Rapid effect of osimertinib re-challenge on brain metastases developing during salvage cytotoxic chemotherapy after osimertinib treatment failure: A case report

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Abstract. We herein report a case of symptomatic brain metastases (BM) from lung adenocarcinoma in a 73-year-old female patient, which developed during salvage cytotoxic chemotherapy following failure of osimertinib treatment. The patient was proven to have a T790M mutation prior to osimertinib therapy, and achieved a clinical benefit from osimertinib for 3 years until the primary tumor progressed. Although active BM were not detected prior to initiating salvage cytotoxic chemotherapy, the patient developed numbness of the left hand, severe dizziness, and disturbance of behavior and thought after the 3-month course of the salvage cytotoxic chemotherapy. Brain magnetic resonance imaging revealed multiple BM with severe peritumoral brain edema. To avoid radiation-induced cognitive impairment, osimertinib re-challenge was undertaken. At 2 weeks after osimertinib initiation, the patient's neurological symptoms drastically improved. One month later, radiological evaluation revealed apparent shrinkage of the BM and subsiding brain edema, although the primary lung tumor remained stable. Therefore, osimertinib re-challenge may be a viable treatment option for BM developing during salvage cytotoxic chemotherapy.

Introduction

Epidermal growth factor-tyrosine kinase inhibitors (EGFR-TKIs) have been proven to be effective for non-small-cell lung cancer (NSCLC) with EGFR mutations. With the advent of EGFR-TKIs, the prognosis of NSCLC has markedly improved, but the incidence of brain metastases (BM) and leptomeningeal metastases (LM) is reportedly increasing, with a reported cumulative incidence of BM of ~46.7% at 3 years (1). Of note, EGFR-TKIs may also be effective for BM as well as extracranial disease (2); therefore, they are considered as one of the most important therapeutic options. Osimertinib is a third-generation EGFR-TKI, which was designed for NSCLC patients with T790M mutation, and has also been reported to be effective for the treatment of BM (3). However, it remains unclear what treatment strategy would be preferable for BM developing during salvage cytotoxic chemotherapy after osimertinib failure. We herein report a case of a successful osimertinib re-challenge for multiple BM from NSCLC developing during salvage cytotoxic chemotherapy.

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Case report

A 73-year-old female patient was diagnosed with stage IVb lung adenocarcinoma (T1bN2M1b, brain metastases) in April 2013. As there were only two small BM lesions, stereotactic radiosurgery was performed (Fig. 1A). Subsequently, 250 mg gefitinib was administered daily, as the patient was found to harbor an EGFR gene mutation (exon 19 deletion). After 1.5 years of partial response, multiple lung metastases developed. As T790M was detected in the specimen collected by transbronchial lung biopsy, daily treatment with 80 mg osimertinib was initiated, based on the AURA 3 clinical study (AstraZeneca, Cambridge, UK; NCT02151981) (4), resulting in rapid and apparent shrinkage of the primary tumor and multiple lung metastases. Three years later, the primary tumor enlarged, with the cranial lesion remaining stable (Fig. 1B). As one cycle of docetaxel and two cycles of S-1 were ineffective, the patient was administered pemetrexed as fifth-line chemotherapy. Two weeks after the initiation of pemetrexed therapy, however, she developed numbness of the left hand, severe dizziness, and disturbances of behavior and thought, resulting in worsening of the performance status (PS) score to 3. Radiological evaluation revealed the development of

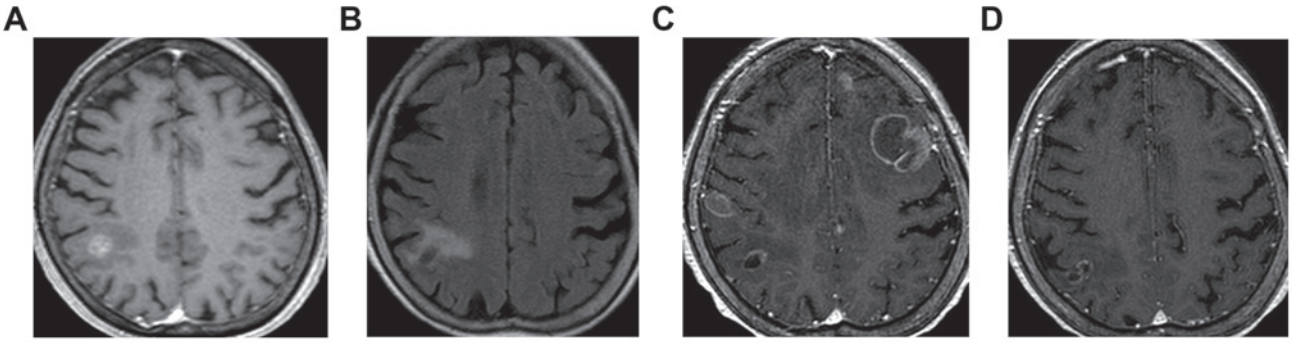

Figure 1. (A) At initial diagnosis, Gadrium-enhanced T1-weighed brain magnetic resonance imaging showing a mass in the right cerebrum with mild peritumoral edema. (B) Only one high-density area was observed (fluid-attenuated resonance imaging). (C) Multiple brain metastases with apparent peritumoral edema developed during salvage cytotoxic chemotherapy. (D) Shrinkage of the multiple brain metastases after initiating osimertinib re-challenge.

