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【 CASE REPORT 】

Dramatic Response of Brain Metastasis from *EGFR*-mutation-positive NSCLC to Dacomitinib

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Abstract:
The central nervous system efficacy of dacomitinib, a key agent used in the treatment of epidermal growth factor receptor (*EGFR*)-mutant non-small-cell lung cancer (NSCLC), is unclear. We herein present our experience in the use of dacomitinib for the treatment of multiple brain metastatic lesions from EGFR-mutation-positive NSCLC in an elderly patient. This case report demonstrates that dacomitinib can be an essential treatment option for patients with brain metastases.

Key words: brain metastasis, dacomitinib, non-small cell lung cancer

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Introduction

Dacomitinib - a second-generation, oral, irreversible, highly selective pan-HER tyrosine kinase inhibitor - prolongs progression-free survival (PFS) and overall survival in comparison to gefitinib in patients with epidermal growth factor receptor (*EGFR*) gene mutations (1, 2). However, the efficacy of dacomitinib in the treatment of brain metastasis has not defined. We herein report a clinical case in which brain metastasis showed a dramatic response to dacomitinib.

Case Report

The patient was a 67-year-old woman who was diagnosed with stage IV adenocarcinoma harboring an *EGFR* mutation in October 2015. She had been treated with afatinib, an EGFR tyrosine kinase inhibitor, as a first-line therapy for approximately one year. Magnetic resonance imaging (MRI) performed in November 2016 showed multiple brain metastases that disappeared after whole-brain irradiation (WBI) in December 2016. After treatment with several cytotoxic chemotherapeutic agents and eight cycles of docetaxel-ramucirumab as a fifth-line treatment, MRI showed progressive brain metastatic lesions in July 2019 (Figure A). She had no symptoms related to brain metastasis and her ECOG-PS was 0. She received dacomitinib (45 mg), the dose of which was tapered down twice in two weeks to 15 mg due to diarrhea, as the sixth-line therapy. At a dose of 15 mg, the patient's diarrhea subsided and she was able to continue treatment. Two months later, almost all of the brain lesions were undetectable on MRI (Figure B), and there was no recurrence in other organs. Dacomitinib allowed the control of central nervous system (CNS) metastasis and lesions below the thorax and abdomen. At present, the patient has been receiving dacomitinib for five months.

Discussion

We present the first case of brain metastasis in a patient with *EGFR*-positive non-small-cell lung cancer (NSCLC), who showed a dramatic response to treatment with dacomitinib. In the ARCHER 1050 Phase III trial, dacomitinib as a first-line agent significantly improved PFS in patients with *EGFR*-mutation-positive NSCLC in comparison to gefitinib (1, 2). This trial excluded patients with brain metastasis, and hence the efficacy of dacomitinib for CNS metastasis was unclear. However, one patient relapsed with brain metastasis in ARCHER 1050. After the administration of a single-dose of [^{14}C] dacomitinib (4.98 mg/kg, oral) to male Long-Evans rats, the [^{14}C] dacomitinib-derived radioactivity was detectable for 48 hours, and was found to pass through

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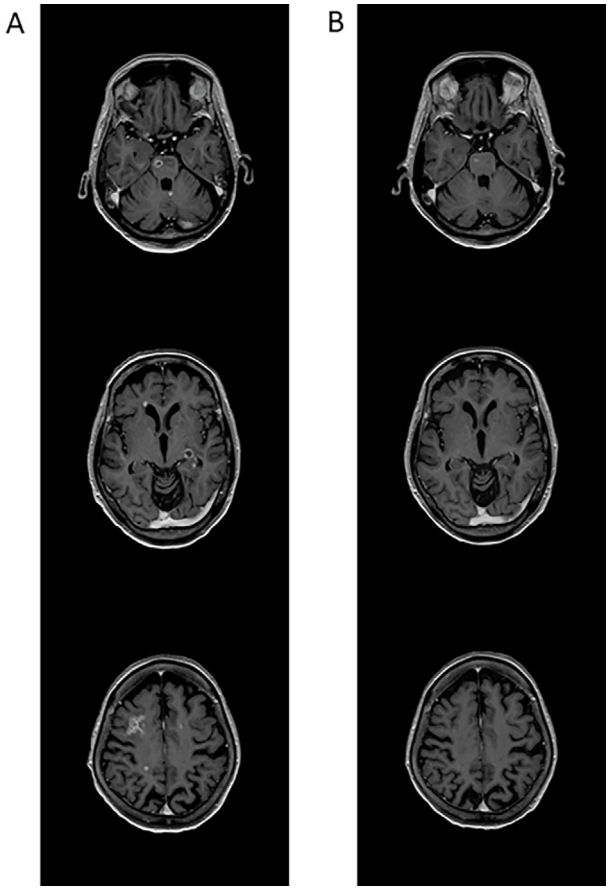

Figure. MRI of the brain showing a dramatic response of metastatic brain lesions to dacomitinib treatment. (A) Brain metastasis before dacomitinib treatment (B) The metastatic brain lesions were reduced in size after 2 months of dacomitinib treatment.

the blood-brain barrier (BBB), central nervous system tissues and cerebrospinal fluid (unpublished results/investigator brochure provided by Pfizer). Additionally, dacomitinib was shown to inhibit tumor growth in patient-derived xenograft models of glioblastoma (3). These data demonstrate the effective BBB permeability of dacomitinib in mice and rats. A small group of patients with glioblastoma significantly benefited from dacomitinib, even though the effect was limited (4). Thus, there is some evidence that dacomitinib might be effective against CNS metastasis in humans. In the present case, the patient experienced an excellent antitumor effect, even though the dose of dacomitinib was reduced to 15 mg at an early stage. We hypothesize that the patient's BBB could have been compromised by previous WBI (5); thus, dacomitinib, which has a small molecular weight (469.94 daltons), might have easily penetrated the BBB (6). The treatment of patients with brain metastasis after WBI is difficult. Dacomitinib remains a viable treatment option for patients with brain metastasis and might be useful as a late treatment. Further studies are required to investigate the efficacy of dacomitinib in patients with brain metastasis.

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

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