Case report

Salvage therapy of osimertinib plus anlotinib in advanced lung adenocarcinoma with leptomeningeal metastasis: A case report

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ABSTRACT

Leptomeningeal metastasis (LM) is one of the most serious complications of advanced non-small cell lung cancer (NSCLC) and lacks standard treatment. Patients with LM often have a poor prognosis. Here, we report a 51-year-old man diagnosed as advanced lung adenocarcinoma and gene sequencing indicated no sensitive driver gene mutation. Pemetrexed and cisplatin plus bevacizumab was administered as first-line therapy. He received pembrolizumab plus nab-paclitaxel as second-line therapy and developed neurological symptoms soon. Later, he was diagnosed LM by cerebrospinal fluid (CSF) cytology and gene sequencing of lung tissue rebiopsy demonstrated epidermal growth factor receptor (EGFR) sensitive mutation. The patient received high-dose (160mg) osimertinib therapy but still could not tolerate severe neurological symptoms and developed cardiac adverse event. After that, standard-dose (80mg) osimertinib plus anlotinib was administered and this treatment regimen resulted in the alleviation of neurological symptoms. As the recent follow up, the curative effect was evaluated stable disease (SD) and the patient gained a progression-free survival (PFS) of more than 15 months. We report this successful salvage therapy of osimertinib plus anlotinib in an advanced lung adenocarcinoma patient who developed LM after failure on previous treatment until EGFR mutation was confirmed through rebiopsy.

1. Introduction

Non-small cell lung cancer (NSCLC) is still the leading cause of cancer-related death worldwide [1]. Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) have been the first and most important therapeutic options for NSCLC patients with epidermal growth factor receptor (EGFR) sensitive mutation. Leptomeningeal metastasis (LM), the spread of tumor cells into the leptomeninges and cerebral spinal fluid (CSF), occurs in approximately 3%–5% patients of NSCLC(2). However, the incidence of LM rose to about 9% in EGFR-mutated NSCLC(3). LM may result in neurological adverse events that affect the quality of life and the median overall survival (OS) of NSCLC diagnosis after LM ranges from 3 to 11 months [3–5].

Osimertinib, a third-generation, irreversible EGFR-TKI, has been recommended as a preferred first-line therapy option for patients with metastatic NSCLC who have sensitive EGFR mutation [6]. The phase I BLOOM study evaluated the efficacy of osimertinib in patients with LM from EGFR-mutated advanced NSCLC whose disease had progressed on previous EGFR-TKI therapy. Among the 41

Fig. 1. Dynamic changes in the chest CT scan during treatment. (A) On 5 July 2019, chest CT revealed an irregular mass in the left lower lobe. (B) On 7 September 2019, chest CT indicated stable disease after 2 cycles of first-line therapy. (C) On 9 January 2020, chest CT revealed stable disease after 6 cycles of first-line therapy. (D) On 26 May 2020, chest CT showed that the primary lesion was larger than before and progressive disease occurred. (E) On 17 June 2020, after 1 cycle of second-line therapy, the primary lesion was still enlarged and diffuse ground glass of both lungs was increased. (F) On 27 August 2020, chest CT indicated stable disease 1 month after osimertinib plus anlotinib therapy. (G) On 19 May 2021, chest CT revealed stable disease 9 months after osimertinib plus anlotinib therapy. (H) On 14 November 2021, chest CT still showed stable disease 15 months after osimertinib plus anlotinib therapy.

patients enrolled, the ORR was 41% and the LM ORR was 62%, while the median PFS and median OS were 8.6 months and 11 months, respectively [5]. Hence, osimertinib for EGFR-mutated NSCLC patients with LM is also recommended. Anlotinib is a novel oral multi-targeted TKI which has a broad spectrum of inhibitory action on tumor angiogenesis and growth. Based on ALTER 0303 trial, Chinese Society of Clinical Oncology (CSCO) has recommended anlotinib for third-line treatment of advanced NSCLC(7). Post Hoc analysis of ALTER 0303 indicated that anlotinib can benefit patients of NSCLC with brain metastasis and is highly potent in the management of intracranial lesions [8].

