內科學誌 2006 ：17 ：22-27

Successful Gefitinib Treatment of a Case of Bronchioloalveolar Carcinoma with Respiratory Failure

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Abstract

Bronchioloalveolar carcinoma (BAC) is a form of pulmonary adenocarcinoma that presents endobronchial spread and bronchorrhea in advanced stages. The prognosis for BAC patients in advanced stages is poor because of poor response to conventional chemotherapy. Gefitinib ("Iressa") is an orally active, selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (EGFR-TKI) that blocks signal transduction pathways implicated in the proliferation and survival of cancer cells. In this paper, we report on our experience treating with Gefitinib and other life saving measures an 84-year-old man with BAC of RLL and impending respiratory failure. Our selected treatment dramatically reduced the production of serous sputum and the patient was successfully liberated from mechanical ventilation within one week of the onset of treatment. We postulate that ex-smoker who have already quit for an extended period of time (> 20 years) and display a complex papillary structure of bronchioloalveolar carcinoma in the lungs might be suitable candidates for treatment with Gefitinib. Furthermore, this treatment may even be particularly suited for difficult patient subgroups such as the elderly and those with existing serious medical conditions. (J Intern Med Taiwan 2005; 17: 22-27)

Key Words ：**Bronchioloalveolar carcinoma, Respiratory failure, Epidermal growth factor receptor, Gefitinib, Endothelial cell**

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Introduction

Bronchioloalveolar carcinoma (BAC), a variant of adenocarcinoma of the lung, grows without invasive growth in a lepidic fashion along the alveolar septae. BAC is uncommon, accounting for approximately three percent of all lung cancers[1]. The two major histologic types of BAC are nonmucinous and mucinous. While the prognosis for patients with solitary peripheral BAC is excellent, that for patients with advanced-stage BAC is poor - comparable to prognoses for patients with other non-small-cell lung cancer (NSCLC) types[2,3].

Bronchorrhea is generally a sign of advanced BAC development. Recent papers, discussing the use of indomethacin[4] and corticosteroids[5] in the treatment of BAC patients with bronchorrhea report limited effectiveness, with only a transient reduction of bronchorrhea.

Several epithelial tumors display epidermal growth factor receptor (EGFR) overexpression, with or without EGFR gene amplification, frequently associated with increased EGFR ligand production[6,7]. EGFRs have important roles to play in cell proliferation, cell survival, invasion, angiogenesis, and tumor progression.

Gefitinib is an orally active, selective EGFR-tyrosine kinase inhibitor that raises clinical antitumor activity, relieves disease-related symptoms, and improves patient quality of life. Adverse effects are mild, and include drug-related diarrhea, dry skin, and acne.

In this paper, we report on a case involving a patient with BAC with impending respiratory failure who was treated successfully with Gefitinib. Within one week of beginning the Gefitinib treatment, the bronchorrhea had been reduced dramatically and the patient was successfully extubated.

Case Report

An 84-year-old retired construction worker admitted into this hospital checked in at our clinic after experiencing a productive cough with watery sputum for several days. He had no obvious body weight loss and was afebrile. He reported having been a heavy smoker (1-2 packs per day) for 40 years until he quit smoking twenty years ago. A chest radiograph revealed diffuse infiltrates over his right lower lung field (Figure 1). Pneumonia was considered and empiric antiobiotics with Ceftriaxone 500 mg Q12H and Clindamycin 600 mg Q6H was administered. Two days later, progressive dyspnea was noted and the use of accessory muscles was also noted. The arterial blood gas (ABG) showed pH 7.392, PCO_2 54.2 mmHg, PO_2 59.9 mmHg, HCO_3^- 32.2 mEq, SaO_2 90.4%, $AaDO_2$ 241.1 mmHg under FiO_2 50%. Elective endotracheal intubation and mechanical ventilation due to impending mixed type oxygenation and ventilatory respiratory failure were performed. Then, the follow-up ABG revealed pH 7.423, PCO2 49.6 mmHg, PO_2 154.1 mmHg, HCO_3^- 31.7 mEq, SaO_2 99%, $AaDO_2$ 224.6 mmHg in FiO_2 100%. A bacteria

