Thoracic Cancer ISSN 1759-7706

CASE REPORT

Clinically beneficial continued treatment with gefitinib after asymptomatic progression of lung adenocarcinoma

Hayoung Choi, Jinsun Chang, Hong-Joon Shin, Cheol-Kyu Park, In-Jae Oh, Kyu-Sik Kim & Young-Chul Kim

Chonnam National University Hwasun Hospital and Chonnam National University Medical School, Hwasungun, South Korea

Keywords
Epidermal growth factor receptor; gefitinib; non-small cell lung carcinoma.

Correspondence
Young-Chul Kim, Lung and Esophageal Cancer Clinic, Chonnam National University Hwasun Hospital, 322, Seoyang-ro, Hwasun, Jeonnam 519-809, South Korea.
Tel: +82 61 379 7614
Fax: +82 61 379 7619
Email: kyc0923@jnu.ac.kr

Received: 15 August 2014;
Accepted: 24 August 2014.

doi: 10.1111/1759-7714.12171

Thoracic Cancer **6** (2015) 224–226

Abstract

We report a case showing the long-term clinical benefit of the continued use of gefitinib in a patient with asymptomatic progression of lung adenocarcinoma harboring an exon 19 deletion of the epidermal growth factor receptor gene. Although follow-up studies showed smoldering progression of metastatic lesions, continued treatment with gefitinib controlled pulmonary adenocarcinoma for more than six years.

Introduction

The use of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) has improved response rates and progression-free survival (PFS) in non-small cell lung cancer (NSCLC) patients.[1–5] However, despite favorable outcomes with EGFR-TKIs, such as gefitinib and erlotinib, NSCLC eventually progresses via a number of resistance mechanisms.[6] Currently, besides enrolling in a clinical trial, few treatment options are available after the development of acquired resistance (AR).[7] Thus, in contrast to cytotoxic chemotherapy, the use of EGFR-TKIs is recommended even after disease progression.[8]

Case presentation

In March 2005, a 67-year-old Korean woman visited a hospital with a two-month history of coughing. The patient was on antihypertensive treatment and had received treatment for tuberculosis one year before. She had no history of smoking; however, she might have been exposed to passive smoking while working as a washroom cleaner. A 2 cm mass was observed in the upper lobe of her left lung and transthoracic needle aspiration biopsy revealed adenocarcinoma.

The patient underwent a left upper lobectomy in March 2005 and her postoperative stage was determined as T2N0M0. After surgical resection, there was no recurrence for approximately one year. However, multiple growing nodules were detected in the remaining part of her left lung on a follow-up computed tomography (CT) scan performed in June 2006. Serial CT scans revealed that the slow, but continuously growing nodules were recurrent lung cancer.

The patient refused further surgical treatment or any invasive procedure. Therefore, first-line chemotherapy with gemcitabine and cisplatin was initiated in April 2007. Although a follow-up CT after two cycles showed stable disease (SD), administration of chemotherapy was ceased because she could not tolerate the drug toxicity.

After five months of rest, a CT revealed growing nodules; hence, second-line treatment with 250 mg/day gefitinib was started in November 2007. A partial response was shown on follow-up CT in December 2007 (Fig 1). The dose was adjusted depending on tolerability, and eventually decreased to 250 mg every third day because of grade 3 skin toxicity.

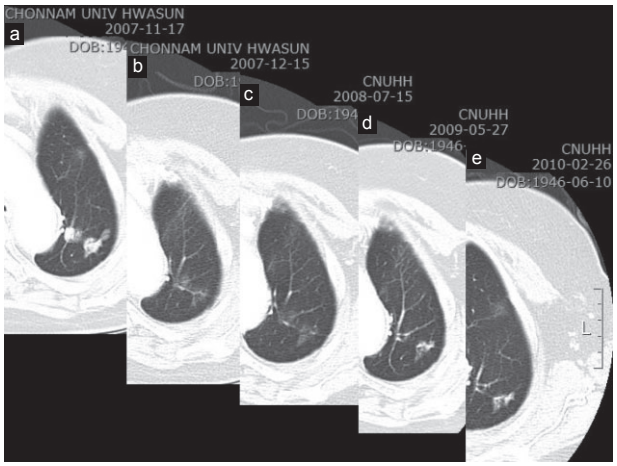

Figure 1 Computed tomography scans show: (**a**) the target nodule before gefitinib treatment; (**b**) partial response one month later; and (**c, d, e**) continued stable disease; (**c**) nine months, (**d**) 19 months, and (**e**) 28 months from baseline.