Here, we report a case of advanced lung adenocarcinoma who developed LM after 2 lines of therapy. After gene sequencing of rebiospy demonstrating EGFR sensitive mutation, high-dose (160mg) osimertinib was administered. However, the patient could not tolerate the severe neurological symptoms and developed cardiac adverse event. Then, osimertinib was reduced to standard-dose (80mg) and anlotinib was added. Till now, the patient has achieved a PFS of more than 15 months and is well tolerated.

2. Case presentation

A 51-year-old man presented with cough and fatigue with an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 1 was admitted to the local hospital in July 2019. Chest computed tomography (CT) indicated a left hilar mass with mediastinal lymphadenopathy (Fig. 1 A). Additionally, abdominal CT revealed a mass in the left adrenal gland and spinal magnetic resonance (MR) revealed diffuse abnormal signals in the vertebral body. No abnormality was observed from the cranial enhanced MR. Then, the patient underwent bronchoscopy and the pathology revealed adenocarcinoma. He was diagnosed as advanced lung adenocarcinoma (stage IVB, cT2N3M1c) with left adrenal metastasis and multiple bone metastasis. The next generation sequencing (NGS) of tissue biopsy indicated negative driver gene mutation.

The regimen of pemetrexed (800mg D1) and cisplatin (40mg D1-3) plus bevacizumab (400mg D1) and maintenance therapy of pemetrexed (800mg D1) plus bevacizumab (400mg D1) was administered every 3 weeks as first-line therapy. The curative effect was evaluated stable disease (SD) during treatment (Fig. 1B and C). However, the patient's cough and short of breath aggravated and the CT scan indicated enlarged primary lesion in May 2020 (Fig. 1 D). Hence, progressive disease (PD) was evaluated and the regimen of pembrolizumab (200mg D1) and nab-paclitaxel (400mg D1) was administered as second-line therapy. After several days, his respiratory symptoms of cough, chest tightness aggravated and chest CT scan showed that the primary lesion was enlarged and diffuse ground glass of both lungs was increased than before (Fig. 2 E). It was relatively difficult to identify immune-related interstitial lung disease (ILD) and progressive disease. He also developed serious headache, nausea and vomiting, but no significant abnormality could
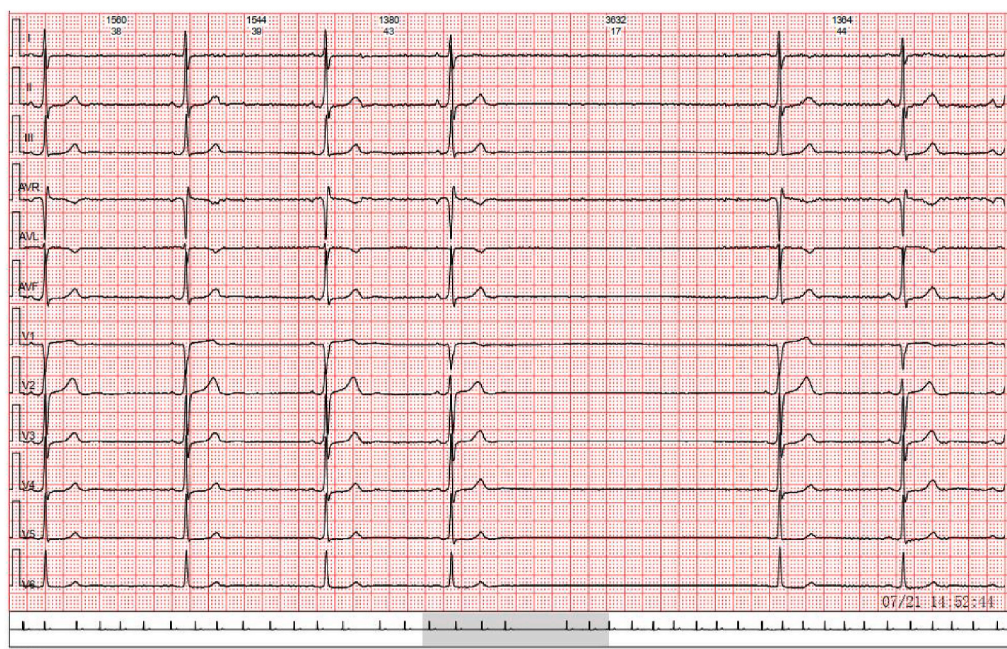

Fig. 2. The 24-h holter demonstrating sinus arrest with a maximum RR interval of 3.63 seconds.