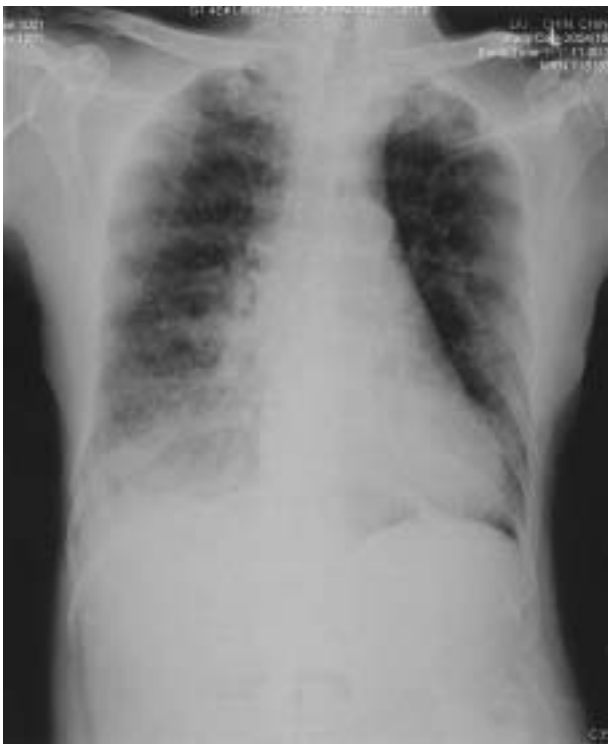

Fig.1.Before treatment with Gefitinib, the chest radiography revealed diffuse infiltrates over right lower lung field.

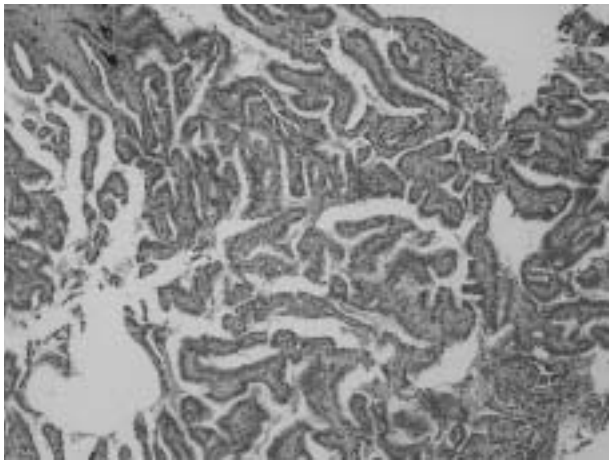

Fig.2.Histology of the lung tissue shows the presence of complex papillary structures and intricate fibrovascular septa lined by atypical columnar epithelium (H & E, X100).

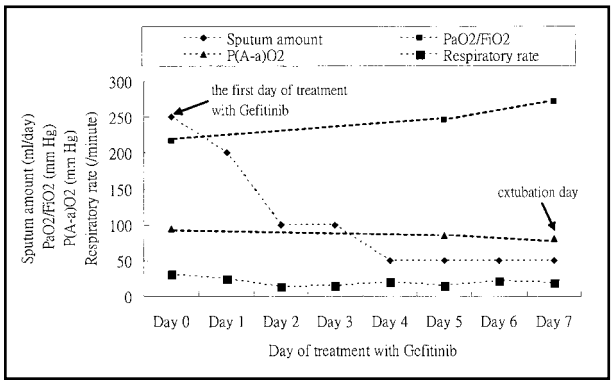

Fig.3.The diagram shows the treatment course and the daily sputum amount: That the amount of sputum decreased gradually after treated with Gefitinib and liberation from mechanical ventilation within one week was successful.

