

Interstitial Pneumonia During Gefitinib Treatment of Non-Small-Cell Lung Cancer

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Gefitinib, an orally active, selective inhibitor of epidermal growth factor-receptor tyrosine kinase, is an effective treatment for patients with advanced non-small-cell lung cancer (NSCLC). Most drug-related adverse events are mild to moderate; however, some patients may develop acute interstitial pneumonia that is sometimes fatal. In a prospective study of gefitinib in 76 patients with advanced NSCLC, 69 patients were evaluable for toxicity, and 4 cases (5.8%) of gefitinib-related interstitial pneumonia were diagnosed: 1 occurred in the second week; 2 in the second month; and 1 during the fourth month of treatment. When interstitial pneumonia occurred, the patients had stable disease ($n = 2$), a partial response ($n = 1$), or progressive disease ($n = 1$). All 4 patients recovered when gefitinib treatment was stopped and glucocorticosteroid therapy was started; no deaths related to gefitinib therapy were noted in this series. While treating NSCLC patients with gefitinib, it is important to carefully evaluate any new-onset respiratory symptoms and promptly arrange radiographic examinations, and to stop gefitinib treatment and begin glucocorticosteroid therapy whenever pulmonary toxicity is highly suspected. [*J Chin Med Assoc* 2005;68(4):183–186]

Key Words: gefitinib, interstitial pneumonia, non-small-cell lung cancer

Introduction

Gefitinib (Iressa®; AstraZeneca Pharmaceuticals, Wilmington, DE, USA) is an orally active, selective epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) that is an effective treatment for advanced non-small-cell lung cancer (NSCLC).^{1,2} Generally, gefitinib is well tolerated, and most drug-related adverse events are mild and manageable. However, gefitinib-related interstitial pneumonia has been reported, and the incidence seems to differ between Japan and Western countries.^{3,4}

From March 2002 to May 2003, we prospectively enrolled 76 patients with advanced NSCLC in a single-institute study in Taiwan.⁵ Gefitinib was administered orally at a fixed daily dosage of 250 mg, without concomitant cytotoxic agents or radiotherapy. Patients were eligible for study inclusion if they had failed previous systemic chemotherapy, or had poor

performance status during cytotoxic therapy. Sixty-nine patients were evaluated for drug-related toxicity. Here, we present 4 cases in which patients developed interstitial pneumonia during gefitinib treatment: 1 case occurred during the second week; 2 in the second month; and 1 in the fourth month.

Case Reports

Case 1

An 80-year-old man was diagnosed, in June 2002, with adenocarcinoma in the left lower lung lobe (Figure 1A). He received single-agent, systemic chemotherapy with gemcitabine (4 courses). Chemotherapy was stopped because of pulmonary tuberculosis, which was considered to be related to treatment-induced immunosuppression. The patient then received gefitinib, and his disease was stable at

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the response evaluation in the eighth week; however, ground-glass opacities were noted incidentally in both lower lung fields (Figure 1B). No evidence of infection, fluid overload, or disease progression was noted clinically. Laboratory tests revealed a normal blood cell count, and all serologic tests and microbiologic cultures were negative. Because of suspected drug-related interstitial pneumonia, gefitinib was discontinued, and methylprednisolone was prescribed. One week later, a chest computed tomography (CT) scan showed dramatic improvement (Figure 1C).

Case 2

In February 2003, a 70-year-old man with NSCLC presented with multiple lung and bone metastases (Figure 2A). In March 2003, the patient underwent surgery for stabilization of the lumbar spine, and palliative radiotherapy of the lower thoracic spine; because of poor performance status, he received gefitinib as first-line systemic therapy. Progressive shortness of breath, dyspnea on exertion, and mild cough, were noted after 8 weeks' treatment when the patient returned for an evaluation of treatment response. A chest CT scan showed a partial response of the tumor; however, diffuse, ground-glass opacities were noted in both lungs (Figure 2B). There were no clinical signs of infection and fluid overload, and radiation pneumonitis was not favored as the diagnosis since radiographic changes that usually manifest 2–3 months after radiation therapy were absent. Because of suspected gefitinib-induced interstitial pneumonitis, gefitinib was discontinued and glucocorticosteroid therapy was given. Clinical symptoms improved, and a chest CT scan showed remarkable regression of interstitial pneumonia, with residual fibrotic change in the right lower lung lobe (Figure 2C).

