Promising Effects of Afatinib on Leptomeningeal Carcinomatosis Derived from Erlotinib-resistant Lung Adenocarcinoma

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Abstract

We herein report a case of a 67-year-old woman previously treated with erlotinib for adenocarcinoma with an epidermal growth factor receptor (EGFR) mutation in exon 19, which rapidly developed to progressive symptomatic leptomeningeal carcinomatosis. The primary tumor and lung metastases also worsened and the performance status (PS) score declined to 3. With a re-biopsy from the pulmonary metastases, the T790M mutation was detected by the cobas EGFR mutation test, but not the cycleave test, although an exon 19 deletion was detected by both of the tests. A week after afatinib initiation, the neurological symptoms disappeared and the PS improved to 1 with a radiological response in all disease sites. Chest physicians should consider the use of afatinib for patients with leptomeningeal carcinomatosis from 1st-generation EGFR-TKI resistant adenocarcinoma, regardless of the PS score and the presence of the T790M mutation in the extracranial lesion.

Key words: erlotinib, afatinib, performance status, leptomeningeal carcinomatosis, T790M, EGFR


Introduction

Although first-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs), including gefitinib and erlotinib, have been reported to be effective for EGFR-mutant non-small cell lung cancer (NSCLC), the prognosis of leptomeningeal carcinomatosis (LMC) after acquired resistance to first-generation EGFR-TKI is considered to be extremely poor (1). We herein report a case of LMC derived from erlotinib-resistant lung adenocarcinoma that was successfully treated with afatinib.

Case Report

In November 2012, a never-smoker, 65-year-old woman visited our hospital suffering from low back pain, a cough, and body weight loss. She was diagnosed with stage IV, cT4N3M1b adenocarcinoma (BRA, OSS, PUL, and ADR) by a transbronchial lung biopsy. The EGFR mutation status was positive for an exon 19 deletion. First-line gefitinib chemotherapy was initiated in December 2012. Although a partial response was obtained, an elevated liver transaminase level occurred as an adverse event in March 2013; therefore, gefitinib was switched to erlotinib as second-line chemotherapy. In December 2013, the primary tumor and lung metastases worsened; thus, four cycles of third-line cisplatin-pemetrexed chemotherapy was initiated, followed by three cycles of pemetrexed as maintenance therapy. Although a partial response was obtained, the patient developed renal dysfunction and pemetrexed therapy was terminated. In August 2014, the primary tumor and lung metastases deteriorated and were complicated by the development of asymptomatic leptomeningeal carcinomatosis (LMC), as shown in Fig. 1. With a re-biopsy from the pulmonary metastases, the presence of the T790M mutation was confirmed by the co-
bas EGFR mutation test, but not by the cycleave test, although an exon 19 deletion was detected by both of the tests. In September 2014, rapidly progressive neurological symptoms of nausea, dizziness, and vertigo developed, resulting in a performance status (PS) score of 3. A lumbar puncture could not be performed due to the drastic reduction of the PS. Afatinib as fourth-line chemotherapy was initiated with careful observation. A week after afatinib initiation, the neurological symptoms disappeared, leading to an improvement of the PS to 1. A radiological response was confirmed by chest computed tomography (Fig. 2) and brain magnetic resonance imaging (Fig. 3). As adverse effects, grade 2 nausea and grade 3 diarrhea were observed around the time of the improvement in PS, but were manageable by a dose reduction to 20 mg/day. Finally, the PS score improved to 0. Afatinib was continued until deterioration of the asymptomatic brain and lung lesions was revealed by a regular radiological evaluation in March 2015.
Discussion

Although first-generation EGFR-TKIs are effectively used for EGFR-mutant NSCLC, resistance inevitably occurs after a median period of 10-12 months (2). Importantly, up to one-third of patients with EGFR mutations develop central nervous system (CNS) metastases after the administration of first-generation EGFR-TKI; among them, LMC was observed in 40% of the patients (3, 4). The prognosis of LMC after acquired resistance to EGFR-TKIs is reported to be extremely poor (1); therefore, new treatment strategies are needed.

