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【 CASE REPORT 】

Osimertinib Administration as the Primary Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy for Brain Metastasis of *De Novo* T790M-positive Lung Cancer

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Abstract:
A 69-year-old woman underwent left upper lobectomy for left upper lobe lung adenocarcinoma. She later perceived a left visual field defect, and a brain metastasis was detected on head magnetic resonance imaging (MRI). Epidermal growth factor receptor (EGFR) testing identified two separate EGFR mutations: an L858R mutation in exon 21 and a *de novo* T790M mutation in exon 20. Treatment with osimertinib was started. After one month, head MRI showed that the brain metastasis had shrunk, and the visual field defect had also improved. In this case, first-line osimertinib was effective for treating brain metastasis of *de novo* T790M-positive lung cancer.

Key words: osimertinib, *de novo* EGFR T790M, brain metastasis, primary EGFR-TKI therapy, lung cancer

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Introduction

Osimertinib is a potent irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) selective for both EGFR-sensitizing mutations and EGFR T790M resistance mutations. Osimertinib is currently approved for the primary treatment of EGFR mutation-positive lung cancer and for the secondary treatment of lung cancer patients with T790M mutations. Its effect on patients with *de novo* T790M-positive lung cancers and *de novo* T790M-positive brain metastases has not yet been established. The T790M mutation is occasionally reported to be present before treatment, although it is more commonly acquired after EGFR TKI treatment as a resistance mechanism. We herein report a case of brain metastasis of lung carcinoma that was successfully managed with osimertinib administration.

Case Report

A 69-year-old woman underwent chemoradiotherapy (cisplatin + docetaxel + 60Gy radiation) prior to surgery for left upper lobe lung adenocarcinoma, followed by left upper lobe resection in November 2017. Postoperative adjuvant chemotherapy was refused, and she was followed up by respiratory surgery. She experienced defects in visual acuity on the left side in November 2018, and in December 2018, she underwent respiratory surgery. At that time, a 30-mm brain metastasis in the right occipital lobe was observed on head magnetic resonance imaging (MRI). There were no other sites of recurrence. She was referred to the respiratory medicine department for treatment.

A genetic analysis of EGFR performed on the preoperative bronchoscopic specimen identified two EGFR mutations: an L858R mutation in exon 21 and a *de novo* T790M mutation in exon 20. An EGFR analysis was performed by real-time polymerase chain reaction (cobas z 480; Roche Diagnostics Japan, Tokyo, Japan). Neither surgery nor radiation therapy was desired for the brain metastasis. She preferred anti-cancer drug treatment, and osimertinib was started. One month later, MRI showed decreased brain metastasis (Figure), indicating a partial response, and the visual field disorder had also improved. No apparent adverse events were observed, and the patient has been receiving

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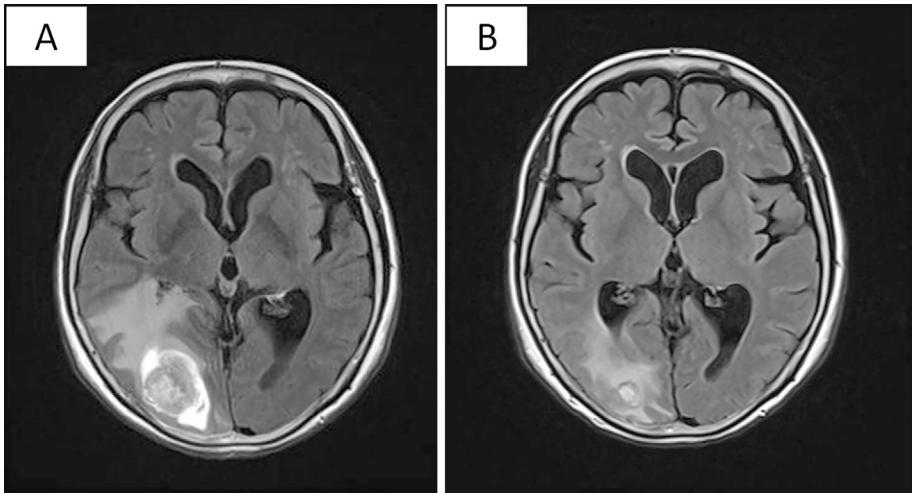

Figure. **(a) Brain metastasis before osimertinib administration. Head magnetic resonance imaging showing metastasis in the right occipital lobe. (b) Magnetic resonance imaging one month after treatment with osimertinib showing a reduction in brain metastasis.**

treatment for four months.

Discussion

We herein report a case in which osimertinib was used as the primary EGFR-TKI treatment for a *de novo* T790M-positive patient. *De novo* T790M mutations have been reported to be present in 0.5-8% of EGFR mutation-positive cases (1-3). In addition, the *de novo* T790M mutation is frequently reported to co-exist with the L858R mutation (1, 2), as in this case. The progression-free survival (PFS) in *de novo* T790M-positive cases is shorter than that in T790M-negative cases, and EGFR-TKIs are less effective in positive cases. For example, for first-generation EGFR-TKIs such as gefitinib and erlotinib, response rates of 8-10% and a PFS of 1.5- 4.1 months have been reported in patients harboring the T790M mutation (1, 2, 4). The third-generation TKI osimertinib has been shown to have greater efficacy in cases with acquired T790M mutations (5).

With regard to the efficacy of osimertinib as the primary treatment for *de novo* T790M-positive cases, a previous report observed a partial response in six of seven cases (3). Although it has not been established as a treatment for these cases, the present case supports those previous findings. In the current AZENT phase II trial (NCT028425), the efficacy of osimertinib in patients with T790M mutations at the diagnosis is being examined. In addition, osimertinib has been reported to have a 91% response rate in patients with central nervous system lesions that have untreated EGFR-sensitizing mutations, and T790M is no longer detectable in the spinal fluid after osimertinib treatment (6, 7).

The median overall survival for patients with a solitary brain metastasis, wherein the primary lesion was controlled, was 19.7 months after local treatment with stereotactic radiosurgery (SRS) or surgery (8). Our patient was eligible for SRS or surgery; however, she refused to undergo surgery, and we opted to perform drug therapy instead. Although the optimal treatment for tumors with a *de novo* T790M mutation is unknown, in our case, osimertinib was effective as the primary treatment against untreated brain metastasis, even in the presence of a *de novo* T790M mutation.

The limitations of this case are as follows: no EGFR mutation analysis was performed for the brain metastasis, and chemotherapy was administered before chest surgery. However, with respect to EGFR mutations, it is extremely rare for the EGFR mutations in the primary and metastatic lesions to be different before EGFR-TKI treatment (9). Since the T790M mutation was present in the patient before chemotherapy administration, and EGFR-TKIs had not been administered, the mutation was considered to be a *de novo* T790M mutation, and the effect of osimertinib on our patient was the same as that expected in a patient with a *de novo* T790M mutation.

It will be necessary to accumulate and examine more cases; however, for patients with *de novo* T790M-positive lung cancer, osimertinib as first-line treatment seems to be promising.

The authors state that they have no Conflict of Interest (COI).

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