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Short Communication

Successful treatment with weekly high-dose erlotinib against meningeal metastases from epidermal growth factor receptor (EGFR)-mutated lung adenocarcinoma

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1. Introduction

Meningeal carcinomatosis worsens the clinical course and prognosis among patients with non-small cell lung cancer (NSCLC), with a median survival of approximately 4–6 months and a prevalence of 2.4–5% [1]. Traditionally, systemic chemotherapeutic treatment of metastases in the central nervous system (CNS) is considered to have limitations as a therapeutic strategy due to the blood–brain barrier (BBB). While therapeutic concentrations of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in the CNS cannot be easily established across the BBB at standard dosing regimens, erlotinib, an EGFR TKI, has been reported to achieve some penetration across the BBB, demonstrating a higher concentration than gefitinib, another EGFR TKI, in the cerebrospinal fluid [2]. In several series of patients

Abbreviations: BBB, blood–brain barrier; CNS, central nervous system; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor

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with EGFR-mutated lung adenocarcinomas, clinical benefits have been reported with high-dose weekly and pulsatile erlotinib for treatment of carcinomatous meningitis [3,4]. However, although an initial response to EGFR TKIs suggests favorable prognosis, the progression of the disease is inevitable because of resistance to EGFR TKIs that develops due to secondary mutations of the lesions among patients with EGFR-mutated lung adenocarcinomas [5,6]. We herein present a case report of a 64-year-old woman with carcinomatous meningitis from lung adenocarcinoma with EGFR exon 19 deletion, who was treated successfully with weekly high-dose erlotinib despite the existence of secondary mutations of T790M in exon 20.

2. Case report

The patient was a 64-year-old woman diagnosed with stage IV (T4N3M1) lung adenocarcinoma in 2007. Mutational analysis showed an EGFR exon 19 deletion. She maintained stable disease for 10 months after treatment with a combination of carboplatin + paclitaxel as the first-line therapy. In 2008, when she began to exhibit progressive disease, she was treated with gefitinib, and maintained stable disease for 18 months. However, as she was unable to maintain stable disease following treatment with gefitinib, she subsequently received treatment with several regimens, including pemetrexed sodium hydrate, cisplatin + gemcitabine hydrochloride + bevacizumab, carboplatin + paclitaxel + bevacizumab, tegafur, vinorelbine ditartrate, docetaxel, carboplatin + gemcitabine hydrochloride, and irinotecan hydrochloride hydrate, from 2010 to 2014. During this period, she not only received erlotinib and rechallenge with gefitinib in 2010, but she was also treated with whole brain radiotherapy (30 Gy) for multiple brain metastases in 2012. In addition, when she underwent fiberoptic bronchoscopy in 2012 for rebiopsy of the primary lesion, T790M mutation in exon 20 was detected by mutational analysis. In 2014, the patient experienced dysesthesia and muscle weakness in the right arm and leg, and subsequently developed ataxia. She additionally developed disturbance of bladder and bowel function, and required care for the worsening of her general condition to Eastern Cooperative Oncology Group (ECOG) 3 performance status. A computed tomography (CT) scan revealed progression of the primary lesion with pulmonary metastases (Fig. 1C and D), and spinal magnetic resonance imaging (MRI) demonstrated spinal dissemination and metastasis (Fig. 2A and C). Brain MRI revealed no evidence of relapsed brain metastases. Lumbar puncture cytology demonstrated class V adenocarcinoma, and mutational analysis revealed EGFR exon 19 deletion but not T790M mutation in exon 20. Since steroid therapy did not improve the patient's neurological symptoms, erlotinib pulsatile therapy was initiated at a dose of 1050 mg once a week. Although erlotinib pulsatile therapy is not yet recommended in Japan, it was explained to the patient, as to other trial participants, that she was in urgent need of it because of the worsening of her general condition and the lack of other therapeutic options. Written informed consent was obtained from all trial participants before the introduction of erlotinib pulsatile therapy. Follow-up MRI on the 15th day revealed a regression of spinal dissemination and metastasis in response to the initiation of weekly high-dose erlotinib (Fig. 2B and D). The weekly high-dose erlotinib also improved the patient's neurological symptoms, as she was able to walk by herself without any support within two months. The

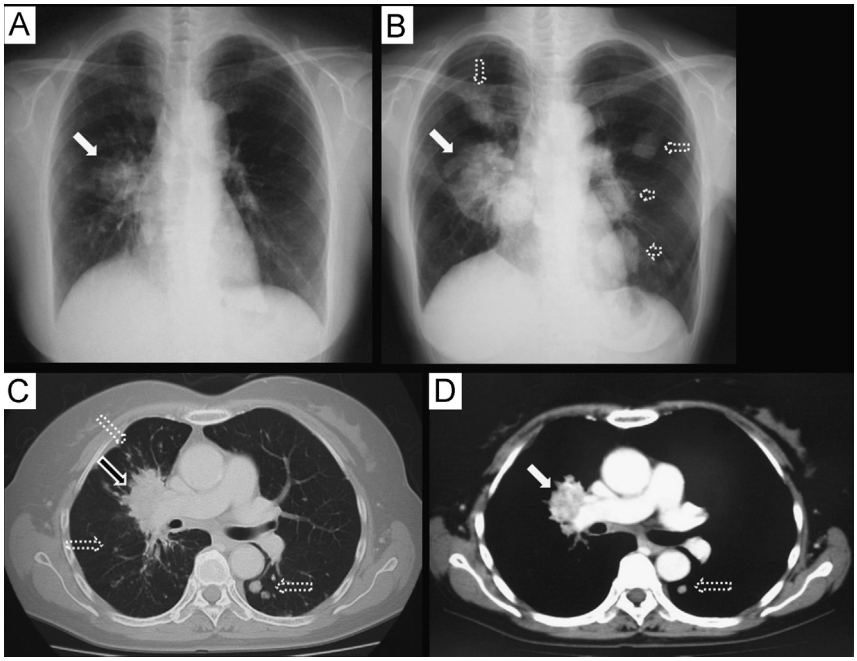

Fig. 1 – (A) Chest radiograph shows a primary lesion (arrow) in the right middle lobe before treatment with weekly high-dose erlotinib. (B) The primary lesion (arrow) and pulmonary metastases develop (dashed arrows) during treatment with weekly high-dose erlotinib. (C and D) Chest computed tomography shows a primary lesion (arrow) in the right middle lobe and pulmonary metastases (dashed arrows) before treatment with weekly high-dose erlotinib.