analysis of the patient's sputum culture showed *Acinetobacter baumanni* and *Staphylococcus aureus.* Therefore, antibiotics were switched to Teicoplanin 200 mg QD and Ciprofloxacin 400 mg Q12H according to sensitivity test. Because his condition did not improve, we performed a bronchoscopy that revealed a moderate amount of whitish and copious sputum on bilateral bronchial trees. A pathology of the transbronchial lung biopsy from the patient's right lower lobe (RLL) revealed a nonmucinous bronchioloalveolar carcinoma with complex papillary structure (Figure 2). He agreed to receive Gefitinib 250 mg QD. Within one week of treatment, the bronchorrhea began to decrease and extubation was successfully performed (Figure 3). Chest X-ray film showed the infiltrates on the right lower lung field to be almost completely resolved (Figure 4). He was discharged from the hospital and received regular follow-ups in the outpatient department.

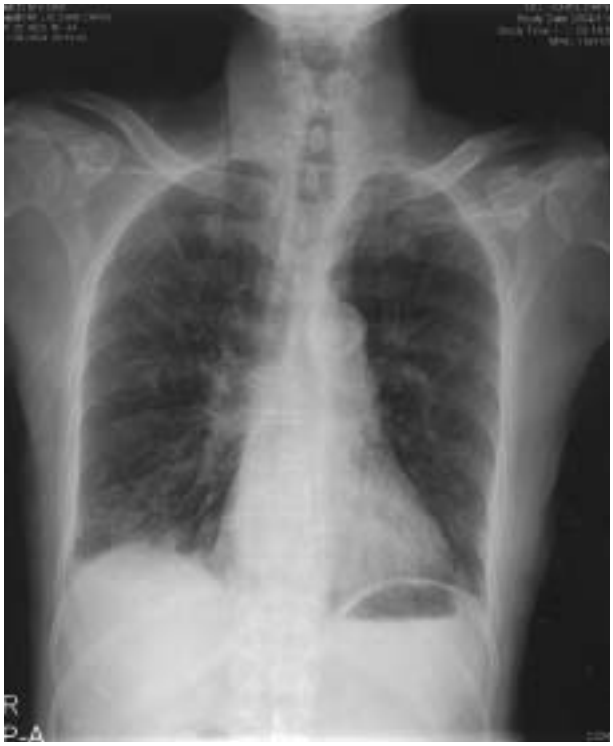

Fig.4.After treatment with Gefitinib for one week, the chest radiography revealed that the infiltrates on right lower lung field were almost completely resolved.

Discussion

A BAC patient with respiratory failure and bronchorrhea was treated with the EGFR-TKI Gefitinib (250 mg/day). The treatment resulted in a rapid reduction of bronchorrhea, improved dyspnea, hypoxia, and radiographic abnormalities, and lead to successful extubation.

The EGF-EGFR system plays a role in the production of goblet cells and in the synthesis of mucin and surfactant phospholipids in airways[8]. Blockade of the EGFR system by EGFR tyrosine kinase inhibitors and antisense inhibition of EGFR transduction have been shown to prevent goblet cell produc-

tion of mucin and decrease surfactant protein A expression [9]. Our patient's sputum volume decreased from 250 ml/day to 50 ml/day following Gefitinib treatment. Gefitinib was the only drug used during the treatment period. It is possible that Gefitinib effected a reduction in our patient's bronchorrhea by inhibiting the EGFR signal for secretion. In 2003, Yano[10] and Chang[11] reported about BAC patients with respiratory failure and bronchorrhea, and they all treated with the Gefitinib. The treatment resulted in rapid reduction of bronchorrhea, hypoxia, and radiographic abnormalities within one week to two weeks.

Severe bronchorrhea may cause intrapulmonary shunting and refractory hypoxia. These are conditions typically observed in patients with advanced BAC [3], caused by the filling of alveoli with malignant cells and mucus and leading to ventilation-perfusion mismatch and shunting. Our patient required endotracheal intubation with ventilator support because of impending respiratory failure and complications from bronchorrhea. Bronchorrhea began to decrease and oxygenation improved immediately after beginning treatment with Gefitinib, allowing mechanical ventilation to be removed within one week.

