 1001 study [3], the median Duration of Response (DoR) of patients who received crizotinib as a first-line treatment was 17.6 months [95% Confidence Interval (CI) 14.5 - Not Reached (NR)], and the mean Progression-free Survival (PFS) was 19.2 months [95% CI 14.4-NR]. However, crizotinib does not easily cross the blood-brain barrier, and therefore, the incidence of brain metastasis after 5 years in ROS1-positive NSCLC patients is approximately 35% [4]. When leptomeningeal metastasis occurs, patient prognosis is extremely poor [5]. The treatment regimen for ROS-1-positive NSCLC patients with leptomeningeal metastasis is relatively limited. In this paper, we report the efficacy of lorlatinib combined with whole brain radiotherapy in an advanced NSCLC patient with leptomeningeal metastasis.

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Case Presentation

Patient information

A 34-year-old male was admitted to Fujian Provincial Hospital on August 10, 2017, due to coughing for 2 weeks and worsening of cough symptoms with shortness of breath for 3 days. He had no history of hypertension or smoking or drinking and denied a history of familial malignancies.

Diagnostic evaluation

Several examinations were performed on August, 2017. The blood concentration of Carcinoembryonic Antigen (CEA) was 39.28 ng/ml. Plain chest Computed Tomography (CT) plus enhanced CT suggested a mass occupying the right upper lobe near the hilum, suggesting the possibility of central lung cancer with multiple pleural metastases. Multiple nodular lesions in the left lung and ground-glass opacities were observed. Bone imaging showed an abnormally high concentration of bone-scanning agents in the spine, sternum, and bilateral ribs,

suggesting bone metastasis. Thoracoscopic pleural biopsy of the right side was performed on August 15, 2015, and the pathological examination revealed moderately differentiated Adenocarcinoma. The immunohistochemistry findings were as follows: Ki67 (15% +), CK7 (+++), CK20 (-), villin (-), thyroid transcription factor 1 (TTF-1, +++), napsin-A (+++), caudal-type homeobox 2 (CDX-2, -), and Anaplastic Lymphoma Kinase (ALK) p80 (-). ROS1 rearrangement was detected by Amplification-Refractory Mutation System (ARMS). Based on the 7th Edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual and the Future of TNM, this patient was diagnosed with right lung Adenocarcinoma with pleural and bone metastases (cT4N2M1c stage IVB).

Treatment intervention

Beginning August 30, 2017, the patient received oral crizotinib (250 mg bid), and 1 month later, treatment efficacy was evaluated based on Partial Response (PR) (Figure 1A and B), and zoledronate was administered to inhibit bone metastasis. In March 2019, the patient experienced dizziness, headache, involuntary shaking of the right upper limb, and numbness of the right hand. Brain Magnetic Resonance Imaging (MRI) suggested extensive enhancement and thickening of the pia mater (Figure 1C), and Cerebrospinal Fluid Cytology (CSFC) revealed tumor cells in cerebrospinal fluid (Figure 2). Next-generation Sequencing (NGS) results for the cerebrospinal fluid and plasma samples suggested CD74-6: ROS1-34 mutation. On March 7, 2019, the patient began taking oral ceritinib (450 mg qd) as second-line targeted therapy. One month later, intracranial symptoms were not relieved, and cranial MRI re-examination suggested lesion progression (Figure 1D) (compared to the previous examination, there was an increase in multiple abnormally enhanced small nodules in the pia mater area, right insula and left cerebellar hemisphere). Therefore, whole brain radiotherapy was performed in April 2019, with the whole brain considered as the Clinical Target Volume (CTV) (Planning Clinical Target Volume (PCTV) DT30Gy/10f), and the patient was switched to third-line treatment with lorlatinib (50 mg qd). One month later, the patient's symptoms had improved significantly, and the involuntary shaking of the right upper limb disappeared. Cranial MRI re-examination revealed alleviation of the lesions compared with the previous MRI (Figure 1E) (a portion of the pia mater was slightly thickened and enhanced linearly, indicating significant alleviation compared with the previous examination).

In April 2020, the patient presented significant abdominal distension. Abdominal drainage was performed, and cancer cells were observed on ascites smears. NGS of ascitic fluid suggested ROS1 gene mutations. These findings suggested disease progression. In June 2020, the patient began receiving first-line chemotherapy with a pemetrexed 0.85 g plus carboplatin 550 mg regimen. Currently, the patient has received 2 cycles of chemotherapy.

