Osimertinib administration via nasogastric tube in an EGFR-T790M-positive patient with leptomeningeal metastases

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Abstract
Patients with an epidermal growth factor receptor (EGFR) mutation are usually administered EGFR-tyrosine kinase inhibitors (TKIs) as standard-of-care treatment. However, acquired resistance occurs between 9 and 13 months. The T790M-resistant mutations are the most common, and osimertinib has been found to be effective in treating EGFR-T790M-positive patients. A 73-year-old female lung cancer patient with an EGFR-sensitizing mutation was receiving fourth-line chemotherapy when she complained of anorexia, headache, and irritability. A lumbar puncture showed adenocarcinoma in the cerebrospinal fluid (CSF), which led to the diagnosis of leptomeningeal metastasis. Her performance status (PS) deteriorated quickly and she also developed dysphagia. The EGFR mutation testing of the CSF demonstrated L858R+T790M double mutations, and an osimertinib suspension was subsequently administered through a nasogastric tube. The PS improved to 1, oral intake became possible after 20 days, and further improvements were observed by gadolinium-enhanced magnetic resonance imaging. The patient remains progression-free for 10 months after osimertinib administration.

Introduction
Epidermal growth factor receptor (EGFR) mutations occur in approximately 30% of patients with non-small-cell lung cancer (NSCLC), and EGFR-tyrosine kinase inhibitors (TKIs) have been used as standard-of-care treatments. However, acquired resistance to EGFR-TKIs occurs between 9 and 13 months. The T790M-resistant mutation is the most common and is observed in half of the cases. Osimertinib is an irreversible EGFR-TKI that acts against both EGFR-sensitizing and T790M-resistant mutations. A phase III randomized control study demonstrated that osimertinib is effective in treating T790M-positive NSCLC patients [1]. Furthermore, osimertinib has shown promising results in the treatment of brain metastases (BM) and leptomeningeal metastases (LM). However, patients with LM tend to have poor performance status (PS) and have difficulties in swallowing tablet formulations.

Case Report
A 73-year-old female presented with dry cough. Chest computed tomography (CT) suggested lung cancer and transbronchial biopsy showed lung adenocarcinoma with EGFR mutation (L858R point mutation in exon 21). The clinical stage was cT3N3M1b (OSS) stage IV.

A combination treatment of carboplatin and pemetrexed was selected as the first-line chemotherapy and resulted in partial response (PR) with progression-free survival (PFS) of 6 months. Gefitinib was administered as the second-line treatment resulting in stable disease with PFS of 2 months. A combination treatment of erlotinib and bevacizumab was subsequently chosen as the third-line treatment and resulted in PR; however, she rejected the treatment at the seventh cycle, 5 months after the induction of this regimen. Nivolumab was selected as the fourth-line treatment; however, soon after the third administration, she complained of anorexia and headache. These symptoms were
also accompanied by irritability, delirium, and personal and emotional changes. Though the primary site remained stable, T1-weighted gadolinium-enhanced brain magnetic resonance imaging (MRI) revealed diffuse and linear enhancements on the surface of the cerebrum, along the cerebellar folia, and in the subarachnoid space (Fig. 1A, B). This suggested LM. Lumbar puncture showed adenocarcinoma in the cerebrospinal fluid (CSF). As a result, EGFR mutation testing of the CSF was conducted by the PCR-Invader method (BML Inc. Ltd., Tokyo, Japan). As the PS deteriorated to 4 and dysphagia developed 5 days after lumbar puncture, the patient was hospitalized. Eight days later, results showed that the EGFR mutations were L858R + T790M double mutations. Osimertinib was selected for therapy based on the presence of T790M and its efficient delivery to the CSF. As the oral administration of osimertinib in the tablet form was difficult, a simple suspension method was adopted. An 80-mg osimertinib tablet was suspended in 50 mL of sterile hot water (55°C) for 10 min and subsequently administered through a nasogastric tube once a day. Twenty days after the administration of osimertinib, the PS improved to 1 and oral intake of foods and drugs became possible with significant improvements in the gadolinium-enhanced MRI (Fig. 2A, B). Lumbar puncture performed 40 days after osimertinib administration showed only a few atypical cells without any EGFR mutations. Further amelioration in the gadolinium-enhanced MRI was observed after 60 days (Fig. 2C, D), and the primary site also remained stable. The remarkable clinical improvement resembles the "Lazarus response" observed in patients harbouring EGFR-sensitizing mutations with a PS of 3–4 in those who were treated with gefitinib. The patient currently remains at a PS of 1 and is progression-free for 10 months after the administration of osimertinib.

Discussion

The BM and LM of NSCLC are challenging conditions to treat due to factors such as the blood–brain barrier (BBB) and increased interstitial pressure around the metastases that make drug delivery to the central nervous system (CNS) difficult. In the treatment of LM, erlotinib is more efficient than gefitinib in the cytologic conversion rate of the CSF [2]. Osimertinib has satisfactory penetration into the CNS metastases compared with other EGFR-TKIs. In a preclinical comparison of osimertinib with other EGFR-TKIs in an EGFR-mutant NSCLC BM model, osimertinib demonstrated greater penetration of the mouse BBB than gefitinib, rociletinib, or afatinib [3].

Due to its efficient drug delivery to the CNS, osimertinib is a promising treatment for LM. Furthermore, the detection of EGFR-T790M is essential when considering the benefit of osimertinib in T790M-positive NSCLC patients [1].

Patients with LM tend to have poor PS and are usually accompanied by dysphagia, which make swallowing medication in the tablet form difficult. For these patients, it may be more beneficial to administer the medication in a
liquid form through a nasogastric or gastrostomy tube. The relative bioavailability and safety profile of gefitinib administration as a dispersion preparation have been investigated in healthy volunteers. The pharmacokinetics and adverse events profile for those administered a gefitinib solution through a nasogastric tube were similar with those administered a whole tablet [4]. The administration of an osimertinib suspension through a nasogastric tube could be advantageous in the treatment of EGFR-T790M-positive patients with dysphagia considering the similarities between gefitinib and osimertinib in chemical formula and coating agents. However, further studies are required to support this hypothesis.

As patients with LM tend to have poor PS and cytotoxic chemotherapy is not recommended under these conditions, there are currently no alternative therapeutic options other than providing supportive care. However, first-line gefitinib therapy has been proved to be efficient in EGFR-mutant patients, and the response in PS of 3–4 in patients treated with gefitinib has been dramatic [5]. Therefore, osimertinib therapy could be promising in treating EGFR-T790M-positive NSCLC patients with LM and poor PS. Furthermore, based on their physical condition, osimertinib administered as a suspension may be more beneficial.

Disclosure Statements
No conflict of interest declared.
Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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