be observed from the cranial enhanced MR. Later, lumbar puncture was performed and adenocarcinoma cells were found in CSF. Biochemical examination of CSF also indicated elevated protein level. LM was diagnosed and there was more reason to believe that the patient experienced progressive disease. Bronchoscopy was performed again to verify the disease progression and the NGS of the intrapulmonary metastasis indicated EGFR 19 exon deletion mutation on July 10, 2020. Then, high-dose osimertinib (160mg QD, oral) was administered as subsequent therapy. Despite this, his headache was still severe and he experienced epilepsy several times. Additionally, during treatment, the ECG (electrocardiograph) monitoring showed a slow heart rate between 36 and 45 seconds per minute at night, and the 24-h holter indicated sinus arrest (Fig. 2). Since the patient denied personal history of cardiac disease, we considered that the bradycardia might be caused by the adverse event of osimertinib therapy. Then, the dose was reduced to 80mg daily from July 18, 2020. However, the patient's short of breath and headache were similar than before and then anlotinib (12mg, D1-14, Q3W, oral) was added to osimertinib therapy from July 23, 2020.

After several days, his symptoms of short of breath and headache were significantly improved than before. The chest CT scan indicated stable disease 1 month later (Fig. 1 F). The tumor marker, CEA (carcinoembryonic antigen), dropped dramatically later (Fig. 3). During osimertinib plus anlotinib treatment, the adverse events were controllable rash (grade 2), pruritus (grade 2), diarrhea (grade 2) and paronychia (grade 2).

We continued CEA, chest CT and cranial enhanced MR measurements regularly during osimertinib plus anlotinib administration. As the recent follow up, chest CT indicated that the curative effect was still SD (Fig. 1G and H). The patient has achieved a PFS of more than 15 months and is still receiving the combined therapy.

3. Discussion

Recently, management of NSCLC after diagnosis of LM remains a challenge and there exists no standard treatment. Osimertinib (AZD9291) has high central nervous system (CNS) penetration with higher CSF distribution compared with first- and second-generation TKIs [9]. The patient was administered with high dose of osimertinib at first for we considered the following reasons. Firstly, preclinical pharmacokinetic and pharmacodynamic modeling simulations indicated that a dose of 160 mg osimertinib may increase CNS tumor shrinkage [10,11]. Secondly, based on the result of the BLOOM study, osimertinib showed meaningful therapeutic efficacy in the CNS and a manageable safety profile at 160 mg once daily in patients with EGFR-mutated NSCLC and LM(5). Anlotinib is a novel oral antiangiogenic multitargeted TKI which selectively inhibits VEGFR (vascular endothelial growth factor receptor) and other targets, all of which contribute to inhibitory action on tumor angiogenesis and partial tumor cell growth function [7]. VEGF (vascular endothelial growth factor) and EGFR share many overlapping and parallel downstream pathways [12]. Several angiogenic growth factors including VEGF increased through EGFR signaling regulation [13]. In turn, up-regulation of VEGF contributes to resistance to EGFR inhibition. Biological rationale shows that the inhibition of the EGFR and VEGFR signaling pathways could improve the efficacy of antitumor therapy and remove the resistance of EGFR inhibition [14]. Currently, a Phase II study (NCT04438902) is ongoing which evaluates osimertinib combined with anlotinib in EGFR T790M mutated NSCLC patients with progression on osimertinib treatment.

The patient in the current case is a middle-aged man of lung adenocarcinoma who developed LM after failure on previous treatment and sustained durable benefit from salvage therapy of osimertinib plus anlotinib, which is worthy of our thinking. Firstly, gene sequencing of first biopsy indicated that there was no sensitive driver gene mutation. While after disease progression on 2 lines of therapy, the second biopsy demonstrated EGFR 19exon deletion mutation. We speculate that the negative result before treatment may be caused by the heterogeneity of the tumor. The primary lesion and the metastatic lesion might show different phenotypes. So, tissue rebiopsy is of great significance for lung adenocarcinoma patients who progressed on prior therapies that may lead to significant changes in treatment strategies. Secondly, the patient's disease progressed soon after second-line immunotherapy and EGFR mutation was indicated by rebiopsy later. This is in line with previous studies that EGFR-mutated NSCLC is not a dominant population for immunotherapy and immunotherapy should be considered only after failure of targeted therapy in this population [15,16]. Thirdly, the patient developed serious headache, nausea and vomiting after second-line therapy, which was highly consistent with typical manifestation of LM. However, the cranial enhanced MR showed no abnormality and LM was eventually confirmed by the cytology of
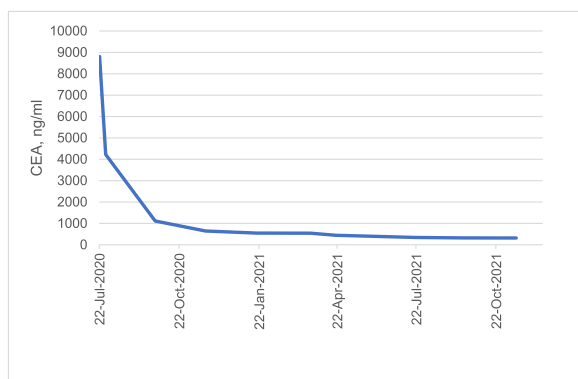

