Original Article

Clinical efficacy analysis of Osimertinib treatment for a patient with leptomeningeal metastasis of *EGFR*+ non-small cell lung cancer without the *T790M* mutation

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Background: To find the method of therapy of leptomeningeal metastasis (LM) to non-small cell lung cancer (NSCLC) patient with *EGFR* mutation (*EGFR*+) but without *T790M* mutation.

Methods: A retrospective analysis was reviewed for 5 NSCLC patients with *EGFR*+ who develop to LM from January 2018 to February 2019 in our hospital.

Results: All five NSCLC cases were adenocarcinoma, four cases were verified existed *EGFR* mutation with *19 exon* deletion in the first diagnosed by biopsy tissue, the other tissue was verified *21 exon* mutation. Two cases were initially diagnosed with LM, and the other three cases were found metastasis with leptomeningeal respectively after 64, 3 and 4 months when the lung cancer was diagnosed. There were not verified to exist *T790M* mutation with *EGFR*+ when all the five cases developed to LM. The major symptom was headache and blurred vision. In the image scanning, two cases were not revealed, but other three cases show that multiple metastatic lesions with brain and meninges. All patients were identified existed adenocarcinoma cells in cerebrospinal fluid (CSF). Four cases were treated by the first epidermal growth factor receptor tyrosine kinase inhibitor (*EGFR*-TKI) and joint therapy including chemotherapy and radiotherapy, and the other case was treated by temozolomide and intrathecal chemotherapy in their earlier therapy. The curative effect was significant when they took osimertinib orally 80 mg once a day, for the disease progressing. The neurological symptoms were relieved in patient about 5–10 days after osimertinib treatment. The remission time was 10, 7, 7, 5, 4 months respectively until last following time to June 2019. The survival time was respectively 74, 7, 27, 18, and 4 months. The side effects were not increased.

Conclusions: Whether *EGFR*+ with *T790M* mutation was positive or negative, osimertinib is an effective drug and can improve quality of life and prolong the survival for NSCLC patient with *EGFR* mutation to progress LM.

Keywords: Osimertinib; *T790M* negative; non-small cell lung cancer (NSCLC); leptomeningeal metastasis (LM); clinical efficacy

Accepted for publication Sep 10, 2019. Accepted for publication Oct 17, 2019.
doi: 10.21037/apm.2019.10.13
View this article at: http://dx.doi.org/10.21037/apm.2019.10.13

Introduction

Lung cancer metastases to the brain are a common phenomenon. Most of them present as brain parenchymal lesions, but, simple leptomeningeal metastasis (LM) or cerebrospinal fluid (CSF) metastasis is rare (1). Brain metastasis often showed the patient had poor prognosis, but it can be improved by cranial radiotherapy and intracranial chemotherapy. However, simple LM or CSF metastasis often lack effective imaging evidence (2), some hospitals do not have the methods to test CSF, that lead the diagnosis exceedingly difficult for these patients, and lacked effective treatment method, so the prognosis became worse. In recent years, with the widespread application of comprehensive treatment for lung cancer, the survival rate of patients has gradually improved, and the probability of LM has also increased (3). More than 10% of patients with non-small cell lung cancer (NSCLC) with epidermal growth factor receptor mutations (*EGFR*+) have been reported to show LM (4). As a third-generation epidermal growth factor receptor tyrosine kinase inhibitor (*EGFR*-TKI), osimertinib had been shown effective in patients with *T790M* mutation-positive LM (5). However, there are few reports on the treatment of osimertinib in *T790M* negative patients with LM of lung cancer (6). We reported the clinical data of 5 patients with *EGFR* mutated NSCLC with LM treated in our department from January 2018 to February 2019, and analyzed the treatment process and outcome of osimertinib, to seek effective methods for the treatment of such patients.

