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Dramatic intracranial response to osimertinib in a poor performance status patient with lung adenocarcinoma harboring the epidermal growth factor receptor T790M mutation: A case report

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Abstract. We herein report a case of dramatic intracranial response to osimertinib in a poor performance status patient with lung adenocarcinoma harboring the epidermal growth factor receptor (*EGFR*) T790M mutation encoded in exon 20. The patient was a 59-year-old woman with *EGFR* exon 19 deletion-positive lung adenocarcinoma, who relapsed with multiple brain metastases. Computed tomography-guided biopsy of the left pleural tumor revealed adenocarcinoma harboring an *EGFR* exon 19 deletion and an *EGFR* T790M mutation encoded in exon 20. The patient was treated with osimertinib, a third-generation EGFR tyrosine kinase inhibitor. Two days after treatment initiation, the patient displayed profound disturbance of consciousness, possibly due to carcinomatous meningitis, and treatment had to be discontinued due to difficulty in taking osimertinib. However, the patient gradually started to recover consciousness and, after 3 days, she was again able to take osimertinib. One month after the initiation of osimertinib treatment, magnetic resonance imaging revealed an apparent reduction in brain metastases. The patient is currently under continued treatment with osimertinib. At the last follow-up (February, 2017) she exhibited partial response to the treatment.

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Introduction

There have been major advances in the medical treatment of advanced non-small-cell lung cancer (NSCLC) with the use of molecular-targeted therapies (1). The efficacy of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib, erlotinib and afatinib, in the treatment of NSCLC has been proven, particularly in EGFR mutation-positive patients (2). Efficacy has been shown even in patients with poor Eastern Cooperative Oncology Group performance status (PS), particularly those who had previously been solely treated with best supportive care (3). However, *EGFR* mutation-positive patients eventually develop resistance to EGFR-TKIs. The most frequent reason for such resistance is a secondary EGFR T790M mutation encoded in exon 20 (4).

A third-generation EGFR-TKI, osimertinib, was recently approved for NSCLC patients harboring the *EGFR* T790M mutation (5). Since osimertinib is now used for patients who have been previously treated with an EGFR-TKI and/or chemotherapy, such patients include cases with poor PS. We herein report a case of dramatic intracranial response to osimertinib in a poor PS patient with lung adenocarcinoma harboring the *EGFR* T790M mutation.

Case report

A 59-year-old woman with *EGFR* exon 19 deletion-positive lung adenocarcinoma was admitted to the Nagoya City University Hospital (Nagoya, Japan) due to relapse with multiple brain metastases in September, 2017. Brain metastases were already present at her diagnosis 4 years prior. At first, the patient received whole-brain radiation therapy. Subsequently, she was treated with carboplatin/pemetrexed/bevacizumab for ~6 months [achieving partial response (PR)], erlotinib for 3 months (PR), afatinib for 4 months [stable disease (SD)] and carboplatin/albumin-bound paclitaxel for

2 months (SD). Tumor tissue specimens were obtained by computed tomography (CT)-guided biopsy (CTGB) of the left pleural tumor, in which only *EGFR* exon 19 deletion was detected. Therefore, the brain metastases were treated with gamma knife radiosurgery and then re-challenged with erlotinib treatment. However, 2 months after this re-challenge, the brain metastases, multiple pulmonary nodules and pleural metastases all exhibited progression (Figs. 1A and 2A). CTGB of the left pleural tumor was again performed, and this time adenocarcinoma harboring both the *EGFR* exon 19 deletion and the *EGFR* T790M mutation encoded in *EGFR* exon 20 was detected. Although the patient's PS was 4, treatment with oral osimertinib was initiated at a dose of 80 mg per day. Two days after treatment initiation, the patient displayed profound disturbance of consciousness with neck stiffness, and treatment could not be continued. The clinical diagnosis was carcinomatous meningitis caused by progression of the brain metastases. Although treatment had been discontinued, the patient gradually recovered consciousness over the next 3 days and was again able to take osimertinib. The PS improved from 4 to 2. One month after osimertinib treatment initiation, magnetic resonance imaging revealed regression of the brain metastases (Fig. 1B). The chest CT images also revealed reduction of the multiple pulmonary nodules and pleural metastases (Fig. 2B). The serum level of carcinoembryonic antigen also decreased from 72.1 to 22.7 ng/ml (upper limit of normal value, 5.0 ng/ml). One adverse event, namely grade 3 leukopenia, as determined by the National Cancer Institute Common Terminolog y Criteria, version 4.0 (https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf), was observed, which recovered after discontinuation of osimertinib treatment for 1 week and one-time subcutaneous administration of 100 µg lenograstim. The patient is currently under continued treatment with daily osimertinib at a decreased dose of 40 mg per day; at the last follow-up (February, 2017) she exhibited PR to the treatment.