Discussion and Conclusion

ROS1 and ALK have highly homologous structural and functional domains. Based on results from the PROFILE 1001 study, crizotinib has been approved by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) for advanced NSCLC patients with ROS-1 rearrangement [6]. However, drug resistance is still unavoidable. Currently, there is no standardized treatment plan for ROS1-positive NSCLC patients with leptomeningeal metastasis. It has been reported that ceritinib treatment may have an appropriate therapeutic effect on ROS1-positive NSCLC patients with leptomeningeal metastasis [1]. The patient in this study received ceritinib treatment, and unfortunately, he did not respond to the drug. Gainor et al. [7] reported that ROS1 mutations were detected in 62.5% of the patients resistant to crizotinib. The ROS1-G2032R mutation is the main mechanism by which ROS1-positive NSCLC patients become resistant to crizotinib treatment. However, in this study, all drug-resistant disease samples were from non-Central Nervous System (CNS) sites, and no ROS1 mutations were found in 3 CNS specimens. Although limited by a small sample size, drug resistance in these samples may reflect the pharmacokinetic failure of the treatment, rather than actual biological resistance.

Lorlatinib is a third-generation ALK inhibitor and has a high ability to penetrate the CNS. For patients who do not respond to first- and second-generation ALK treatments, lorlatinib treatment

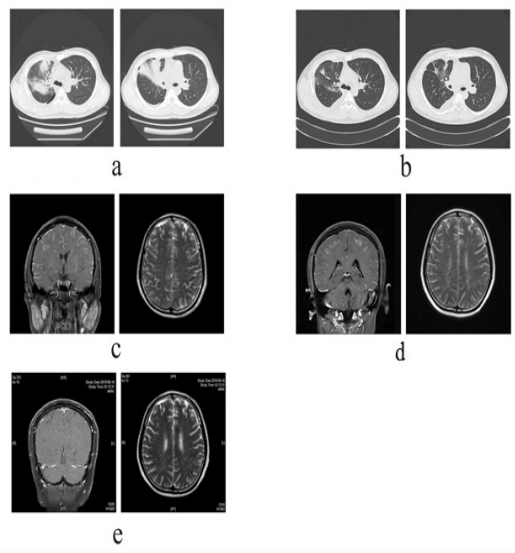

Figure 1: Clinical response of the patient. A. Lung tumor before receiving crizotinib treatment. B. PR achieved after crizotinib treatment for 1 month. C. Leptomeningeal metastasis after arizotinib treatment for 18 months. D. Progressive Disease (PD) after ceritinib treatment for 1 month. E. PR achieved after whole brain radiotherepy combined with lorlatinib for 1 month.

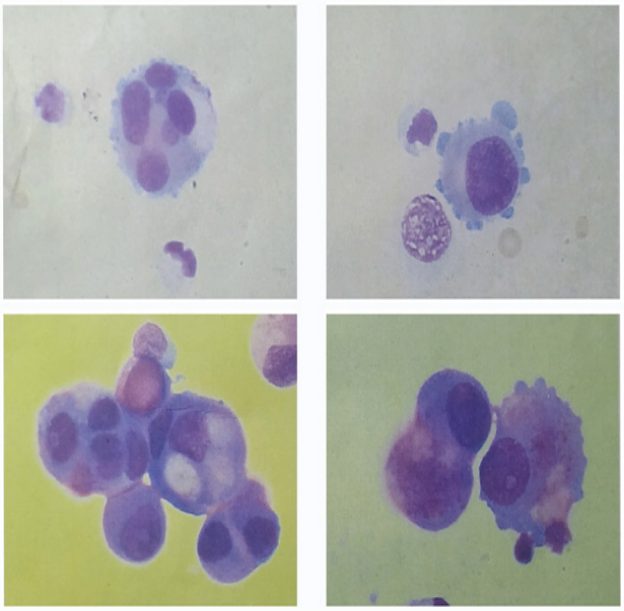

Figure 2: Tumor cells in cerebrospinal fluid.

may be an option. In 1 single-arm phase I/II clinical trial, a total of 12 patients with ROS1-positive NSCLC were included. After treatment with lorlatinib, 5 patients had measurable intracranial lesions, and 3 patients had objective intracranial responses, including 2 patients who were nonresponsive to crizotinib therapy [8].

Currently, there are few reports on the treatment of ROS1-positive NSCLC patients with leptomeningeal metastasis. The efficacy of ALK inhibitors is not well known. Because whole brain radiotherapy can treat tumor lesions that are visible and non visible to the naked eye, it has become a first-line treatment for patients with extensive disseminated brain metastasis. However, the effect of whole brain radiotherapy alone is not known [9]. For ROS1-positive NSCLC patients with leptomeningeal metastasis who do not respond to first-generation and second-generation ALK inhibitor treatment, lorlatinib combined with whole brain radiotherapy may be a potential treatment option.

The patient in this study was resistant to first-generation and second-generation ALK inhibitors. After treatment with the third-generation ALK inhibitor lorlatinib combined with whole brain radiotherapy, the patient achieved PFS for 11 months. Currently, PD was observed in the patient. The progression was mainly abdominal metastasis; the CNS was still stable.

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