Unexpected outcome (positive or negative) including adverse drug reactions

Long-term survival of a patient with carcinomatous meningitis due to non-small cell lung cancer treated with erlotinib following gefitinib

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Summary

The treatment of carcinomatous meningitis in patients with non-small cell lung cancer is unsatisfactory with a median survival ranging from 4 to 6 weeks without treatment. This report presents a rare case of a long-term survivor with carcinomatous meningitis which was revealed during gefitinib therapy, and was treated with erlotinib. A 55-year-old female never-smoker was diagnosed with adenocarcinoma of the lung and underwent a right upper lobectomy. Four years had passed since surgery, she started gefitinib therapy for recurrent lung cancer. During gefitinib therapy, she presented with headache and was diagnosed with carcinomatous meningitis. After changing her treatment to erlotinib, her symptoms temporarily improved and she remained alive for 10 months. Erlotinib therapy may represent a candidate treatment option for carcinomatous meningitis after gefitinib therapy.

BACKGROUND

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) such as gefitinib and erlotinib have been widely used for the treatment of non-small lung cancer (NSCLC). It has been reported that gefitinib produced prolonged survival in NSCLC patients with mutations of the EGFR.¹ On the other hand, with increasing use of gefitinib, the central nervous system (CNS) was a frequent site of disease recurrence in patients with NSCLC after an initial response to gefitinib.² CNS metastasis is a prevalent and serious complication, with negative effects on the quality of life and overall survival of patients.³

Erlotinib is also an orally available, quinazoline-based, reversible inhibitor of EGFR tyrosine kinase activity. As second- or third-line therapy, erlotinib has demonstrated

a significant survival benefit for whole lung cancer populations.³ Recently, several authors have reported the efficacy of erlotinib for CNS metastasis developed during gefitinib therapy.^{4 5} This report describes a rare case of a patient with carcinomatous meningitis who obtained prolonged survival during treatment with erlotinib following gefitinib therapy.

CASE PRESENTATION

In 2004, a 55-year-old female never-smoker was diagnosed with adenocarcinoma of the lung and underwent a right upper lobectomy. The pathological tumour node metastasis stage was stage IIIA with mediastinal lymphnode metastasis, therefore she received postoperative radiotherapy to the mediastinum. In 2007, small nodules were detected in

Figure 1 A chest CT showing small nodules in the residual right lung which were diagnosed as the recurrence of lung cancer.

Figure 2 MRI of the brain was negative for brain metastasis.

the residual right lung and diagnosed to be recurrences of NSCLC. Chemotherapy consisting of four cycles of carboplatin and gemcitabine followed by oral fluoro pyrimidine therapy was performed, but the serum carcinoembryonic antigen (CEA) level continued to increase. In 2008, gefitinib (250 mg/day) was administered, which led to a decrease in the CEA and stabilisation of the pulmonary lesions (figure 1). The EGFR mutation status was not investigated at the start of gefitinib therapy. In 2009, the patient suffered from headache and nausea.

INVESTIGATIONS

MRI of the brain was negative for brain metastasis (figure 2). A lumbar puncture was performed revealing findings consistent with carcinomatous meningitis. The EGFR mutation status was evaluated, and a deletion mutation in exon 19 was identified.

TREATMENT

Erlotinib and steroids were coadministered to the patients.

OUTCOME AND FOLLOW-UP

The erlotinib reduced her symptoms of head ache and nausea and improved her quality of life. She continued to take erlotinib for about 300 days until shortly before her death in 2010 of sudden respiratory distress.

DISCUSSION

Erlotinib and gefitinib are both epidermal growth receptor tyrosine kinase inhibitors (EGFR-TKIs). Omuro *et al.* reported the incidence of disease recurrence in NSCLC patients after the response to gefitinib.² According to the report, 33% of the patients developed recurrence in the brain and leptomeninges after an initial response to gefitinib.² The number of patients with CNS metastases during gefitinib treatment is increased with increasing gefitinib therapy. In the present case, carcinomatous meningitis was revealed 11 months after gefitinib treatment was initiated. Several mechanisms of acquired resistance to EGFR-TKIs, such as the T790M point mutation, MET amplification,

etc. after an initial response have been described.⁶ In this case, there was no mutation of the EGFR gene except for a deletion mutation of exon 19.

Jackman *et al.* reported that the administration of the standard dose of gefitinib (250 mg/body) could not reach a sufficient concentration in the cerebrospinal fluid (CSF) level to have anticancer efficacy.⁷ The CSF penetration (AUC_{CSF}:AUC_{plasma}) of erlotinib was reported to be 6.9% relative to the total plasma concentration.⁸ This high level of potential cerebrospinal transfer of erlotinib may lead to efficacy for CNS metastasis.

In conclusion, salvage treatment with erlotinib may be an option for patients after treatment failure with gefitinib, especially those with CNS involvement.

Learning points

- ▶ The central nerve system metastasis with NSCLC is a prevalent and serious complication, with negative effects on the quality of life and overall survival of patients.
- ▶ The central nerve system was a frequent site of disease recurrence in patients with NSCLC after an initial response to gefitinib.
- ▶ Salvage treatment with erlotinib may be an option for patients after treatment failure with gefitinib, especially those with CNS involvement.

Competing interests None.

Patient consent Obtained.

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