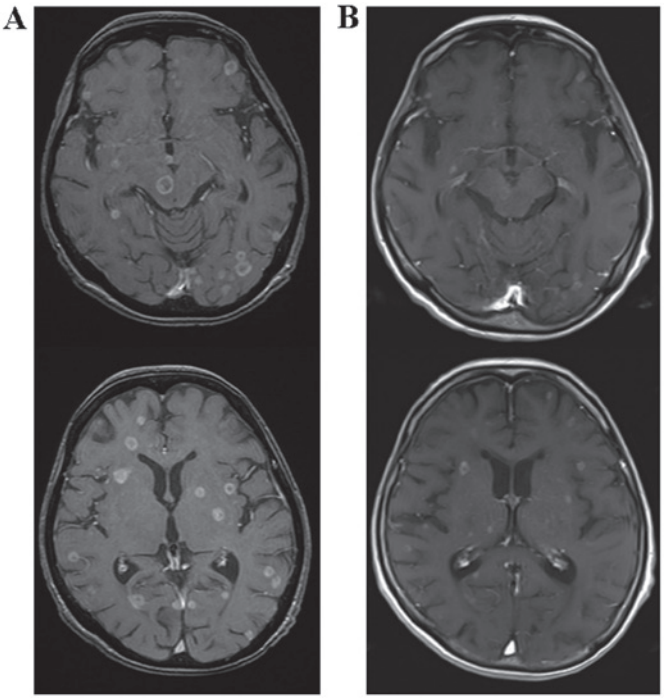

Figure 1. T1-weighted magnetic resonance images of the brain with gadolinium enhancement (A) prior to and (B) after treatment with osimertinib.

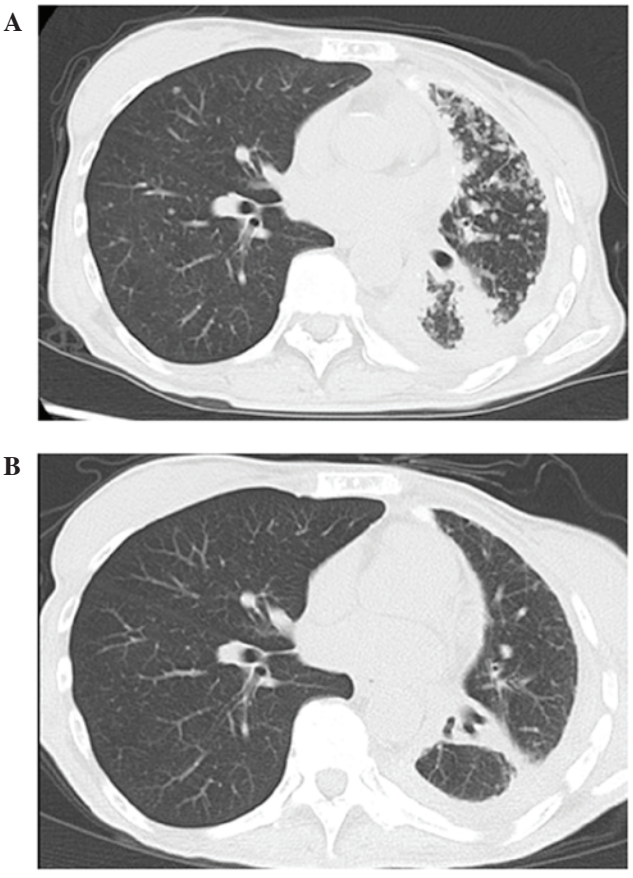

Figure 2. Chest computed tomography (A) prior to and (B) after treatment with osimertinib.

Discussion

In the present case, an NSCLC patient with a poor PS due to brain metastases, who harbored the *EGFR* T790M mutation, was successfully treated with osimertinib.

It has been demonstrated that individual NSCLC patients with oncogenic drivers who receive a matched targeted agent exhibit improved survival (1). *EGFR* mutation is an oncogenic driver mutation, and treatment with an EGFR-TKI is recommended as first-line therapy for *EGFR* mutation-positive NSCLC patients (2), even for those with a poor PS or for elderly patients (3). However, *EGFR* mutation-positive patients eventually develop resistance to these EGFR-TKIs.

