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Long-term Effect of Gefitinib (ZD1839) on Squamous Cell Carcinoma of the Lung

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Abstract. *This case report describes the effects of long-term treatment with the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) gefitinib ('Iressa', ZD1839) on a patient with squamous cell carcinoma of the lung. Gefitinib is an orally active agent that blocks signal transduction pathways implicated in the proliferation and survival of cancer cells and host-dependent processes that promote tumor growth. A 62-year-old Japanese man with a history of heavy smoking was diagnosed with squamous cell carcinoma of the lung, clinical stage IIIB (T4N3M0), in August 2000. He received two cycles of cisplatin-based chemotherapy and subsequently underwent left upper lobectomy followed by thoracic radiotherapy. After these treatments, he underwent partial lobectomy and pneumonectomy because of disease recurrence. In June 2002, he started treatment with gefitinib 250 mg/day orally because of mediastinal lymph node recurrence and an elevated serum cytokeratin 19 fragment (CYFRA) level. As a result, the mediastinal lymph node markedly regressed and the serum CYFRA level became normalized. Although he experienced recurrence three times during the 18 months prior to treatment with gefitinib, recurrence has not been experienced in the 13 months since the start of gefitinib treatment, while tolerability has been acceptable.*

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Case Report

The patient, a 62-year-old Japanese man who formerly smoked 30 cigarettes/day for 35 years, was admitted to our hospital on June 10, 2002.

Treatment history. In July 2000, the patient visited his local hospital because of back pain. A chest radiograph showed an abnormal shadow in the left upper lung and he was admitted to the hospital in August 2000. A biopsy specimen taken by fiberoptic bronchoscopy showed squamous cell carcinoma of the lung and a clinical stage of IIIB (T4N3M0) was diagnosed. He received two cycles of chemotherapy (cisplatin 80 mg/m^2 on day 1, mitomycin C 8 mg/m^2 on day 1, and vinorelbine 20 mg/m^2 on days 1 and 8) and achieved a partial response (PR). Following referral to the Department of Surgery II, Okayama University Hospital, Japan, on November 29, 2000, he underwent left upper lobectomy, followed by adjuvant radiotherapy at a dose of 2 Gy daily to a total dose of 50 Gy. The pathological stage went down to stage IIB (pT3N0M0). In July 2001, chest radiography showed a nodule in the left lower lung field. A transcutaneous biopsy specimen revealed recurrence of squamous cell carcinoma. On July 30, 2001 he received partial lower lobectomy with chest wall resection followed by oral uracil/tegafur (UFT) as adjuvant therapy. In February 2002, he noticed his left chest wall swelling. Chest computed tomographic (CT) scan revealed a mass in the remaining left lower lung with direct invasion to his left second to fourth ribs. White blood count (WBC) was 17,300/mm^3 and C-reactive protein (CRP) was elevated to 1.8 mg/dl (normal range, 0.0-0.3mg/dl). The serum cytokeratin 19 fragment (CYFRA) level was markedly elevated to 32.9 ng/ml (normal range, 0.0-2.8 ng/ml). He