Methods

This retrospective analysis was approved by The Clinical Medical Research Ethics Committee of The First Affiliated Hospital of Anhui Medical University. This study was only concluded about clinical cases, image data and laboratory results, without experimental animals and human tissues. The privacy consent was achieved by all patients. A retrospective analysis was reviewed for 5 NSCLC patients with *EGFR*+ whose develop to LM from January 2018 to February 2019 in the Department of Medical Oncology, the First Affiliated Hospital of Anhui Medical University. Total survival was obtained by outpatient or telephone follow-up to June 2019. Through the analysis of previous treatment regimens, disease changes, imaging manifestations related to LM, CSF testing, gene testing and blood CEA changes of 5 patients, the efficacy of osimertinib orally 80 mg once a day in treating *EGFR*+ NSCLC with LM and its relationship to *T790M* were studied.

Results

Clinical and imaging findings

Clinical data were shown in *Table 1*.

Among the 5 patients with LM of lung cancer, 2 were male, and 3 were female. The median age was 43 years (38 to 62 years). LM was found in 2 patients at the first diagnosis, and in the other 3 patients, LM occurred about 64, 3, and 4 months after the diagnosis of lung cancer. All the 5 patients presented with non-localized neurological symptoms, including cranial hypertension headache and dizziness, and 3 patients presented with cranial nerve involvement, blurred vision, and decreased vision. These imaging findings of 5 patients were different (*Figure 1*), among which 2 patients were negative with no signs of brain and LM (*Figure 1C,E*), 3 patients suggested multiple enhanced foci of brain parenchyma and leptomeninges (*Figure 1A,B,D*), and *Figure 1F*.

CSF examination

Adenocarcinoma cells were detected in CSF in all the 5 patients, and biochemical examination of CSF suggested that glucose was decreased, the protein was increased, and CEA was increased compared with normal value (*Table 2*).

Gene testing

High-throughput sequencing (NGS) of puncture tissues and peripheral blood was performed in 5 patients after the diagnosis of LM, which improved the gene detection. All cases showed negative *T790M*.

Treatment regimen and survival

LM was present in 2 of the 5 patients at first diagnosis; the gene detection results of the two patients were *19 exon* deletion and *T790M* negative. One patient was treated with intrathecal chemotherapy (methotrexate + cytarabine) combined with temozolomide, but the symptoms of headache and dizziness were not significantly relieved. When the treatment was replaced by osimertinib orally 80 mg once a day and the neurological symptoms disappeared significantly 10 days later. The other patient developed intracranial lesions after gefitinib combined with

Table 1 Five cases clinical data

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	Male	Female	Female	Female	Male
Age (years)	38	54	62	40	43
Source of tumor tissue	Lumbar vertebra puncture	Lumbar puncture	Lung puncture	Right cervical lymph node puncture	Lung puncture
Histological subtype	Moderately differentiated adenocarcinoma	Moderately differentiated adenocarcinoma	Poorly differentiated adenocarcinoma	Adenocarcinoma	Moderately differentiated adenocarcinoma
EGFR status	*19 exon* deletion	*19 exon* deletion	*19 exon* deletion	*19 exon* deletion	*21 exon* mutation
Treatment before osimertinib	Pemetrexed + cisplatin; erlotinib	Intrathecal chemotherapy (methotrexate + cytarabine); temozolomide	Gefitinib; temozolomide; whole brain radiotherapy	Pemetrexed + cisplatin; gefitinib	Pemetrexed + cisplatin; icotinib
Symptoms for leptomeningeal metastasis	Headache; lower limb muscle strength decreased; mental symptom	Dizziness; headache	Dizziness; headache; blurred vision; lower limb muscle strength decreased	Dizziness; headache; blurred vision	Headache; blurred vision
Leptomeningeal change in brain MRI	Linear enhancement	Negative	Linear enhancement	Negative	Small patched enhancement
CSF cell examination	Adenocarcinoma cell	Adenocarcinoma cell	Adenocarcinoma cell	Adenocarcinoma cell	Adenocarcinoma cell
T790M mutation	Negative	Negative	Negative	Negative	Negative
Time to onset for osimertinib orally (days)	7	10	7	5	8
Remission time (months)	10	7	7	5	4
Overall survival (months)	74	7	27	18	4

temozolomide treatment, but the disease was not controlled after cranial radiotherapy. *T790M* gene testing was still negative at that time. Then the patient developed nausea, vomiting, and blurred vision, and the therapy was replaced by osimertinib orally 80 mg once a day. Her symptoms reduced gradually after 1 week.