The lung nodules had started growing since May 2009. While Response Evaluation Criteria in Solid Tumors (RECIST)[9] indicated progressive disease, she did not experience any worsening of symptoms; therefore, we continued treatment with gefitinib. Although a follow-up CT showed a smoldering progression of metastatic lesions (Fig 2), continued treatment with gefitinib controlled the pulmonary adenocarcinoma for more than six years. Treatment with gefitinib was discontinued in April 2014 because she no longer received reimbursement from the health insurance review and assessment service of Korea and could not afford the cost of therapy.

Recently, peptide nucleic acid (PNA) clamping real-time polymerase chain reaction was performed using DNA extracted from paraffin block-fixed tissue acquired during surgery in 2005. PNA clamping revealed an activating mutation of the EGFR gene, an exon 19 deletion.

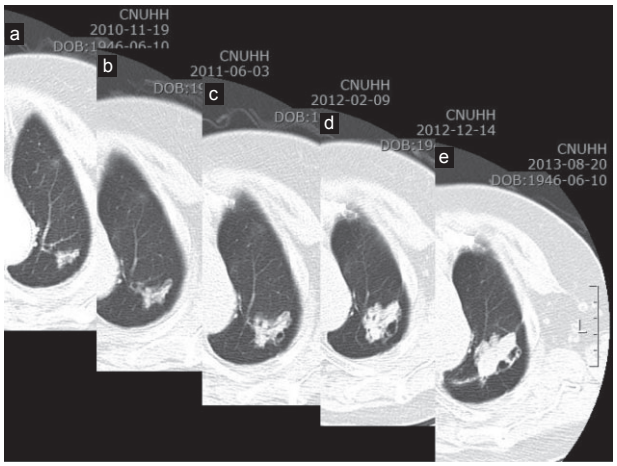

Figure 2 Follow-up computed tomography scans show smoldering progression: (**a**) 36 months; (**b**) 43 months; (**c**) 51 months; (**d**) 61 months; and (**e**) 69 months from baseline.

Discussion

EGFR inhibitors were proven superior to a cisplatin-based doublet as an initial treatment for NSCLC with sensitizing EGFR mutations in several phase III studies.[1–5] The patient in this case was an East Asian female non-smoker who had an activating EGFR mutation; therefore, she was expected to have a good response to gefitinib or erlotinib.[10,11] However, as seen in this case, initially good responders to EGFR-TKIs almost always experience AR and disease progression after approximately 12 months.[12]

Several mechanisms of AR have been reported, which could be grouped into four main categories: (i) the acquisition of secondary mutations in EGFR, such as the T790M mutation; (ii) parallel activation of downstream signaling pathways (by-pass track), such as MET amplification and hepatocyte growth factor overexpression; (iii) phenotypic transformation from NSCLC to small cell lung cancer; and (iv) genetic alteration in addition to EGFR mutation, for instance, HER2 amplification or BRAF mutation. However, up to 30% of AR mechanisms are unexplained.[13]

As most patients experiencing AR to first-line EGFR-TKI have good performance status (PS), they are expected to receive second-line treatment. The next-line of cytotoxic chemotherapy is recommended in symptomatic relapse with multiple metastases. However, National Comprehensive Cancer Network (NCCN) treatment guidelines recommend continuous use of EGFR-TKI in asymptomatic patients.[8] While discontinuation of erlotinib or gefitinib may lead to rapid disease progression, continued treatment provides a beneficial effect even after progression.[7,14,15] In symptomatic progression, different strategies are required according to the extent and site of metastasis.[8] For instance, local therapy or whole brain radiation treatment may be added for brain metastasis, whereas radiation treatment can be added for symptomatic relapse of isolated extra-cranial lesions.[16]

In daily practice, it is not uncommon for clinicians to continue EGFR-TKI therapy for asymptomatic progressive disease. To the best of our knowledge, however, reports on the long-term follow-up of such cases are limited. The patient in this case had no symptoms despite disease progression on imaging studies; therefore, we decided to continue gefitinib. We hypothesize that continued use of EGFR inhibitors prevents disease flare-up. She has had a PS of 1 and experienced tolerable toxicity with continued gefitinib treatment for more than six years. Therefore, we believe that our case reinforces the NCCN guidelines on asymptomatic NSCLC.