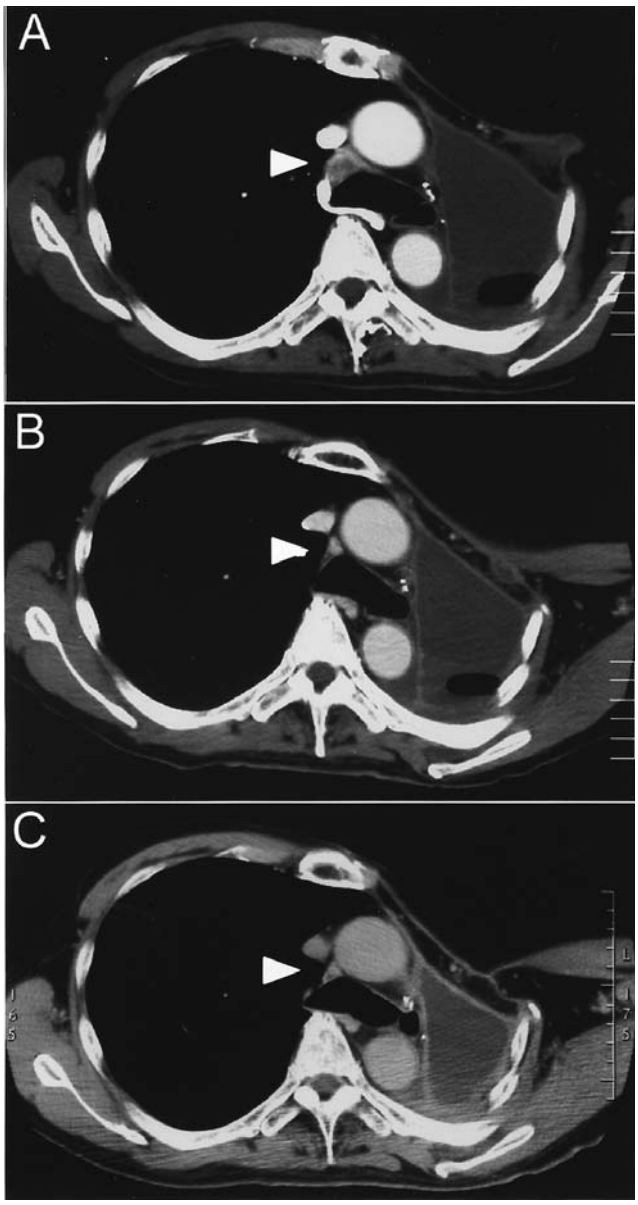

Figure 1. *Contrast-enhanced chest CT scans before and after gefitinib treatment. Before gefitinib treatment (a) single mediastinal lymph node (21 x 16 mm, white arrowhead) was detected. Twenty-eight days (b) and 12 months (c) after gefitinib treatment, the mediastinal lymph node was markedly regressed.*

underwent left pneumonectomy with chest wall reconstruction on March 18, 2002. After pneumonectomy, the serum CYFRA level and WBC returned to normal.

Patient status before gefitinib treatment. On June 10, 2002 the patient was admitted to our hospital following contrast-enhanced CT scans of the chest showing a single mediastinal lymph node swelling (21 x 16 mm) (Figure 1), which was not detected in the chest CT scan of April 2002. He applied for inclusion in a compassionate use program of gefitinib. He had felt anterior chest pain possibly due to operation and had a performance status (PS) of 1. On physical examination, he had tenderness at the site of his operation scar on the left anterior chest and breathing was not audible on the left side of the lung. The WBC was elevated to 14,100/mm^3 and platelet count and CRP were slightly elevated. The serum CYFRA level was again elevated, to 3.8 ng/ml, although carcinoembryonic antigen and squamous cell carcinoma-related antigen were within the normal range. There were no other metastatic lesions of lung, abdomen, brain or bone. We concluded that he had progressive disease, because of a single mediastinal lymph node swelling supported by elevation of the serum CYFRA level.

In histological assessments of the first and the third operation specimens (Figure 2), a majority of the cells did not show a uniform differentiation, but cells with stratification and keratinization were detected in a focal area (white arrowhead in Figure 2) and the patient was diagnosed with poorly-differentiated squamous cell carcinoma of the lung.

Gefitinib treatment. The patient began treatment with gefitinib 250 mg/day orally on June 12, 2002. On July 9, 2002, marked mediastinal lymph node regression was noted, as shown in Figure 1b and the serum CYFRA level and WBC returned to within the normal range. Adverse events were grade 1 (National Cancer Institute common toxicity criteria version 2.0) acne-like rash and diarrhea, and grade 2 liver dysfunction. Skin rash and diarrhea were mild and transient. Grade 1 liver dysfunction was assessed on September 5, 2002 and gefitinib was continued for a further 3 weeks, when grade 2 liver dysfunction occurred. Gefitinib was interrupted for 14 days until complete liver recovery. However, liver dysfunction occurred again on readministration of gefitinib. Therefore, after a further interruption of 14 days, the patient resumed gefitinib 250 mg once daily for 14 consecutive days followed by 14 days off, according to a schedule used in a phase I trial (1). Using this schedule, liver dysfunction has not occurred since January 2003. Contrast-enhanced CT scan of the chest on June 12, 2003 did not detect regrowth of a mediastinal lymph node (Figure 1c). The serum CYFRA level remained within the normal limit for more than 12 months (ongoing at the time of reporting), at which time the patient remains in full-time employment. He continues to take gefitinib 250 mg/day, with no additional treatment and visits our hospital once a month.

Discussion

This is the first case report to describe the long-term effects of gefitinib on a patient with squamous cell carcinoma of the lung. This patient initially received cisplatin-based

