Sudden Onset of Interstitial Lung Disease Induced by Gefitinib in a Lung Cancer Patient with Multiple Drug Allergy

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Abstract. Gefitinib is an oral selective inhibitor of the epidermal growth factor receptor tyrosine kinase which is effective for patients with advanced non-small cell lung cancer. A 75-year-old man with advanced adenocarcinoma of the lung was treated with gefitinib. He had a history of allergy to several antibiotics and Welder's lung. Two days after initiation, he developed acute interstitial lung disease (ILD) and died of respiratory failure due to progression of ILD. Critical assessment pointed to gefitinib as the likely cause of this complication. This is the first report of rapid gefitinib-induced ILD. This case should alert physicians to the potential for dangerous pulmonary side-effects of gefitinib therapy, especially in patients with drug allergy.

Gefitinib (Iressa; ZD1839, AstraZeneca) is a member of a new class of oral drugs that selectively inhibit receptor tyrosine kinases including epidermal growth factor; however, the precise anticancer mechanism of action has not been established (1). Recent studies showed that gefitinib was effective for patients with advanced non-small cell lung cancer who did not respond to platinum-based chemotherapy (2-6). Gefitinib is now being used as second- or third-line chemotherapy for this disease worldwide. Common adverse events associated with gefitinib include diarrhea, skin rash, acne, dry skin, nausea and vomiting. Oral anticancer agents are generally considered to be safer than other agents and are tolerated better by patients with poor performance status or organ failure who cannot be treated with standard cytotoxic chemotherapy. Gefitinib is regarded as a safe agent. However, several cases of interstitial lung disease (ILD) associated with gefitinib have been reported recently (7, 8).

We describe a patient with adenocarcinoma of the lung who developed acute ILD only 2 days after exposure to gefitinib. Critical assessment implicated gefitinib as the likely cause of this complication.

Case Report

A 75-year-old Japanese man was admitted to our institution for treatment of relapse of adenocarcinoma of the lung. He underwent partial resection of the left upper lobe for a T1N0M0 adenocarcinoma of the lung in May 2002. He had a 14-pack-year history of cigarette smoking and had quit 28 years previously. He had been an ironworker for 19 years and had had a history of Welder's lung for 38 years.

Pulmonary function tests revealed forced expiratory volume in 1 second (FEV1.0), FEV1.0%, vital capacity (VC) and %VC to be 1.4 L, 68%, 2.19 L and 70%, respectively. Arterial blood gas analysis revealed pH 7.42, PaO2 73 mm Hg, and PaCO2 46 mm Hg on admission. He had a history of allergy to cephem-antibiotics and minocycline.

After the diagnosis of relapse, he received supportive care for 8 months. His disease progressed gradually, and he developed malignant pleural and abdominal effusions. Gefitinib (250 mg/day) was then started. One day later he complained of slight chest discomfort and the next day he suddenly developed dyspnea. His temperature was 35.2°C, pulse 92/min, systolic blood pressure 154 mm Hg, respiratory rate 24/min, and oxygen saturation (SaO2) 80% in room air. Arterial blood gas analysis revealed pH 7.42, PaO2 73 mm Hg, and PaCO2 46 mm Hg on admission. He had a history of allergy to cephem-antibiotics and minocycline.

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Arterial blood gas analysis showed pH was 7.35, PaO2 52 mm Hg and PCO2 48 mm Hg. Fine crackles were audible in the right lung. The white blood cell count was 9890/mm³ with 77% neutrophils and 12% lymphocytes. Serum C-reactive protein, lactate dehydrogenase and KL-6 were 23 mg/dl, 544 U/l and 4996 U/ml, respectively. The chest radiograph showed diffuse shadows in the right upper lung field and patchy shadows in the middle and lower lung fields. Computed tomography (CT) of the chest demonstrated ground-glass...
opacities in the right upper lung field (Figure 1). Therefore, we determined that he had gefitinib-induced ILD.

Immediately, methylpredonisolone (1 g/day) and icepamycin sulfate were administered. However, his symptoms and the interstitial shadows on the chest radiograph did not improve. He died 20 days later of respiratory failure due to progressive ILD. Autopsy was done. Histopathology in the lung (Figure 2) showed diffuse alveolar damage (DAD), with hyaline membranes, desquamation or regeneration of alveolar epithelia, macrophage accumulation in the alveolar space, and organization of exudates involving the alveolar walls. Although multiple foci of metastatic cancer cells were distributed through the specimen, the activity of the DAD lesion was not related to the presence of metastatic cells. There were no pathogenic organisms: fungi, mycoplasma, Pneumocystis carinii or cytomegalovirus. The findings were considered most consistent with drug-induced ILD.

Figure 1. Computed tomography of the chest on admission (A) and 3 days after starting gefitinib (B).
Discussion

Accumulating evidence has demonstrated that gefitinib can induce severe ILD (7, 8). According to a detailed analysis of the drug safety database that included 50,005 patients (including 18,960 from in Japan), a total of 408 cases of ILD were identified (9). Worldwide, the incidence of ILD associated with gefitinib treatment was about 1% (2% in the Japanese experience and 0.3% in approximately 23,000 patients treated in the United States). In randomized studies of gefitinib combined with chemotherapy, the ILD rate was about 1%, and the rate was similar in gefitinib and control (chemotherapy plus placebo) arms (10, 11).

The median time to onset of ILD was 24 days in Japan and 42 days in the United States. Inoue et al. reported a median time to onset of ILD of 50 days (4 to 119 days) (7). The present patient developed acute ILD only 2 days after exposure to gefitinib. Although the patient had a history of allergy to antibiotics, no other drug was started during this period. We believe that our case of ILD was related to gefitinib, since extensive investigation disclosed no convincing alternative explanation. We speculate that the sudden onset of ILD may be attributed to his history of drug allergy. Risk factors for ILD associated with gefitinib are male gender, squamous cell carcinoma, idiopathic pulmonary fibrosis, performance status, smoking history and absence of gemcitabine treatment. There has been no mention of an association with allergy to other drugs. Further studies verifying this point are needed.

In conclusion, we report a case of advanced lung cancer developing gefitinib-induced, acute fatal ILD. Physicians should be alert to this possibly life-threatening adverse effect of gefitinib which can occur rapidly after gefitinib is started, especially in patients with a history of drug allergy.

References


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