Efficacy of a Lumbo-peritoneal Shunt for Meningeal Carcinomatosis Refractory to Gefitinib Treatment

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Abstract. *A 51-year-old female presented with left facial palsy. She had adenocarcinoma of the lung with multiple brain metastases. The primary tumor regressed after treatment with gefitinib, however, neurological symptoms progressed rapidly because of meningeal carcinomatosis, when a deletion mutation in exon 19 of the epidermal growth factor receptor in cells from her cerebrospinal fluid was detected. After performing lumbo-peritoneal shunting, her symptoms improved dramatically and she had been well without peritoneal dissemination for 15 months, continuing gefitinib treatment. Finally, she died 18 months after lumbo-peritoneal shunting. A T790M acquired-resistance mutation in exon 20 of the epidermal growth factor receptor was found from her mesenteric lymph nodes and cerebrospinal fluid at autopsy. A lumbo-peritoneal shunt might be considered for meningeal carcinomatosis refractory to gefitinib treatment without an emergence of a T790M mutation.*

Meningeal carcinomatosis occurs in from 4% to 15% of patients with solid tumors. The lung is the second most frequent primary tumor site (22% - 36%), following the breast (1). Meningeal carcinomatosis presents with various symptoms such as headache, emesis and neurological dysfunction, and causes a poor performance status (PS). The median survival time of untreated patients with meningeal carcinomatosis is 4 to 6 weeks (1, 2). The treatment is mainly systemic and intrathecal chemotherapy, radiotherapy, and surgery such as the insertion of an intraventricular catheter or a ventriculo-peritoneal shunt. However, the median survival time is at most 4 to 6 months even in appropriately treated patients (1). We herein describe a lung cancer patient with meningeal carcinomatosis whose disease was well controlled with gefitinib and a lumbo-peritoneal shunt.

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Case Report

A 51-year-old Japanese female who had never smoked presented at a local hospital with left facial palsy. Contrast-enhanced computed tomography (CT) of the head revealed a few enhanced small nodules in her cerebrum. CT of the chest revealed a mass in the right lower lobe. A transbronchial biopsy revealed adenocarcinoma of the lung. A bone scan showed multiple bone metastases. The patient was given gefitinib (250 mg) once daily as the first-line treatment. After one month, the primary lesion had regressed, while the neurological symptoms progressed rapidly, and she became stuporous and confined to bed. Adenocarcinoma cells were found in the cerebrospinal fluid (CSF) and the carcinoembryonic antigen (CEA) level (178.3 ng/ml) in the CSF was 10 times higher than that (17.2 ng/ml) in the serum.

A lumbo-peritoneal shunt was placed and she continued to receive gefitinib. Since a deletion mutation in exon 19 of the epidermal growth factor receptor (*EGFR*) without T790M second mutation in exon 20 was detected in tumor cells from her CSF, we postulated that the gefitinib would prevent peritoneal dissemination. The hydrocephalus due to meningeal carcinomatosis improved markedly; the primary lesion in her right lower lobe regressed further, and only a little ascitic fluid was detected in the recto-uterine pouch on a CT. The CSF and serum CEA levels decreased to 0.21 and 3.80 ng/mL, respectively. Her performance status improved to 1. She had been well without peritoneal dissemination for 15 months. Finally, meningeal peritonitis occurred and she died 18 months after lumbo-peritoneal shunting. A T790M point mutation of *EGFR* was detected from both her mesenteric lymph nodes and CSF at autopsy (Figure 1).

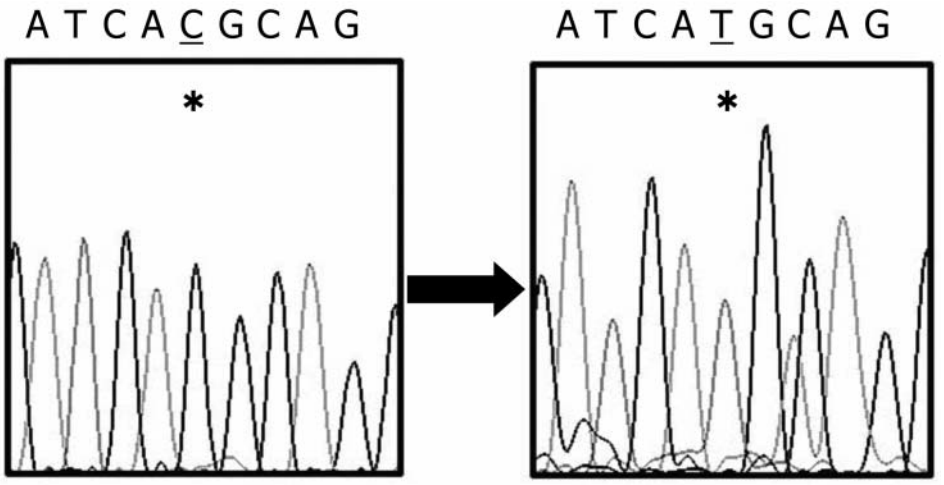

Figure 1. *Sequencing of exon 20 of epidermal growth factor receptor is shown. A point mutation (from ACG to ATG) was detected in the cerebrospinal fluid not before placing a lumbo-peritoneal shunt (left), but at autopsy (right).*

Discussion

Some patients with meningeal carcinomatosis due to pulmonary adenocarcinoma which harbored activating *EGFR* mutations have been treated successfully with gefitinib (250 mg/day) (3, 4). By contrast, in one case even 500 mg/day of gefitinib did not achieve CSF drug concentrations sufficient to inhibit the growth of the cancer cells (5). The discrepancy between these reports may be due to the association between the achievement of concentrations of gefitinib in the CSF and the sensitivity of the tumor cells to gefitinib. Although the primary lung tumor was well controlled by gefitinib in our patient, the meningeal carcinomatosis progressed. Because an activating *EGFR* mutation was detected in the tumor cells in the CSF, we thought gefitinib might not have reached an effective concentration in the CSF. We expected that gefitinib could achieve an effective concentration in the peritoneum and might prevent peritoneal dissemination through a lumbo-peritoneal shunt. This improved her consciousness level and quality of life. Gefitinib was administered to the frail patient safely and other disease sites were well controlled.

Finally, an acquired T790M mutation, which was a gefitinib-resistant mutation (6, 7), was detected from both her mesenteric lymph nodes and CSF at autopsy. In a patient who developed brain metastases late in the course of gefitinib therapy, a T790M mutation was found in multiple metastatic sites but not in the brain (8). To the best of our knowledge, this is the first report to demonstrate T790M from CSF. A lumbo-peritoneal shunt might be considered for meningeal carcinomatosis refractory to gefitinib treatment without an emergence of a T790M mutation.

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