

Erlotinib-associated Near-fatal Interstitial Pneumonitis in A Patient with Relapsed Lung Adenocarcinoma

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Erlotinib (Tarceva[®]) is a human epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor used for treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen. Interstitial lung disease, associated with gefitinib (Iressa[®]) use, has been reported in approximately 1% of patients worldwide. However, the adverse pulmonary effects of erlotinib remain poorly documented. Reviewed English language publications in MEDLINE and PubMed suggest that this report is to be the first case report in English of a histologically-confirmed case of near-fatal interstitial pneumonitis with acute lung injury, associated with erlotinib, in East Asian patients. Physicians are hereby encouraged to promptly evaluate new or worsening pulmonary symptoms so that they can detect early radiographic signs of pulmonary toxicity in patients on erlotinib. If toxicity is confirmed, erlotinib should be discontinued and the patient treated appropriately. The case presented suggests that the outcome of erlotinib-associated pulmonary toxicity with acute respiratory failure may be favorable with adequate early management. (*Chang Gung Med J 2010;33:100-5*)

Key words: erlotinib, EGFR, lung cancer, interstitial pneumonitis, East Asia

Erlotinib (Tarceva[®]; OSI Pharmaceuticals, Inc.; and Genentech, Inc.) is a reversible and highly specific inhibitor of human epidermal growth factor receptor type-1/epidermal growth factor receptor (HER1/EGFR) tyrosine kinase.^(1,2) Initial clinical safety and efficacy studies showed erlotinib as improving the survival rate in patients treated for non-small-cell-lung cancer (NSCLC) and improving tumor-related symptoms and quality of life in advanced NSCLC patients as a second or third-line treatment.^(3,4)

Interstitial lung disease (ILD) has been observed in patients receiving gefitinib (Iressa[®]). The global incidence is about 1% (2% in the Japanese post-mar-

keting experience and about 0.3% in a U.S. expanded access program); approximately one-third of these cases were fatal.⁽⁵⁾ In a small prospective study of gefitinib for advanced NSCLC in Taiwan, 69 patients were evaluated for toxicity; 4 cases (5.8%) of gefitinib-related interstitial pneumonia were diagnosed.⁽⁶⁾ The most common adverse reactions were diarrhea and rash.⁽¹⁾ However, the propensity of erlotinib-associated pulmonary toxicity is not well documented. We report a histologically-confirmed case of near-fatal interstitial pneumonitis, with acute lung injury, associated with oral erlotinib, taken for relapsed lung adenocarcinoma.

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CASE REPORT

The subject was a 53-year-old male smoker with a history of left lingular lobe adenocarcinoma with left lower lobe metastasis (T4N2M1, stage IV), diagnosed in January 2006 in Chang Gung Memorial Hospital in Linkou, a tertiary center in Northern Taiwan. The patient reported three weeks of chronic cough, chest tightness and progressive exertional dyspnea. He had received two successive regimens of clinical trial chemotherapy for lung adenocarcinoma: cisplatin/gemcitabine plus bevacizumab (Avastin®; Genentech Inc.), an anti-vascular endothelial growth factor monoclonal antibody (March to July, 2006) and sequential bevacizumab monotherapy (August to December, 2006). The response to chemotherapy was adequate and resulted in the diagnosis being downgraded to T2N0M1 in December. He then received surgery, including a lobectomy of the left upper lobe, wedge resection of the left lower lobe mass, and mediastinal & thoracic lymph node dissections, the following January. He received subsequent adjuvant docetaxel from April to June, 2007.

Brain metastasis in the left frontal lobe was noted in July and irradiated with intensity-modulated radiotherapy (IMRT) via 5 angled fields to 3500 cGy in 14 fractions. He started erlotinib (150 mg daily) on August 1, 2007.