Endothelial cells from several neoplasms have been demonstrated to express EGFR. The EGFR system plays a key role in the angiogenic response to EGF/TGF α. In Hirata et al's study[12], Gefinitib inhibits EGF-induced angiogenesis by blockade of EGF/TGF α-EGFR signaling. The EGF-induced angiogenic factors, vascular endothelial growth factor (VEGF) and interlukine-8, was markedly blocked by Gefinitib. The study reveals that Gefinitib has antiangiogenic activity in vitro and in vivo. The cardiomegaly and congested pulmonary vessels (Fig. 1) improved in the following film (Fig. 4) within one week. Therefore, the role of antiangiogenic activity of Gefinitib in the clinical improvement of this patient is not known but can't be excluded.

Treatment of non-small-cell lung cancers in elderly patients is a challenge in clinical practice because this patient group is not eligible for aggressive therapies due to the age-related reductions in the functional reserves of many organs as well as the presence of comorbidities. Gefitinib is an orally administered, synthetic anilinoquinazoline that inhibits the EGFR tyrosine kinase and blocks signal transduction pathways implicated in the survival and proliferation of cancers. In Cappuzzo et al's[13] evaluation of response rates and safety factors for Gefitinib in elderly non-small-cell lung cancers patients, Gefitinib was shown to achieve an overall disease control rate of 50%. The study indicates that Gefitinib is safe and well tolerated in elderly patients with pretreated non-small-cell lung cancers and that this drug is a valid option in the management of this difficult subgroup of patients. Miller et al[14] correlated the response rate to Gefitinib of different bronchioloalveolar pathologic subtypes with smoking history in 139 patients with advanced non-small-cell lung cancers. It revealed that the presence of adenocarcinoma with any bronchioloalveolar features and never having been a smoker were independent response predictors. This study suggests that individuals in whom Gefitinib is efficacious are more likely to have adenocarcinomas of the bronchioloalveolar subtype and to have never been smokers. Our patient, a former smoker (albeit a non-smoker for the past two decades) presented with impending respiratory failure, responded excellently to treatment with Gefitinib. He experienced improvements in disease-related symptoms, radiographic tumor regressions, and recuperation from a life-threatening critical condition. Whether ex-smokers who have already quit for an extended period of time and display a complex papillary structure of bronchioloalveolar carcinoma in the lungs might be suitable candidates for treatment with Gefitinib or not, deserve further observation. This treatment may even be suitable for difficult patient subgroups such as the elderly and those with serious medical conditions. However, these hypotheses merit further study.

In summary, we found that bronchioloalveolar

carcinoma responds to the EGFR-tyrosine kinase inhibitor Gefitinib. This molecular-targeted drug may improve prognoses for patients suffering from advanced bronchioloalveolar carcinoma. Gefitinib is safe and well tolerated in pretreated unfavorable elderly BAC patients.

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Gefitinib 成功治療細支氣管肺泡肺癌併呼吸衰竭病人

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摘 要

細支氣管肺泡肺癌是肺癌的一種，在末期常以由支氣管擴散以及支氣管漏 (bronchorrhea) 來表現。細支氣管肺泡肺癌末期患者對傳統化學治療反應差而且預後差。Gefinitib ("Iressa") 是一種口服、具活性、具選擇性之上皮生長因子受體酥胺酸(tyrosine) 激酶抑制劑，可以阻斷癌細胞增殖以及存活的訊號傳遞路徑。我們在此報告一84 歲男性，臨床上以右下肺葉浸潤，抗生素使用無效而併呼吸衰竭，經支氣管鏡肺生檢確診爲細支氣管肺泡肺癌，後以Gefitinib 合併其他治療的經驗。我們給予的治療，明顯地減少漿液狀痰液的量以及使患者在治療一週之後成功地脫離呼吸器。文獻上有研究顯示細支氣管肺泡肺癌從未吸菸者是對此藥有反應獨立因子，我們經此例經驗推論：戒菸超過20 年以上併有複合乳突狀結構之細支氣管肺泡肺癌患者，亦適於以Gefitinib 治療，而勿放棄有可能改善的機會。另外，此一治療方法對於老年人以及併有嚴重內科疾病患者特別合適。