Fig. 3. The fluctuation of serum tumor marker, CEA, during osimertinib plus anlotinib treatment.

CSF. Of note, a normal MRI could not rule out LM [17]. In a large retrospective analysis in which 334 (64%) of 519 patients had advanced lung cancer, 35% were diagnosed with LM by MR alone, 22% by CSF cytology alone and 42% by both [18]. Hence, repeated CSF sampling through lumber puncture is usually necessary and diagnosis of LM relies on clinical, CSF and radiographic findings [2]. Lastly, the patient received high-dose osimertinib therapy when rebiopsy indicated EGFR sensitive mutation. However, cardiac adverse events occurred soon and he still could not tolerate the severe intracranial symptoms. After dose reduction of osimertinib and the add of anlotinib therapy, his neurological symptoms relieved later. The AURA study included 60 patients with locally advanced or metastatic EGFR-mutated NSCLC who received osimertinib 80mg or 160mg once daily (30 patients per cohort). In the 80-mg group, 3 patients (10%) experienced AEs leading to dose reduction while in the 160-mg group, 18 patients (60%) had their dose reduced to 80 mg, of whom 16 had dose reductions as a result of an AE. Electrocardiogram QT prolongation occurred in one patient in the 160-mg group while no patient developed in the 80-mg group [19]. Hence, more attention should be paid to the AEs when osimertinib treated at high dose.

However, there still exist some limitations of our study. Firstly, anlotinib was only approved by China National Medical Products Administration (NMPA) for the treatment of advanced NSCLC. Hence, the treatment strategy of osimertinib plus anlotinib is only available in clinical setting in China. Secondly, gene sequencing was performed on lung tissue but not on plasma simultaneously before first-line therapy, which may cause deviation of the results. In addition, due to the limited amount of CSF sample taken from the patient and considering that the sensitivity of tissue gene sequencing is superior to cellular gene sequencing, the patient received gene sequencing of lung rebiopsy without CSF. Gene sequencing of CSF is certainly a better choice if it can be performed at the same time. Thirdly, the appropriate dose and sequence of osimertinib plus anlotinib in the treatment of specific NSCLC population with LM needs further investigation.

4. Conclusion

Our case showed that osimertinib plus anlotinib could be a promising therapeutic option for advanced EGFR-mutated lung adenocarcinoma with LM.

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Declaration of interests

The authors have no conflicts of interest to declare.

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References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2020, CA A Cancer J. Clin. 70 (1) (2020) 7–30.

[2] H. Cheng, R. Perez-Soler, Leptomeningeal metastases in non-small-cell lung cancer, Lancet Oncol. 19 (1) (2018) e43–e55.

[3] Y.S. Li, B.Y. Jiang, J.J. Yang, H.Y. Tu, Q. Zhou, W.B. Guo, et al., Leptomeningeal metastases in patients with NSCLC with EGFR mutations, J. Thorac. Oncol. 11 (11) (2016) 1962–1969.

[4] B.C. Liao, J.H. Lee, C.C. Lin, Y.F. Chen, C.H. Chang, C.C. Ho, et al., Epidermal growth factor receptor tyrosine kinase inhibitors for non-small-cell lung cancer patients with leptomeningeal carcinomatosis, J. Thorac. Oncol. 10 (12) (2015) 1754–1761.

