Erlotinib and bevacizumab combination therapy for afatinib-refractory leptomeningeal carcinomatosis from EGFR-mutated lung cancer

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Abstract

Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors remains the main hurdle in treating EGFR-mutated lung cancer. Besides, when leptomeningeal carcinomatosis occurs during treatment, it often leads to treatment failure. We herein report a case of lung adenocarcinoma involving a patient with an EGFR exon 19 deletion mutation who developed leptomeningeal carcinomatosis after afatinib treatment for post-operative recurrence. He received right lower lobectomy, followed by four cycles of cisplatin and pemetrexed treatment. Follow-up CT/MRI revealed multiple pulmonary metastases and brain metastases at 7 months after surgery, and afatinib (40 mg/day) was administered after stereotactic radiotherapy for brain metastasis. At 28 months after surgery, follow-up MRI revealed asymptomatic leptomeningeal carcinomatosis, which was cytologically proven from the cerebrospinal fluid. Because EGFR T790M was not detected in plasma cell-free DNA or cerebrospinal fluid, erlotinib and bevacizumab combination treatment was administered. He remained asymptomatic and was radiographically clear of LM at 2 months after treatment. In comparison to other EGFR-TKIs, erlotinib shows penetrance into the cerebrospinal fluid. Furthermore, the addition of bevacizumab might enhance the treatment effect, because it is known to relieve brain edema from metastatic brain tumors by normalizing immature vascularity and improving drug penetrance into the cerebrospinal fluid by reducing interstitial fluid pressure.

Keywords Leptomeningeal metastasis · Erlotinib · Bevacizumab · EGFR mutation · Non-small cell lung cancer

Introduction

In patients with non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR)-sensitive mutations, acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) remains the main cause of treatment failure [1]. Although osimertinib, a third-generation EGFR-TKI, is effective for patients whose tumors acquire T790M mutations [2], cytotoxic chemotherapy is often chosen for several reasons.

Leptomeningeal carcinomatosis (LM) is a severe condition associated with lung cancer, and which occurs in 9.4%

of patients with EGFR-mutated lung cancer [3]. The median survival time (MST) of patients with LM is reported to be 8.9 months [3], with conventional cytotoxic chemotherapy only having limited efficacy. Recent reports have suggested that erlotinib (E) and bevacizumab (B) combination treatment (E + B treatment) could be a useful option for treating patients harboring EGFR-sensitive mutations who develop LM after first-generation EGFR-TKI therapy [4, 5]. However, there are currently no published reports on the usefulness of E + B therapy in patients who developed LM after treatment with a second-generation EGFR-TKI, afatinib. We herein report a case in which E + B was effective for treating LM after the development of acquired resistance to afatinib.

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Case report

A 69-year-old man with a 2.3 pack-year smoking history was diagnosed with right lung cancer of the lower lobe (clinical stage IA, T1bN0M0). He underwent right lower lobectomy and lymph node resection. The postoperative pathological diagnosis was invasive adenocarcinoma, papillary predominant (mixed subtype: papillary 55%, acinar 25%, lepidic 20%), and the tumor size was 2.5 × 1.5 cm with pulmonary metastasis; thus, the pathological stage was IIIA, T3(pml) N2M0. The EGFR of the tumor showed exon 19 deletion. Four cycles of cisplatin and pemetrexed were administered as postoperative adjuvant treatment.

However, follow-up CT/MRI revealed multiple pulmonary metastases and brain metastases at 7 months after surgery (Fig. 1a). After stereotactic radiotherapy for brain metastasis, afatinib was administered at a dose of 40 mg/day. At 1 month after the initiation of afatinib treatment, chest CT revealed the marked shrinkage of the metastatic lesions (Fig. 1b). He continued to receive afatinib, despite the presentation of grade 2 diarrhea and rash.

At 28 months after surgery (21 months after the initiation of afatinib treatment), brain MRI revealed leptomeningeal enhancement and he was diagnosed (Fig. 2b) with leptomeningeal carcinomatosis (LM), which was cytologically proven by a cerebrospinal fluid (CSF) analysis. The patient's tumor marker levels were also increased in comparison to the preoperative levels (CEA 3.1–23.0 ng/ml; CYFRA 1.6–2.8 ng/ml) (Fig. 3). At the time of the diagnosis of LM, the patient was asymptomatic, and no progression of pulmonary metastasis was observed. Because plasma cell free DNA and CSF samples were negative for EGFR T790M, he was treated with bevacizumab (15 mg/kg every 3 weeks) and erlotinib (150 mg/day). Surprisingly, follow-up MRI at 2 months showed that the leptomeningeal enhancement was markedly decreased (Fig. 2c) and that the tumor marker levels had also declined (CEA 23.0–15.2; CYFRA 2.8–2.5) (Fig. 3). The disease control period was maintained for 4 months from the start of treatment. Unfortunately, a dose reduction of erlotinib was required because of grade 3 AST/ALT elevation. With the patient's LM having progressed and his PS having gradually declined after 7 months of E + B

Fig. 1 Chest CT showing lung metastasis before and after treatment with afatinib. **a** Seven months after surgery, two small solid nodules appeared in right upper lobe and one appeared in the left upper lobe.

