Lung Adenocarcinoma with Good Response to Erlotinib after Gefitinib Treatment Failure and Acquired T790M Mutation

To the Editor:

Epidermal growth factor tyrosine kinase inhibitors (EGFR TKIs) are useful in treating advanced non-small cell lung cancer. So far, it remains unclear whether EGFR-TKIs, namely gefitinib and erlotinib, share cross-resistance, which, after failure of one drug, excludes the use of the other one. Here, we report a 72-year-old woman, never smoker, who suffered from dry cough for 3 months. In November 2004, the chest computed tomography (CT) revealed left-side pleural effusion, nodules at left upper lobe, and left lower lobe (Figure 1A). Both cytology and cell block of the pleural fluid showed adenocarcinoma with positive stain of thyroid transcription factor-1. Epidermal growth factor receptor (EGFR) sequencing showed L858R mutation. Gefitinib was prescribed as the first-line treatment for the stage IV NSCLC. A chest CT performed 3 months later showed partial response. However, a follow-up chest CT after another 3 months showed massive left pleural effusion and progression of the tumors (Figure 1B). The EGFR sequencing from the pleural fluid, in June 2005, showed acquired T790M mutation in addition to the original L858R mutation. Because of acquired resistance to gefitinib, she received pleurodesis and systemic chemotherapies, including gemcitabine, vinorelbine, and pemetrexed. A chest CT in June 2006 disclosed disease progression with accumulating left loculated pleural effusion (Figure 1C). A repeated EGFR mutation analysis of the pleural effusion still showed L858R plus T790M. Erlotinib was given as the fifth-line treatment from July 2006. The tumors shrunk, and a partial response was achieved (Figure 1D). The duration of response to erlotinib lasted for 8 months before progression.

Although both the reversible EGFR TKIs share the same mechanism of drug sensitivity, erlotinib seems to achieve more survival benefit than gefitinib. After a certain period of erlotinib or gefitinib therapy, acquired resistance almost inevitably developed, sometimes from a secondary EGFR T790M mutation. Tumors with T790M mutation usually become highly resistant to gefitinib or erlotinib. Yet, it is still inconclusive whether cross-resistance is shared between these two drugs. Viswanathan et al. reported five patients with advanced NSCLC failed to respond to erlotinib after progression on gefitinib. Cho et al. showed that patients responding to erlotinib after failure of gefitinib had wild-type EGFR in tumors and had stable disease while receiving gefitinib. Chang et al. demonstrated a male nonsmoker who had in-frame deletion of exon 19. The patient had partial response to erlotinib treatment after failure of gefitinib treatment, but did not develop T790M. Our patient developed acquired T790M mutation of EGFR after 6 months treatment of gefitinib with best partial response, and still responded to erlotinib therapy. Therefore, patients with T790M EGFR mutation may still response to erlotinib after gefitinib treatment failure. The frequency of this is unknown.

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To the Editor:

The epidermal growth factor receptor (EGFR) has been validated in several preclinical studies as an important target for novel molecular targeted therapy for human carcinomas. Strategies to inhibit EGFR include the use of blocking antibodies and small-molecule tyrosine kinase inhibitors. Gefitinib was approved in the USA by the US Food and Drug Administration in May 2003 for the treatment of advanced non-small-cell lung cancer. In patients previously treated with chemotherapy. However, a large phase III randomized clinical trial did not find a significant benefit from gefitinib, when compared with placebo, whereas other reports have described an association between clinical response to gefitinib and activating mutations of the EGFR kinase domain.2,3

Han et al.4 performed an analysis of EGFR mutation in a large series of NSCLC cases reporting EGFR mutations in 10% of the 375 adenocarcinomas, but none in the 454 squamous-cell carcinomas examined; 26% of 86 bronchioloalveolar carcinomas (BAC) and 6% of 289 conventional adenocarcinomas harbored EGFR mutations. Two independent groups have provided evidence of significantly increased survival of NSCLC patients with mutated EGFR in response to gefitinib.5,6

Here, we report the case of a 48-year-old man, nonsmoker with metastatic BAC of the lung that responded to gefitinib. BAC of the right lung was diagnosed in May 2003. After radical pneumonectomy and hilar and mediastinum nodes excision (pT4N2M0), the patient was treated with four courses of adjuvant chemotherapy with cisplatin-gemcitabine.

One year later, the patient developed cough, bronchorrea, and dyspnea. A total body computed tomography (CT) scan showed a contralateral diffuse relapse of disease, with ground glass lesions in the entire left lung. Sputum cytology confirmed BAC cells. The patient was treated with two courses of cisplatin-gemcitabine. In May 2005, he presented a serious dyspnea requiring permanent O2-delivery and a CT of the chest showed disease progression (Figure 1A). ECOG performance status was 4. On the basis of the histologic diagnosis, nonsmoker, chemotherapy-refractory disease, we decided to start treatment with gefitinib (Iressa, Astra Zeneca, Pharmaceuticals, Wilmington, DE) 250 mg/os/daily. The patient’s respiratory status and general condition improved over a few days, and a CT scan showed a partial remission with minimal residual disease and ground glass areas still scattered in the pulmonary parenchyma. In September 2006, a new CT scan (Figure 1B) demonstrated a complete remission, which is still long-lasting. In

Long-Lasting Complete Remission with Tyrosine Kinase Inhibitor in Bronchioloalveolar Carcinoma with a so far Unknown EGFR Mutation

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