Beyond current treatment options, several on-going clinical trials have been conducted to overcome NSCLC

progression. Second-generation EGFR-TKIs (Afatinib, Dacomitinib), which are irreversible ErbB-family blockers, were developed to combat acquired or adaptive resistance. Although both drugs improved PFS, afatinib[17] and dacomitinib[18] failed to improve overall survival compared to the placebo after the failure of gefitinib or erlotinib. Thus, afatinib was moved to first-line treatment of NSCLC with activating EGFR mutations,[19,20] and dacomitinib is currently being studied in frontline clinical trials.

Furthermore, third-generation EGFR mutant selective inhibitors (EMSI) such as AZD9291, CO1686, and HM61713 are being investigated, and were recently presented at the 2014 Annual Meeting of the American Society of Clinical Oncology. Development of EMSIs is eagerly awaited, as they are effective in treating AR resulting fromT790M mutation, with minimal skin and mucosal toxicities.

Disclosure

None of the authors reports any conflicts of interest.

References

1 Maemondo M, Inoue A, Kobayashi K *et al*. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010; **362**: 2380–8.

2 Mitsudomi T, Morita S, Yatabe Y *et al*. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010; **11**: 121–8.

3 Mok TS, Wu YL, Thongprasert S *et al*. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; **361**: 947–57.

4 Rosell R, Carcereny E, Gervais R *et al*. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012; **13**: 239–46.

5 Zhou C, Wu YL, Chen G *et al*. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011; **12**: 735–42.

6 Kosaka T, Yatabe Y, Endoh H *et al*. Analysis of epidermal growth factor receptor gene mutation in patients with non-small cell lung cancer and acquired resistance to gefitinib. *Clin Cancer Res* 2006; **12**: 5764–9.

7 Lee JC, Jang SH, Lee KY, Kim YC. Treatment of non-small cell lung carcinoma after failure of epidermal growth factor receptor tyrosine kinase inhibitor. *Cancer Res Treat* 2013; **45**: 79–85.

8 National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology, Non-Small Cell Cancer: NCCN; 2014 [Cited 16 Sep 2014.]: Available from URL: http://www.nccn.com/patient-guidelines.html.

9 Eisenhauer EA, Therasse P, Bogaerts J *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228–47.

10 Shigematsu H, Lin L, Takahashi T *et al*. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst* 2005; **97**: 339–46.

11 Kim KS, Jeong JY, Kim YC *et al*. Predictors of the response to gefitinib in refractory non-small cell lung cancer. *Clin Cancer Res* 2005; **11**: 2244–51.

12 Cataldo VD, Gibbons DL, Pérez-Soler R, Quintás-Cardama A. Treatment of non-small-cell lung cancer with erlotinib or gefitinib. *N Engl J Med* 2011; **364**: 947–55.

13 Remon J, Moran T, Majem M *et al*. Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in EGFR-mutant non-small cell lung cancer: a new era begins. *Cancer Treat Rev* 2014; **40**: 93–101.

14 Chaft JE, Oxnard GR, Sima CS, Kris MG, Miller VA, Riely GJ. Disease flare after tyrosine kinase inhibitor discontinuation in patients with EGFR-mutant lung cancer and acquired resistance to erlotinib or gefitinib: implications for clinical trial design. *Clin Cancer Res* 2011; **17**: 6298–303.

15 Riely GJ, Kris MG, Zhao B *et al*. Prospective assessment of discontinuation and reinitiation of erlotinib or gefitinib in patients with acquired resistance to erlotinib or gefitinib followed by the addition of everolimus. *Clin Cancer Res* 2007; **13**: 5150–5.

16 Yu HA, Sima CS, Huang J *et al*. Local therapy with continued EGFR tyrosine kinase inhibitor therapy as a treatment strategy in EGFR-mutant advanced lung cancers that have developed acquired resistance to EGFR tyrosine kinase inhibitors. *J Thorac Oncol* 2013; **8**: 346–51.

17 Miller VA, Hirsh V, Cadranel J *et al*. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol* 2012; **13**: 528–38.

18 Ellis PM, Liu G, Millward M *et al*. NCIC CTG BR.26: a phase III randomized, double blind, placebo controlled trial of dacomitinib versus placebo in patients with advanced/metastatic non-small cell lung cancer (NSCLC) who received prior chemotherapy and an EGFR TKI. 2014 ASCO Annual Meeting Proceedings *J Clin Oncol* 2014; **32** (Suppl. 15): 8036.

19 Sequist LV, Yang JC, Yamamoto N *et al*. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013; **31**: 3327–34.

20 Wu YL, Zhou C, Hu CP *et al*. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol* 2014; **15**: 213–22.