Afatinib is a second-generation irreversible TKI of EGFR, human epidermal growth factor receptor-2 (HER2), and HER4 (5, 6). This drug has been reported to be effective for in vitro models of EGFR-mutant clones with the T790M mutation (5, 6), which is the most common mechanism of acquired resistance to first-generation EGFR-TKIs (2). Although a few reports have shown a potential effect of afatinib on NSCLC with the T790M mutation (7, 8), afatinib did not provide an adequate efficacy in patients with EGFR-TKI resistance (9-11). However, in the present case, a dramatic response was obtained in all disease lesions including LMC. Although we do not have any definitive evidence to explain the dramatic response of LMC to afatinib, we hypothesize the following two mechanisms. First, a TKI-free interval could restore the sensitivity to first-generation EGFR-TKIs due to regrowth of the initially sensitive clones. Indeed, the present patient was treated with cytotoxic chemotherapy before initiating afatinib. In addition, the results of the EGFR mutation status differed between the two detection tests used in the present study: the T790M mutation was not detected by the cycleave test, despite the highly sensitive method (12). These results strongly indicate that the percentage of T790M-positive tumor cells was extremely low and the sensitivity to first-generation EGFR-TKIs was restored in most of the tumor cells. Second, afatinib itself

Figure 3. Two weeks after afatinib initiation, abnormal leptomeningeal enhancement in the sulci (arrows) was improved, and the multiple small nodules on the cortical surface (arrow-head) disappeared (A: before afatinib initiation and B: after afatinib initiation).
would be more effective compared to first-generation EGFR-TKIs when treating CNS lesions, regardless of whether the T790M mutation is detected in the extracranial lesions. In our case, the presence of the T790M mutation was confirmed in a lung lesion, not in the CNS lesion. Recently, the T790M mutation was reported to occur more frequently in extracranial lesions than CNS lesions (1, 13, 14), indicating that the presence of the T790M mutation in the extracranial lesion does not always correspond to the positivity of the T790M mutation in the CNS lesion. In addition, the superior effect of afatinib over first-generation EGFR-TKIs on CNS lesions has also been demonstrated in the following two reports: Hata et al. reported a case of T790M-negative NSCLC with BM, which developed during erlotinib treatment but responded to afatinib immediately after erlotinib therapy (15); and Hoffknecht et al. reported that CNS metastases were controlled by afatinib in 66% of patients heavily treated with first-generation EGFR-TKIs (16). In the report by Hoffknecht et al., a case of T790M-positive adenocarcinoma with LMC was successfully treated with afatinib, which reached an effective concentration in the cerebral spinal fluid (CSF), although the penetration rate remained less than 1% (16). Taking those reports into consideration together with the present case, afatinib treatment should be considered for CNS metastases, regardless of the presence of the T790M mutation in the extracranial lesion.

Until now, the efficacy and feasibility of afatinib therapy in patients with a PS of 3/4 has remained uncertain. Despite the promising effect of afatinib for patients with EGFR mutations, recent large trials enrolled only patients with a PS of ≤1 (9, 17). To the best of our knowledge, there has been only one reported case of a patient with a PS of 3/4 treated with afatinib (9, 17). The previously mentioned paper by Hoffknecht et al. described a patient with LMC with a drastic improvement in PS from 3/4 to 1/2 a few days after afatinib initiation, although the dose was reduced from 50 mg to 40 mg due to the development of diarrhea and elevated liver transaminase levels (16). Similarly, in the present case, the PS of 3 improved to 1 within a week, and the side effects were manageable by a dose reduction. The most important point of these cases was that both patients achieved a rapid clinical improvement in the PS after afatinib treatment. In addition, a recent paper reported by Kato et al. revealed that afatinib was more effective in NSCLC patients who required a dose reduction of afatinib due to adverse effects (18), indicating that a concern regarding manageable adverse effects may not be a sufficient reason to withhold afatinib treatment.

In conclusion, we presented a case of rapidly progressive erlotinib-resistant LMC, which cause a drastic reduction in the PS but responded to afatinib therapy. Considering the nature of LMC, which often causes a poor PS (19), chest physicians should consider the use of afatinib, even for a short period, for patients with LMC derived from first-generation EGFR-TKI-resistant adenocarcinoma, regardless of the PS score and the presence of the T790M mutation in the extracranial lesions. Nevertheless, our results should be confirmed in a future prospective study.

Author’s disclosure of potential Conflicts of Interest (COI).
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References


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