[5] J.C.H. Yang, S.W. Kim, D.W. Kim, J.S. Lee, B.C. Cho, J.S. Ahn, et al., Osimertinib in patients with epidermal growth factor receptor mutation-positive non-small-cell lung cancer and leptomeningeal metastases: the BLOOM study, J. Clin. Oncol. : Off. J. Am. Soc. Clin. Oncol. 38 (6) (2020) 538–547.

[6] S.S. Ramalingam, J. Vansteenkiste, D. Planchard, B.C. Cho, J.E. Gray, Y. Ohe, et al., Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC, N. Engl. J. Med. 382 (1) (2020) 41–50.

[7] B. Han, K. Li, Q. Wang, L. Zhang, J. Shi, Z. Wang, et al., Effect of anlotinib as a third-line or further treatment on overall survival of patients with advanced non-small cell lung cancer: the ALTER 0303 phase 3 randomized clinical trial, JAMA Oncol. 4 (11) (2018) 1569–1575.

[8] S. Jiang, H. Liang, Z. Liu, S. Zhao, J. Liu, Z. Xie, et al., The impact of anlotinib on brain metastases of non-small cell lung cancer: post hoc analysis of a phase III randomized control trial (ALTER0303), Oncol. 25 (5) (2020) e870–e874.

[9] N. Colclough, K. Chen, P. Johnström, N. Strittmatter, Y. Yan, G.L. Wrigley, et al., Preclinical comparison of the blood-brain barrier permeability of osimertinib with other EGFR TKIs, Clin. Cancer Res. 27 (1) (2021) 189–201.

[10] S. Nanjo, H. Ebi, S. Arai, S. Takeuchi, T. Yamada, S. Mochizuki, et al., High efficacy of third generation EGFR inhibitor AZD9291 in a leptomeningeal carcinomatosis model with EGFR-mutant lung cancer cells, Oncotarget 7 (4) (2016) 3847–3856.

[11] P. Ballard, J.W. Yates, Z. Yang, D.W. Kim, J.C. Yang, M. Cantarini, et al., Preclinical comparison of osimertinib with other EGFR-TKIs in EGFR-mutant NSCLC brain metastases models, and early evidence of clinical brain metastases activity, Clin. Cancer Res. 22 (20) (2016) 5130–5140.

[12] K. Perdrizet, N.B. Leighl, The role of angiogenesis inhibitors in the Era of immune checkpoint inhibitors and targeted therapy in metastatic non-small cell lung cancer, Curr. Treat. Options Oncol. 20 (3) (2019) 21.

[13] A. De Luca, A. Carotenuto, A. Rachiglio, M. Gallo, M.R. Maiello, D. Aldinucci, et al., The role of the EGFR signaling in tumor microenvironment, J. Cell. Physiol. 214 (3) (2008) 559–567.

[14] J. Tabernero, The role of VEGF and EGFR inhibition: implications for combining anti-VEGF and anti-EGFR agents, Mol. Cancer Res. 5 (3) (2007) 203–220.

[15] C.K. Lee, J. Man, S. Lord, W. Cooper, M. Links, V. Gebski, et al., Clinical and molecular characteristics associated with survival among patients treated with checkpoint inhibitors for advanced non-small cell lung carcinoma: a systematic review and meta-analysis, JAMA Oncol. 4 (2) (2018) 210–216.

[16] J. Mazieres, A. Drilon, A. Lusque, L. Mhanna, A.B. Cortot, L. Mezquita, et al., Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry, Ann. Oncol. 30 (8) (2019) 1321–1328.

[17] M. Chamberlain, R. Soffietti, J. Raizer, R. Rudà, D. Brandsma, W. Boogerd, et al., Leptomeningeal metastasis: a Response Assessment in Neuro-Oncology critical review of endpoints and response criteria of published randomized clinical trials, Neuro Oncol. 16 (9) (2014) 1176–1185.

[18] J.W. Hyun, I.H. Jeong, A. Joung, H.J. Cho, S.H. Kim, H.J. Kim, Leptomeningeal metastasis: clinical experience of 519 cases, Eur. J. Cancer (Oxford, England : 1990) 56 (2016) 107–114.

[19] S.S. Ramalingam, J.C. Yang, C.K. Lee, T. Kurata, D.W. Kim, T. John, et al., Osimertinib as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer, J. Clin. Oncol. : Off. J. Am. Soc. Clin. Oncol. 36 (9) (2018) 841–849.