b At 1 month after starting afatinib, the metastatic lesions of the lung showed marked shrinkage (partial response)

Fig. 2 Brain MRI of leptomeningeal enhancement before and after treatment with erlotinib plus bevacizumab combination therapy. **a** After 2 months of stereotactic irradiation for brain metastasis. **b** At 21 months after starting afatinib, leptomeningeal enhancement appeared.

c Two-month follow-up MRI after the start of erlotinib plus bevacizumab combination therapy showed that the leptomeningeal enhancement was markedly decreased

Fig. 3 Tumor marker trends (CEA). At 28 months after surgery (21 months after the initiation of afatinib treatment), brain MRI revealed asymptomatic LM, and increased tumor marker levels (CEA 23.0 ng/ml, CYFRA 2.8 ng/ml). E + B therapy was initiated. 2-month follow-up MRI showed that the LM was markedly decreased and that the tumor marker levels (CEA 15.2 ng/ml, CYFRA 2.5 ng/ml) had improved. However, dose reduction of erlotinib was required because of grade 3 AST/ALT elevation. With the LM having progressed, the tumor marker levels increased

treatment, he received best the supportive care from 35 months after surgery.

Discussion

In the present case, we demonstrated that erlotinib plus bevacizumab combination treatment significantly improved leptomeningeal carcinomatosis from EGFR mutation-positive non-small cell lung cancer after the development of resistance to the second-generation EGFR-TKI, afatinib.

The development of CNS metastasis in lung cancer patients with EGFR-mutations has been considered a “sanctuary” for disease progression because it is considered that blood brain barrier (BBB) prevents EGFR-TKIs

from reaching adequate concentrations in the brain. Thus, two approaches are utilized: one is local therapy for brain metastasis; the other is increasing the dose to maximize the effects of EGFR-TKIs in the treatment of CNS metastasis. Among the EGFR-TKIs, erlotinib has been considered to show greater CSF penetrance in comparison to other EGFR-TKIs [6].

On the other hand, the mechanisms of resistance to EGFR-TKIs due to leptomeningeal carcinomatosis may be different from other organ metastasis. Because the drug transporter of each EGFR-TKI works in a different way between the BBB and the blood–CSF barrier, the drug concentration in the CSF does not reach the therapeutic range. The CSF erlotinib concentration is reported to be much lower than that in plasma due to the limited transport of the drug into the

CSF [4]. A different approach might be required to treat LM in patients who develop acquired resistance to EGFR-TKIs.

Bevacizumab is a recombinant humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF). It is known to relieve brain edema from metastatic brain tumors and improves drug delivery to tumors by altering the tumor vessel physiology and reducing interstitial fluid pressure [5]. Recently, randomized phases II and III studies showed that E + B treatment significantly prolonged progression-free survival in patients with NSCLC harboring active EGFR mutations [7, 8]. Bevacizumab-related adverse events were shown to increase in E + B treatment, but the adverse events were manageable and treatment was well tolerated [9]. In addition, several reports have shown the effectiveness of E + B treatment as secondary treatment for LM after development of acquired resistance to first-generation EGFR-TKIs [10, 11]. Erlotinib and bevacizumab combination treatment has been reported to be an effective regimen for patients with NSCLC harboring an EGFR mutation with CNS metastasis [10, 11].

Bevacizumab may increase the CSF concentration of EGFR-TKI for the treatment of CNS metastasis. The CSF penetration rate of patients who are effectively treated with E + B combination treatment was equal to or greater than that reported by a previous report on erlotinib alone [6, 10, 12]. Furthermore, preclinical studies suggest that the re-induction of VEGF and subsequent direct or indirect VEGF-dependent tumor growth may be associated with erlotinib resistance [13–15]. The CSF concentrations of VEGF were elevated in patients with LM and were correlated with a poor prognosis [16].

Unfortunately, in this case, the patient's LM progressed after the inevitable dose reduction of erlotinib. However, because there was no progressive disease of the metastatic lung lesion throughout the treatment period, it might have been possible to secure a sufficient concentration of erlotinib in the CSF.

There is not enough evidence to suggest which EGFR-TKIs, or which treatment combination is most effective for LM. Osimertinib, a third-generation EGFR-TKI, is a lipophilic agent that does not require an active drug transporter, which may result in the good penetrance of the drug into the brain and CSF [17]. We consider that E + B therapy or osimertinib is recommended for use in the present case with LM. Especially, at the time of the diagnosis of LM, no progression of pulmonary metastasis was observed and progression disease with LM alone. We thought that raising the concentration of EGFR-TKI in CSF would provide a therapeutic effect on LM. In addition, when plasma cell-free DNA and CSF samples were negative for EGFR T790M, E + B treatment is recommended. Further studies are warranted to develop other novel drugs and to accumulate evidence on combination treatment.

In conclusion, we reported a case of lung cancer in which E + B treatment was effective for treating LM after treatment with afatinib for post-operative recurrence. Our case raises the possibility that E + B treatment might be useful not only in the first-line treatment setting but also as secondary treatment or for patients who developed LM after treatment with first-line EGFR-TKIs.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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