Three weeks later, while on erlotinib, a clinical examination revealed severe facial exanthema, a common side effect of erlotinib. The dose was decreased to 150 mg on alternate days. Three days later, the patient was admitted to the emergency room after two days of cough, fever, malaise and general soreness. His temperature was 39°C, with a blood pressure of 163/86 mmHg and a pulse of 121. He was tachypnoeic (22 breaths/min). The cardiovascular evaluation was normal, with no evidence of significant jugular venous distension or peripheral oedema. The chest examination revealed bibasilar inspiratory crackles. The leukocyte count was $10.7 \times 1000/uL$ (80.2% neutrophils). Empiric oxacillin was given out of consideration for possible facial skin infection. However, progressive dyspnea with hypoxemia developed on August 25; chest radiography revealed extensive bilateral infiltration. Piperacillin-tazobactam was prescribed thereafter.

On August 26, the arterial blood gas under a non-rebreathing mask O₂ supply (FiO₂ = 100%) was: pH: 7.156, PaO₂: 55.3 mmHg, PaCO₂: 66.4 mmHg, and SaO₂: 79%. Acute respiratory failure required emergent intubation w/mechanical ventilation.

After ICU admission, a CT scan of the chest revealed new, extensive bilateral ground-glass opacities and alveolar airspace densities (Fig. 1). Pulmonary toxicity, associated with erlotinib, was strongly suspected. Erlotinib was discontinued immediately and the patient began intravenous corticosteroids. Transbronchial lung biopsy revealed acute lung injury features, such as hyaline membranes lining the alveolar surfaces (Fig. 2). Bronchoalveolar lavage for cultures and stains, including bacteria, mycobacteria, fungi, pneumocystis, legionella and viruses, were all negative. Autoimmune diseases were also ruled out. After 11 days of ICU care and intravenous corticosteroids with mechanical ventilation, the patient was extubated on September 5th and downgraded to standard care the following day. He received oral prednisolone, supplemental O₂ therapy and pulmonary rehabilitation. Sequential high-resolution CT revealed improved ground-glass opacities and alveolar airspace densities. He was discharged on October 31, 2007 and received a follow-up as an outpatient.

DISCUSSION

Erlotinib (Tarceva) received FDA approval in 2004 as a monotherapy for locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Erlotinib is considered a promising oral target agent with a favorable safety profile. In the FDA Drug Approval Summary, cases of ILD have been observed in patients receiving erlotinib at an overall incidence of approximately 0.8%, which is similar to the placebo incidence.⁽¹⁾ Nevertheless, the pathogenesis of erlotinib-associated pulmonary toxicity is not well documented, especially in East Asian patients. After the MEDLINE and PubMed review, we deemed this the first individual case report in the English literature of a histologically-confirmed case of near-fatal interstitial pneumonitis with acute lung injury, associated with erlotinib, in East Asian patients.

The introduction of EGFR-tyrosine kinase inhibitors in the treatment of advanced NSCLC led