A third-generation EGFR-TKI, osimertinib, was recently found to be of clinical use for NSCLC patients who have a secondary *EGFR* T790M mutation, which is the most frequent reason for resistance to the first-line treatment with EGFR-TKIs (4,5). Osimertinib exhibited a high activity against NSCLC tumors harboring this *EGFR* T790M mutation, showing a response rate (RR) of 61%. Therefore, osimertinib is currently recommended for such patients who have had disease progression during prior therapy with EGFR-TKIs (6). Young *et al* reported that never-smoker female patients with adenocarcinoma harboring EGFR mutations and a poor PS who were treated with first-line gefitinib exhibited a RR of

50.0%, a median progression-free survival (PFS) of 130 days (95% CI: 51-209 days), and a median overall survival (OS) of 236 days (95% CI: 150-322 days) (7). However, the efficacy of osimertinib treatment for patients with a poor PS remains uncertain. As only few patients in the osimertinib group reported grade ≥3 adverse events in the AURA3 clinical trial (8), the administration of osimertinib was considered to be a viable option for our patient, despite her poor PS. The disturbance of consciousness gradually improved, despite only 2 days of treatment with 80 mg osimertinib. The 20-mg osimertinib dose (RR=52%; 95% CI: 30-57) was found to be as effective in lung cancer patients with the *EGFR* T790M mutation as the 80-mg dose (RR=52%; 95% CI: 40-63) (5). As the Cmax of osimertinib after a single administration of the 80-mg capsule [247.2±173.6 nM (https://ec.europa.eu/health/documents/community-register/2016/20160202133956/anx_133956_en.pdf)] is higher compared with the Cmax of osimertinib after 22 days of multiple once-daily dosing with the 20-mg capsule (106.3 nM; 95% CI: 45.4-280), even 2 days of treatment with the 80-mg capsule would be expected to achieve an effective blood concentration.

A further problem is that it is necessary to prove the presence of the *EGFR* T790M mutation in lung cancer biopsy specimens prior to the administration of osimertinib. In the present case, we were only able to confirm the presence of this mutation in tumor tissue obtained in the second CTGB. Spatiotemporal heterogeneity of the *EGFR* T790M mutation has been previously reported in individual patients, and the presence of this mutation may be proven by repeat biopsies (9). These results indicate that repeat biopsies should be performed in order not to miss the opportunity to administer osimertinib therapy to patients following development of resistance to first-line EGFR-TKIs. Although the effectiveness of EGFR-TKI re-challenge remains unknown (10), erlotinib was again selected in the present case. Hata *et al* have reported that the emergence of *EGFR* T790M in the central nervous system (CNS) is rare compared with other lesions following EGFR-TKI failure (11). As microscopic brain metastases harboring only the *EGFR* exon 19 deletion and not the *EGFR* T790M mutation were detected in the cerebrospinal fluid following gamma knife radiosurgery, erlotinib was administered due to its good penetration into the cerebrospinal fluid (12).

Another concern is that it is difficult to obtain tumor samples when patients develop recurrence, such as brain metastasis or carcinomatous meningitis. As lumbar puncture could not be performed in this patient due to her poor PS, carcinomatous meningitis was diagnosed clinically. In this case, re-challenge with erlotinib was not effective, but osimertinib was effective; thus, the status of *EGFR* T790M in the CNS was likely to be positive.

Osimertinib has exhibited good penetration through the blood-brain barrier in mice, delaying the development of leptomeningeal carcinomatosis in an *EGFR* mutation mouse model (13,14). Furthermore, Pareek *et al* also reported CNS disease improvement by administration of 80 mg osimertinib for 6 weeks in a case report (15). The efficacy and safety of osimertinib treatment for patients with emergence of *EGFR* T790M in the CNS remain uncertain and further investigation is required.

A previous study reported a high incidence of disease recurrence in the brain and the leptomeninges in NSCLC patients following response to gefitinib (16). Moreover, absence of brain metastasis has been shown to be associated with prolonged OS in treatment with EGFR-TKIs (17). Recently, a non-invasive approach to the detection of gene mutations using cell-free DNA extracted from the plasma has been developed (18). Novel methods for detecting gene mutations that develop during treatment with EGFR-TKIs are an important aspect of the optimization of personalized therapy.

We herein report a case of an NSCLC patient with a poor PS who was successfully treated with osimertinib. Therefore, osimertinib may represent a viable therapeutic option for *EGFR* T790M mutation-positive NSCLC patients with a poor PS. However, further prospective studies are required to establish the safety and efficacy of osimertinib for patients with a poor PS or brain metastasis.

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