The remaining 3 patients did not have LM at the first diagnosis. One patient had *19 exon* deletion and *T790M* negative. His first line of treatment was chemotherapy combined with erlotinib, and he was given 64 months of progression-free survival for the first time. After the diagnosis of leptomeningeal progression, the patients have replaced it with osimertinib orally 80 mg once a day, and the psychiatric symptoms were significantly relieved after 1 week. According to the results of genetic testing, LM occurred in the other two patients 3 months after gefitinib and 4 months after icotinib. Osimertinib was used as orally 80 mg once a day when the neurological symptoms were not relieved after applicating analgesia, cranial pressure reduction, and systemic chemotherapy method. In the first case, dizziness, headache, nausea, and vomiting symptoms disappeared, and blurred vision was relieved 5 days after osimertinib treatment, neurological symptoms were relieved in the other patient 8 days after osimertinib treatment (*Table 1*).

All five patients were followed up and survived continuously in June 2019. The remission time was 10, 7, 7, 5, 4 months respectively, and the total survival time was 74, 7, 27, 18, and 4 months correspondingly (*Table 1*). The side

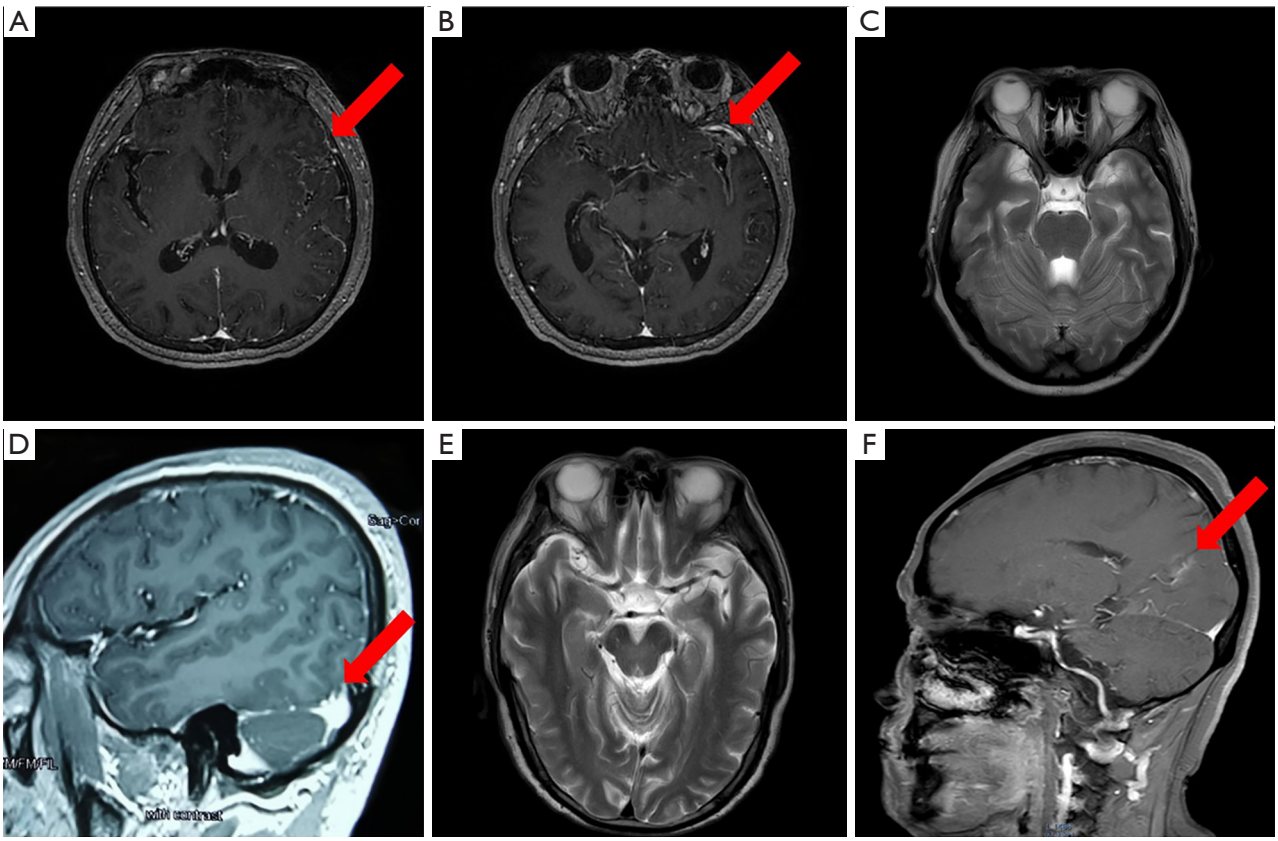

Figure 1 Brain MRI: abnormal line-like enhancement can be seen in the leptomeningeal of both temporal lobes (A,B). None abnormal enhancement lines in leptomeningeal and brain parenchyma, none hypodense edema area (C). Multiple enhancement lines in both cerebellar sulci (D). Cerebral ischemia in periventricular area, none abnormal enhancement lines in leptomeningeal and brain parenchyma (E). Small patched enhancement in occipital lobe (F).

Table 2 CEA, glucose, protein in CSF

Patient	CEA (ng/mL)	Glucose (mmol/L)	Protein (g/L)
1	352.65	1.21	0.57
2	369.54	2.0	0.48
3	255.75	2.12	0.89
4	285.7	1.30	0.65
5	265.25	1.05	0.7

Normal range of CEA: 0–5 ng/mL; normal range of glucose: 2.20–3.90 mmol/L; normal range of protein: 0.15–0.45 g/L.