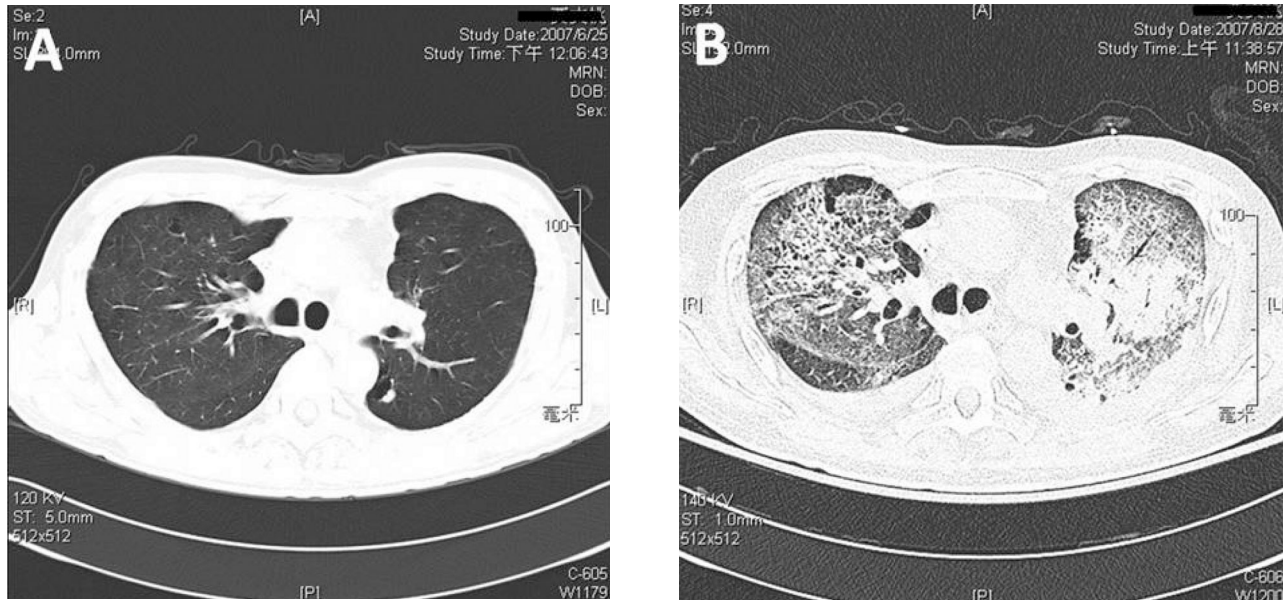


Fig. 1 (A) Computed tomography (CT) scan of the chest before erlotinib therapy. CT scan through the carina level, demonstrating normal lung parenchyma. (B) After three weeks of erlotinib therapy. CT scan through a similar lung section, two months later, demonstrating extensive ground-glass and airspace densities.

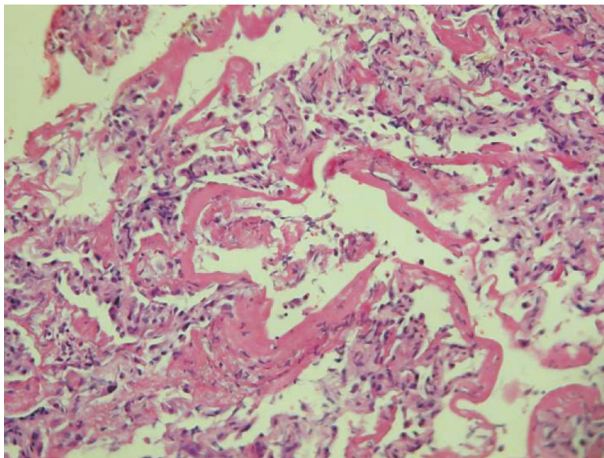


Fig. 2 Lung tissue showing histological features of acute lung injury (interstitial edema, prominent type-II pneumocyte hyperplasia and hyaline membranes lining the alveolar surfaces) (Hematoxylin & Eosin stain, 200X).

to great enthusiasm among chest oncologists in East Asia, since ethnic Asian patients receive significant survival benefits with gefitinib when compared to the placebo.⁽⁷⁾ A high frequency of EGFR mutations, with complex patterns, may play an important role in this phenomenon.⁽⁸⁾ However, the incidence of con-

comitant gefitinib-associated interstitial lung disease appears higher among Orientals than Caucasians, though the reasons for this are not clear.^(5,6) Drug-associated interstitial lung disease diagnosis depends on typical radiological features and the exclusion of other potential causes.⁽⁹⁾ Common histopathological studies of EGFR-tyrosine kinase inhibitor-induced interstitial lung disease have revealed diffuse alveolar damage with alveolar edema, pneumocyte hyperplasia, fibrin accumulation, and hyaline membrane formation; all of these are often seen in patients with acute interstitial pneumonitis, acute respiratory distress syndrome (ARDS) and drug-related pulmonary toxicity.^(10,11) In this case, the radiological signs of pulmonary toxicity (extensive ground-glass and airspace densities) were apparent within the first two months of erlotinib treatment, which corresponds with previous reports.^(10,12-14) Lung tissue showed histological features of acute lung injury (interstitial edema, prominent type-II pneumocyte hyperplasia and hyaline membranes lining the alveolar surfaces) compatible with acute interstitial pneumonitis.

