Abstract

Two Japanese women were diagnosed as having well-differentiated adenocarcinoma of the lung with brain metastases. Since it was considered they could not tolerate conventional chemotherapy, we administered gefitinib without any previous systemic therapy. In both patients gefitinib acted dramatically on all the lesions including the brain metastases, resulting in a marked decrease of the elevated CEA levels, and improvement of their quality of life. Retrospective evaluation of epidermal growth factor receptor expression levels by immunohistochemistry revealed positive results in both cases. Though gefitinib has been recommended for patients previously treated with chemotherapy, it should be considered feasible as a first line therapy.

Case Reports

Case 1

A 74-year-old Japanese woman was referred to our hospital complaining of back pain with an Eastern Cooperative Oncology Group (ECOG) performance status of 4. Chest CT showed a mass in the left lower lobe and bilateral pleural effusions, and brain CT revealed a metastatic lesion (Fig. 1A, B). Biopsy specimens obtained by bronchoscopy showed well-differentiated adenocarcinoma (Fig. 1C). We gave 250 mg/day gefitinib, and at 1 month the primary lesion had shrunk remarkably, and pleural effusion and brain tumors almost disappeared (Fig. 1D, E). Although she initially needed 576 mg/day morphine for analgesia when she started gefitinib, she was able to discontinue morphine in 2 months, and her performance status improved to 2. The CEA level decreased from 19,870 IU/l to 4.5 IU/l in 4 months. The only adverse effect linked to gefitinib was National Cancer Institute common toxicity criteria grade 2 rash. EGFR expression levels were examined in pretreatment biopsy specimens by immunohistochemistry (IHC) using a monoclonal antibody against EGFR (clone EGFR.113, Novocastra, Newcastle upon Tyne, UK), which was raised to the extracellular domain, and both cell membrane and cytoplasm were strongly stained (Fig. 1F).

Case 2

An 84-year-old Japanese woman was referred to our hospital complaining of paralysis of the left arm with an ECOG performance status of 3. Chest CT showed a mass in the left upper lobe and multiple pulmonary metastases, and brain
MRI revealed multiple metastatic lesions (Fig. 2A, B). After biopsy specimens of the lung obtained with CT fluoroscopic guidance revealed well-differentiated adenocarcinoma (Fig. 2C), we initiated 250 mg/day gefitinib. Both the primary lesion and brain tumors became smaller, and pulmonary metastases almost disappeared (Fig. 2D, E). The CEA level decreased from 243.6 IU/l to 12.7 IU/l in 3 months. She was able to reduce morphine from 40 mg/day to 10 mg/day in 6 months, and her performance status improved to 2. The adverse effect induced by gefitinib was grade 1 appetite loss only. EGFR expression levels were also examined in pretreatment specimens by EGFR-IHC. Cytoplasm was moderately stained although the cell membrane did not stain well (Fig. 2F).

Discussion

We describe 2 patients with advanced NSCLC who had poor performance status and who showed remarkable response to gefitinib. Both of them were Japanese and female and had adenocarcinoma, all three factors of which are considered to be prognostic factors (4). Gefitinib has been recommended only as a second line of chemotherapy, especially after the report that mentioned the severe adverse effect of acute interstitial pneumonia, which can be fatal (5). However, gefitinib is probably the only radical therapy for patients who have a poor performance status and who are thought to be unable to tolerate cytotoxic therapies. Therefore we considered that gefitinib could be administered as a first line of therapy in certain selected patients who have better prognostic factors.

In both patients, the brain tumors shrank markedly after commencement of gefitinib therapy. As previously reported (3, 6), the remission of the brain metastases was considered to be an effect of gefitinib. There is a possibility that gefitinib can cross the blood brain barrier because of its low molecular weight (7). More investigation to elucidate its effects on brain tumors is needed.

We considered whether there was any correlation between EGFR expression levels and clinical results. However, Bailey et al (8) reported there to be no supporting evidence of this. The reason is thought to be because sensitivity to gefitinib is determined not simply by EGFR over-expression, but as a result of interaction in the complicated EGFR signaling networks (9). Therefore, new information might be provided if we examine the expression patterns of receptors,
such as phosphorylated EGFR or HER2 (10), in more cases. Further clinical research is necessary.

Gefitinib, a new antitumor agent for advanced NSCLC, is generally well tolerated. To the extent that physicians are aware of possible adverse effects, we suggest that gefitinib can be administered as a first line of therapy for NSCLC when patients have a poor performance status and cannot be treated with conventional cytotoxic chemotherapy.

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References