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.

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 (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 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 Terminology 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.

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
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.

References