Although respiratory viruses have been implicated in the case of pneumonia, infection of cytomegalovirus (CMV) was excluded for this patient by bronchoalveolar lavage. Intranuclear

inclusions and multinucleated giant cells were absent from the transbronchial lung biopsy tissue of this patient. In adults, influenza virus A and B, adenoviruses, parainfluenza viruses, and respiratory syncytial virus (RSV) are the major causes of pneumonia. The annual prevalence shows a seasonal pattern and most cases occur in the winter months. However, this patient suffered acute lung injury in the summer months of 2007. Influenza A was by far the most common viral etiology. Nevertheless, the progression of the influenza A infection from severe community-acquired pneumonia to sepsis and/or septic shock to ARDS is a rare event, in contrast to the human cases of avian influenza virus infection (H5N1) and coronavirus.⁽¹⁵⁾ Worth noting is that no cases of avian influenza or coronavirus reported in Taiwan in 2007. In addition, RSV pneumonia is reported less often in adults than in children and varicella infections are characterized by an accompanying rash. In the presented case it appears less likely that viral pneumonia had occurred.

The mechanism by which erlotinib causes ILD still remains relatively unknown. As for gefitinib, The West Japan Thoracic Oncology Group (WJTOG) conducted a retrospective survey of the prevalence of and risk factors for gefitinib-induced ILD in Japanese patients. They found that gefitinib-induced ILD to be significantly associated with sex (male), smoking history (both of which were the case in our subject) and concomitant interstitial pneumonia.⁽¹⁶⁾ Pre-existing interstitial pneumonia has been reported to contribute to pulmonary toxicity secondary to erlotinib.⁽¹⁰⁾ However, this risk factor was not present in our case. Other potential causes (congestive heart failure, pulmonary infection, prior thoracic radiotherapy or lymphangitic carcinomatosis) were also absent. It should be noted that erlotinib patients have typically received previous treatments with various anti-neoplastic agents. Prior chemotherapy has been reported as a predisposition to gefitinib-related ILD.⁽¹¹⁾ Even for patients who have previously tolerated gefitinib, ILD subsequent to erlotinib has been reported.⁽¹⁴⁾ Prior chemotherapy with gemcitabine/cisplatin, bevacizumab, and docetaxel has been administered on patients and interstitial pneumonitis had been described for gemcitabine⁽¹⁷⁾ and docetaxel.⁽¹⁸⁾ The possible erlotinib induction of interstitial pneumonitis, by a mechanism related to its properties or contribution to pulmonary toxicity, had been

induced by the prior chemotherapy.

Erlotinib may therefore either cause or contribute significantly to near-fatal interstitial pneumonitis, although infrequently. For lung cancer patients on erlotinib in East Asia, this drug should be considered among the antineoplastic agents that can cause or contribute to pulmonary toxicity. Physicians should promptly evaluate new or worsening pulmonary symptoms and detect early radiographic signs of pulmonary toxicity in these patients; erlotinib should be immediately suspended pending evaluation. Empiric corticosteroids could be administered until erlotinib-associated pulmonary toxicity can be ruled out. Our case suggests that the outcome of erlotinib-associated pulmonary toxicity, with acute respiratory failure, may be favorable if timely managed.

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復發肺腺癌病患使用 Erlotinib 併發瀕死性間質性肺炎

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Erlotinib (得舒緩[®]) 是一種上皮生長因子接受器的酪氨酸酶抑制劑，用於治療先前一線以上化學治療失敗的局部晚期或轉移性非小細胞肺癌。全世界使用 gefitinib (艾瑞莎[®]) 的病人中，約有 1% 的病例被報導曾發生間質性肺病。然而，erlotinib 肺部方面的副作用尚未有完整的報告。在瀏覽過 MEDLINE 與 PubMed 上的英文文獻後，我們相信此篇使用 erlotinib 而併發瀕死性間質性肺炎合併急性肺損傷的病例報告，應是東亞第一篇以英語發表並有病理組織切片確定診斷的病例。臨床醫師對於使用 erlotinib 的病人，若肺部出現新的或惡化的症狀，應該立即評估，如此才能及早偵測出肺病變的放射學徵兆。若肺病變一經確診，erlotinib 就應停止使用，同時給予適當治療。此病例顯示，若能及早處置，則 erlotinib 所伴隨的肺病變與急性呼吸衰竭的癒後會較好。(長庚醫誌 2010;33:100-5)

關鍵詞：erlotinib，上皮生長因子接受器，肺癌，間質性肺炎，東亞