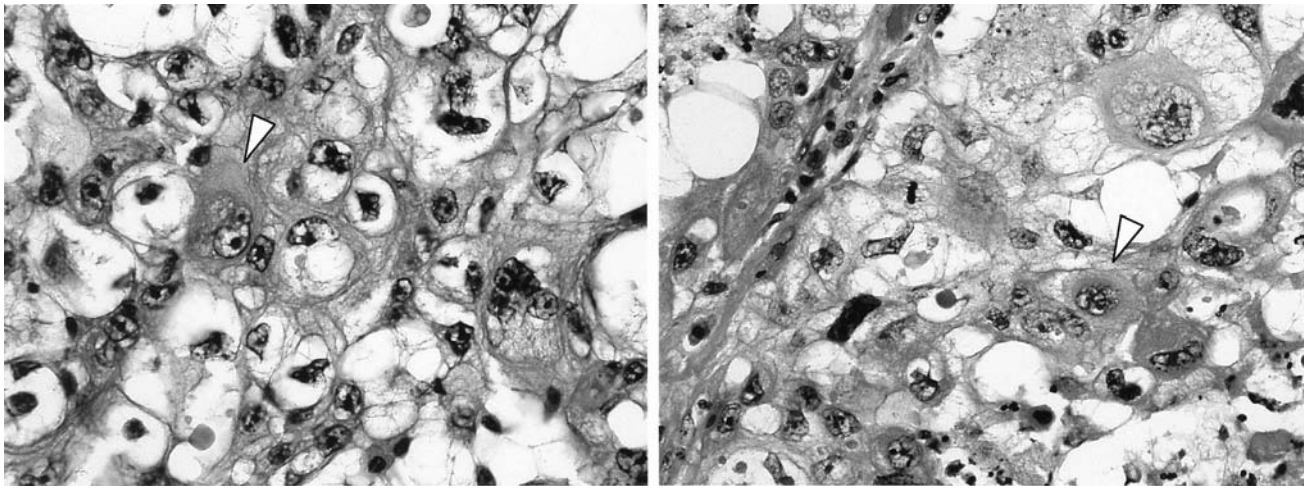

Figure 2. *(a) Specimen from the first operation on November 29, 2000 and (b) specimen from the third operation on March 18, 2002 (hematoxylin and eosin, magnification x340).*

chemotherapy and radiotherapy and underwent surgery three times in 18 months. After gefitinib treatment, recurrence has not been experienced, with acceptable toxicities for 13 months. In this case, gefitinib is working well as the last defensive line.

The two phase II trials showed higher efficacy rates for gefitinib in female patients, patients with good PS and patients with adenocarcinoma (2,3). Nevertheless, both trials support the use of gefitinib in squamous cell carcinoma of the lung: 3/43 patients (7%) in IDEAL 1 and 2/32 patients (6%) in IDEAL 2 with squamous cell carcinoma achieved a PR (2-4). In addition, Ruckdeschel *et al.* reported one PR (7%) among 15 patients with squamous cell carcinoma of the lung (5). Between August 2001 and April 2003, 12/89 (14%) of patients with NSCLC treated with gefitinib in our hospital and the National Shikoku Cancer Center Hospital were diagnosed with squamous cell carcinoma of the lung and 3/12 patients (25%; 95% confidence interval [CI], 9%-43%) with squamous cell carcinoma achieved a PR, including the patient described. Therefore, a relatively small, but significant, population of patients with squamous cell carcinoma of the lung is clearly sensitive to gefitinib. In gefitinib, patients with squamous cell carcinoma may therefore have a valuable additional treatment option other than palliative care, since response rates of carboplatin against chemotherapy-naïve NSCLC patients and docetaxel against refractory NSCLC patients are 9% and 7%, respectively (6, 7).

Tumor burdens were small in two of the three cases of PR we have seen. Of these, the case we describe showed a single mediastinal node recurrence, while a second case, a 59-year-old Japanese woman who smoked 25 cigarettes/day for 39 years, presented with regrowth of primary lung tumor and pulmonary metastasis (new lesions) after cisplatin and docetaxel with concurrent thoracic radiotherapy. The second case has also continued in PR for 10 months, although gefitinib treatment was interrupted transiently because of grade 2 skin rash. The third case, a 67-year-old Japanese man who formerly smoked 20 cigarettes/day for 44 years, revealed total opacification of the left lung after thoracic radiotherapy, five cycles of paclitaxel and carboplatin and two cycles of gemcitabine. At a very advanced stage, under oxygen supplement, he received gefitinib treatment, at which the bulky mass markedly regressed and atelectasis of the left lung disappeared. The duration of response was 4 months. We have previously reported a dramatic effect of gefitinib for a female patient with adenocarcinoma and poor PS (8); our current report shows that a relatively good response rate and long duration of response can also be seen in cases with small tumor burden and good PS.

A strong correlation between smoking history and the effect of gefitinib has been reported (9) and the efficacy of gefitinib might be linked to the etiology of disease in smokers *versus* never-smokers. Gene mutation in lung cancers is more frequent in smokers than non-smokers (10). Therefore in smokers, cancer cells may escape growth control at a high rate, including *via* pathways that are independent of EGFR signaling. Nevertheless, the PRs we have described have been in patients who were heavy smokers.

We have established two cell lines derived from a patient with squamous cell carcinoma of the lung both before and after cisplatin-based chemotherapy (11). Interestingly, EBC-2/R cells, isolated after cisplatin-based chemotherapy, are

8.6-fold more sensitive to gefitinib than EBC-2 cells isolated before chemotherapy (12). We are investigating the mechanistic causes behind this increased sensitivity in a cisplatin-resistant cell line derived from squamous cell carcinoma of the lung.

Since the introduction of gefitinib to Japan in July 2002, there have been reports of patients who developed interstitial lung disease (ILD), possibly due to gefitinib treatment. Out of approximately 80,000 patients who have now received gefitinib worldwide, the ILD incidence and mortality is 1.0%, and 0.4%, respectively (13). In a series of patients treated in a single institute study, 4/18 patients with NSCLC developed acute ILD possibly related to gefitinib treatment, but all had been former smokers (14). Although our case was a former smoker and underwent pneumonectomy and radiation therapy, pulmonary adverse events have not occurred for more than 12 months of gefitinib treatment.

In conclusion, we report that gefitinib is effective for at least 13 months in a patient with squamous cell carcinoma of the lung, without severe adverse events. In the light of his status as a male smoker with squamous cell carcinoma, more intensive basic and clinical research into the mechanisms of gefitinib action is needed.

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