Case 3

A 69-year-old woman presented with NSCLC in the left lower lung lobe in November 2001. She had radiotherapy as her initial treatment; however, tumor progression and lung metastases were noted in February 2002. The patient then received systemic chemotherapy with vinorelbine and cisplatin (6 courses), and the maximal response was stable disease. Two months later, disease progression was noted; the patient then took gefitinib as second-line therapy. However, aggravated dyspnea and cough were noted after 2 weeks of gefitinib treatment. No evidence of infection, fluid overload or disease progression was noted clinically. Laboratory tests revealed a normal blood

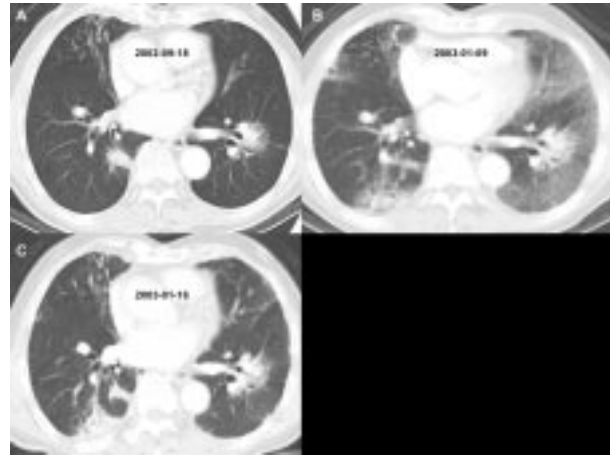


Figure 1. A case of non-small-cell lung cancer: (A) tumor infiltration was noted in the left lower lung lobe at initial presentation; (B) ground-glass opacities were found incidentally in both lower-lung fields at the response evaluation; and (C) the lesion resolved dramatically 1 week after discontinuing gefitinib and starting methylprednisolone.

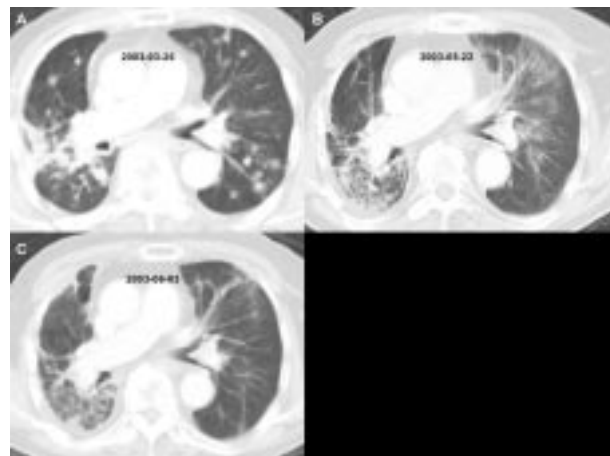


Figure 2. (A) Multiple pulmonary metastases were noted in both lung fields at initial presentation in a patient with non-small-cell lung cancer. (B) Diffuse, ground-glass opacities and interlobular septal thickening in the superior basal segment of the right lower lung lobe were noted after 8 weeks of gefitinib treatment, despite a remarkable tumor response. (C) Remarkable regression of interstitial pneumonia, with residual fibrotic change in the right lower lung lobe, was noted after discontinuing gefitinib and starting methylprednisolone.

cell count, and all serologic tests and microbiologic cultures were negative. A chest radiograph showed a ground-glass opacity and consolidation in the right upper lung lobe. Gefitinib was discontinued immediately, and methylprednisolone was prescribed. A chest radiograph performed 6 weeks later showed prompt resolution of the lesion, despite progression of the main tumor.