effects were not increased.

Discussion

The incidence of LM in NSCLC was 20–40% (7), especially high to 84–96% in adenocarcinoma subtype because of the proportion was high in recent years (8-10). LM was also an important indicator for poor prognosis. Once LM occurred, the median survival time of the patient was only 4–8 months (11). The diagnosis of LM of lung cancer majorly depended on clinical manifestations, including increased intracranial pressure and leptomeningeal stimulating symptoms. It was also accompanied by cranial nerve and spinal nerve root involvement (12). The imaging examination was often negative (8), especially in patients with diffusely LM (13). Some authors had reported that enhanced cranial MRI could display linear and nodular enhancement in meninges (3). In our study, 5 patients presented dizziness and headache due to increased intracranial pressure, and 3 patients presented blurred vision and decreased vision, namely, cranial nerve involvement. Multiple brain MRI examinations showed no abnormality in 2 patients

and revealed leptomeningeal enhancement with LM in 3 patients, which were consistent with the literature reports. Diagnosis of LM needs CSF examination. However, the sensitivity and effectiveness of CSF cytology were only 75% and 83.3% (14). The biochemistry results of CSF had some diagnostic value for LM. It had been reported that the levels of white blood cells and protein in CSF increased and the levels of glucose decreased in patients with LM of NSCLC (15,16). Carcinoembryonic antigen (CEA) in CSF could also be used as a reference for the diagnosis of LM. The level of CEA in CSF of patients with LM of primary lung cancer was significantly higher than that of other tumor species. Combined with the changes in CEA level in patients' blood and CSF, the positive rate of detecting LM could be improved (17). In our study, CEA in blood and CSF increased significantly in 5 patients, and LM could be diagnosed by combining clinical manifestations and imaging examination, which was consistent with literature reports.