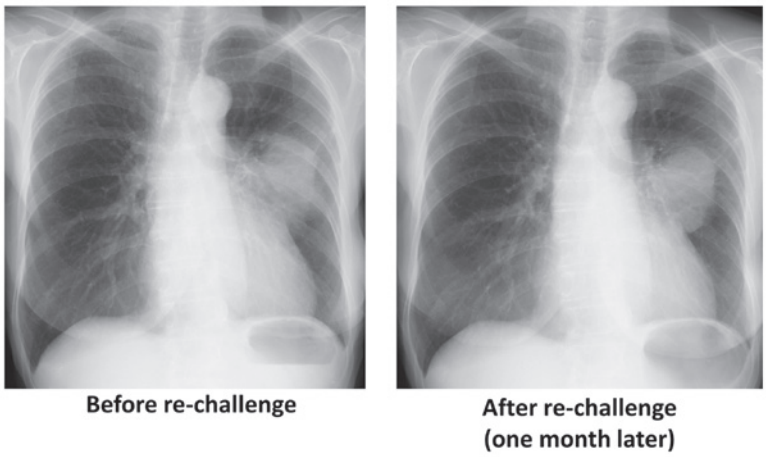

Figure 2. The primary tumor remained stable after initiating osimertinib re-challenge.

multiple BM with severe peritumoral brain edema (Fig. 1C). Whole-brain radiotherapy (WBRT) was excluded due to concerns regarding the exacerbation of the cognitive impairment. Therefore, osimertinib re-challenge therapy (80 mg/day) was selected. At 2 weeks after treatment initiation, the neurological symptoms drastically improved, with a PS score of 1. One month later, brain magnetic resonance imaging revealed apparent shrinkage of the BM and subsiding brain edema (Fig. 1D), although the primary lung tumor remained stable (Fig. 2). In October 2018, 6 months after initiating osimertinib re-challenge, the patient continued osimertinib treatment and BM remained stable.

Discussion

The findings of the present case indicate that osimertinib re-challenge may be a viable therapeutic option for BM developing during the course of salvage cytotoxic chemotherapy. There is currently no established optimal therapeutic strategy for BM that develop during salvage cytotoxic chemotherapy following osimertinib failure and disease progression. Radiotherapy, mainly WBRT, may be effective for BM from EGFR-mutated NSCLC, but it is associated with increased risk of neurocognitive impairment (5). In the present case, osimertinib re-challenge was proven to be effective for BM, although there was no change in the primary tumor. Generally, central nervous system progression has been reported as a major concern in NSCLC patients treated with gefitinib, with a prevalence of 35.1% (6), which is attributable to the penetration rate of the blood-brain barrier (7). With regard to osimertinib, the pre-clinical data indicate favorable penetration into the brain parenchyma (8), which is supported by the marked response of the BM to osimertinib in the present case. Of note, there was a difference in therapeutic efficacy between the BM and the primary lesion; however, as this is beyond the scope of the present case report, this observation is not discussed in detail at present. It is known that there is heterogeneity among T790M-positive cancer cells (9), and it is hypothesized that the difference in therapeutic efficacy in this patient may also be associated with this heterogeneity.

Furthermore, as osimertinib re-challenge acted rapidly on BM, it may be one of the preferable therapies to be considered in the future. Generally, the therapeutic strategy for BM should be decided taking into consideration the activity of extracranial disease and the risk of WBRT-induced cognitive impairment (10). In the present case, osimertinib re-challenge was selected as the patient was elderly and already exhibited signs of cognitive impairment. Due to the rapid and dramatic improvement of the patient's PS within 2 weeks after the initiation of osimertinib re-challenge, there was no need to add radiation to the treatment. Koba *et al* reported two cases of BM from T790M-positive NSCLC: A rapid response was

observed 2 weeks later, and WBRT was therefore deemed unnecessary (11). Taking this report together with ours into consideration, osimertinib treatment, even as re-challenge, may exert a rapid and marked effect on BM. Therefore, osimertinib re-challenge may be valuable for WBRT candidates with a concern for potential development of cognitive impairment.

In conclusion, we herein report a case of successful osimertinib re-challenge for BM from lung adenocarcinoma developing during salvage cytotoxic chemotherapy. Although the optimal therapeutic strategy for BM in NSCLC patients previously treated with osimertinib has yet to be determined, the results in the present case suggest that osimertinib re-challenge is a viable treatment option. Accumulation of clinical information in patients with similar treatment status is required to confirm our results.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

AS and HS participated in the conception and design of the study, analyzed and interpreted the data and wrote the manuscript. AS, SI, TOd and TOg evaluated the patient and participated in the therapy. SI, HS and TOg revised the manuscript for intellectual content. TI and KO evaluated the radiological images or pathological specimens. All authors have read and approved the final draft of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the publication of the case details and any associated images.

Competing interests

Dr Sekine and Dr Ikeda have received lecture fees from AstraZeneca, Boehringer Ingelheim and Chugai Pharmaceuticals. Dr Ogura has received a lecture fee from Boehringer Ingelheim. The remaining authors have stated that they have no conflicts of interest to disclose.

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