Case 4

A 64-year-old man was diagnosed with squamous cell carcinoma of the lung in July 2002. The clinical staging was T₃N₃M₁ at initial presentation. Because of poor performance status, the patient received gefitinib as first-line therapy. The tumor was stable, but progressive shortness of breath and cough were noted after 4 months' gefitinib treatment. A chest CT scan showed a ground-glass opacity in the left lower lung lobe. Microbiologic tests of sputum and blood were all negative, and there was no evidence of fluid overload. Laboratory tests revealed a normal blood cell count, and a normal differential count of white blood cells. Gefitinib-related interstitial pneumonia was highly suspected. Gefitinib was withdrawn and methylprednisolone was prescribed. Clinical symptoms resolved promptly, and a chest CT scan performed 3 months later showed complete resolution of the lesion.

Discussion

Gefitinib is an orally active, selective EGFR-TKI with anti-tumor activity against several kinds of neoplasm. Two large phase II trials, the Iressa[®] Dose Evaluation for Advanced Lung Cancer (IDEAL)-1 and IDEAL-2, showed that gefitinib was effective in NSCLC patients who had failed previous platinum-based chemotherapy,^{1,2} and gefitinib, as a targeted therapy, has a better toxicity profile than conventional cytotoxic chemotherapy. In fact, in the IDEAL-1 and IDEAL-2 trials, most drug-related adverse events were mild to moderate, namely skin toxicity and gastrointestinal disturbances, and were manageable.^{1,2}

Based on these data, gefitinib was first approved in Japan in July 2002. However, some cases of fatal gefitinib-related interstitial pneumonia were noted after the drug was marketed. Inoue et al³ first formally reported, in the English literature, that 4 of 18 gefitinib-treated patients developed severe acute interstitial pneumonia. The authors also cited that, according to an official notice by the Japanese Ministry of Health, Labour, and Welfare, 1.7% of 175,000 patients had suspected interstitial pneumonia during gefitinib therapy. Thus, the US Food and Drug Administration delayed gefitinib approval until May 2003, even though they claimed that the incidence of gefitinib-induced interstitial pneumonia was only about 0.3% in the US expanded access program.⁴ A retrospective survey conducted by the West Japan Thoracic Oncology Group, and performed independently of AstraZeneca Pharmaceuticals and regula-

tory authorities, revealed a 1983 incidence of 4.6% for interstitial pneumonia in NSCLC patients treated with gefitinib; 30 patients (1.5%) had died from this gefitinib-related complication.⁶

A definitive diagnosis of drug-induced interstitial pneumonia is difficult; moreover, the mechanism of gefitinib-induced interstitial pneumonia is unclear. Since the histologic findings of drug-induced interstitial pneumonia are usually non-specific, and as it is not feasible to risk re-injury through re-challenge with gefitinib in most patients with advanced NSCLC who have had such pneumonia, the diagnosis of interstitial pneumonia in our series was based on the following factors: clinical presentation; characteristic findings on CT scan; exclusion of infectious disease and fluid overload; and the prompt resolution of symptoms and imaging findings after gefitinib discontinuation. Gefitinib-related interstitial pneumonia was clinically diagnosed in 4 patients in our series. The time from starting gefitinib to the occurrence of interstitial pneumonia ranged from 2 weeks to 4 months. All patients were treated by gefitinib withdrawal and the concomitant administration of methylprednisolone 16 mg/day. The glucocorticosteroid dosage was tapered progressively according to clinical status, all patients recovered from interstitial pneumonia, and no related deaths were noted.

Interestingly, the occurrence of interstitial pneumonia was irrespective of tumor response. When interstitial pneumonia occurred, 1 patient had a partial response, 2 had stable disease, and 1 had progressive disease. The most common adverse events in our series⁵ were similar to those reported previously. However, the incidence of interstitial pneumonia (5.8%) was greater than that in reports from Western countries, but close to that reported in Japan, thus suggesting ethnic differences that warrant further investigation.

Generally, gefitinib is well tolerated, and most drug-related adverse events are mild to moderate and manageable. Nonetheless, our observations suggest that gefitinib-related interstitial pneumonia is not rare, at least in certain races and regions. Mortality from such pneumonia in gefitinib-treated patients with NSCLC can be prevented by early recognition of new-onset respiratory symptoms and prompt radiographic examination, and by stopping gefitinib but starting glucocorticosteroid therapy whenever pulmonary toxicity is highly suspected.

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