The treatment of LM was different from that of brain parenchymal metastasis in lung cancer. There had no unified standard treatment method yet. Systemic chemotherapy, targeted therapy, intrathecal or ventricular chemotherapy, and radiotherapy were common methods to be used in the clinical treatment. Although first-generation *EGFR*-TKI targeted drugs are now widely used as first-line treatment for patients with advanced NSCLC with *EGFR* mutation, their efficacy for meninges metastasis was still limited due to their weak blood-brain barrier permeability (18). More than 30% of patients with intracranial metastasis had been reported to have disease progression during or after TKI treatment (19). Some authors reported that the first-generation *EGFR*-TKI drugs, such as gefitinib and erlotinib, could improve the efficacy by high-dose pulsed administration, but the effect was still not significant, and the median survival time of patients was not significantly prolonged (20-23). Comparing with the platinum-containing two-drug combined regimen, the third generation of *EGFR*-TKI drugs such as osimertinib showed significantly increased the median PFS (11.7 *vs.* 5.6 months, P=0.004) for the *T790M* mutation-positive NSCLC patients with brain metastasis in the results of AURA3 phase III clinical trial (24). Among the patients in advanced NSCLC who were treated for the first time, whether the *T790M* mutation was negative or positive, the efficacy of osimertinib was better than that of first-generation TKI drugs (8). In preclinical studies, osimertinib was revealed significant efficacy in mouse models of brain metastasis (25), and it had better blood-brain barrier permeability than gefitinib and afatinib (26).

The BLOOM phase I clinical study had assessed the reactivity and safety of osimertinib and compared its advantage to the earlier TKI drug treatment in patients with LM (27). Preliminary results showed that 23 out of 32 patients benefited, 10 had imaging changes, and 13 had stable lesions after 12 weeks of treatment in 32 patients. In this study, 11 patients tested positive for *T790M* mutation, and 21 patients failed the *T790M* mutation test. Patients who fail the genetic test included *T790M* negative; this means that osimertinib may also be effective in *T790M* negative patients. Chalmers *et al.* (28) reported that patients with *T790M* negative remained stable for 1 year when treated with osimertinib in advanced NSCLC. Facchinetti *et al.* (29) also reported that osimertinib was effective in the treatment of meningeal metastasis of *T790M* negative NSCLC patients by imaging changes in brain lesions. According to diagnosis and treatment consensus of brain and LM from lung cancer in China (30), osimertinib also can be used for brain (leptomeningeal) metastases as the disease progressing after TKI treatment without the *T790M* mutation. In our study, *EGFR* mutation was positive, and *T790M* mutation was negative by NGS in puncture tissues and peripheral blood in all the 5 patients when diagnosed as LM. After treatment by osimertinib, neurological symptoms were significantly relieved, clinical benefits were significantly obtained, and survival period was prolonged. Due to the presence of the blood-brain barrier, the acquisition of gene detection for intracranial lesions could be affected, and even false-negative results were obtained. Huang *et al.* (31) reported that in patients with LM, there is a difference between CSF and blood gene detection, and the *T790M* of blood gene detection may be negative, while that of CSF is contrary. Our five patients had not repeated to detect EGFR mutation in CSF, and it was questionable whether there was a false negative to *T790M*. Peripheral blood gene detection is used in clinical to overcome the heterogeneity of tumor tissues in recent years. Therefore, the false-negative rate of *T790M* mutation detection can be reduced by simultaneous detection of EGFR gene mutation and *T790M* gene mutation in CSF in patients suspected of LM.

Conclusions

In conclusion, it is difficult for patients with LM of NSCLC to be diagnosed at an early stage, and comprehensive

consideration should be given to the clinical manifestations, CSF cytology, laboratory examination, and imaging examination. Our study shows that even if *T790M* mutation is negative or cannot be accurately measured, early applicating of osimertinib shall be considered, and it may obtain better efficacy and clinical benefits for patients with LM of lung cancer, especially for patients with LM of NSCLC with *EGFR* gene mutation.

Acknowledgments

Funding: The project is supported by Health Bureau of Anhui Province, China (No. 09B114).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Patients were prospectively reviewed on our retrospective analysis and followed for 1 year. This retrospective analysis was approved by The Clinical Medical Research Ethics Committee of The First Affiliated Hospital of Anhui Medical University (No. Quick PJ 2019-13-11). The privacy consent was achieved by all patients.

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Cite this article as: Hu X, Chen W, Li X, Zhao C, Zhang C, Xiong F, Wu H. Clinical efficacy analysis of Osimertinib treatment for a patient with leptomeningeal metastasis of *EGFR*+ non-small cell lung cancer without the *T790M* mutation. Ann Palliat Med 2019;8(5):525-531. doi: 10.21037/apm.2019.10.13

