Scientific Research and Essays Vol. 5(24), pp. 3967-3971, 18 December, 2010
Available online at http://www.academicjournals.org/SRE
ISSN 1992-2248 ©2010 Academic Journals

Full Length Research Paper

Divergence phenomenon of EGFR-TKI in the treatment of non small cell lung cancer

Xia Zhang*, Chang Liu, Juan Li, Fei-xiang Song, Xin-jian Ruan and Zhi-ling Jia

Department of Oncology, Beijing Military Area General Hospital, Beijing 100007, China.

Accepted 15 November, 2010

The present study investigated the characteristic of the divergent efficacy of epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) Gefitinib in treating non small-cell lung cancer (NSCLC) and discussed the strategy. The divergent efficacy of gefitinib was analyzed in 4 NSCLC patients at Beijing Military Area General Hospital between 2006 and 2010. The divergence phenomenon may occur in gefitinib-treated NSCLC patients with bone or brain metastases. One patient with primary lung disease under control still benefited from continuing Gefitinib therapy after disease progression in metastatic bone lesion. The divergence of efficacy is a common phenomenon in Gefitinib-treated NSCLC patients. The evaluation criteria available for anti-cancer therapies may not be completely suitable for molecular targeted therapies. The underlying mechanism deserves further research to formulate the efficacy evaluation criteria and therapeutic strategy for the molecular targeted therapy.

Key words: Non small-cell lung cancer, tyrosine kinase inhibitor, divergence phenomenon, gefitinib, targeted therapy.

INTRODUCTION

Lung cancer is one of the most common malignant tumors in the world, 75 to 80% of which are Non Small-Cell Lung Cancer (NSCLC). The incidence of lung cancer is increasing year by year. In medium-sized and large cities of China, the incidence of lung cancer is now already on the top of various malignant tumors. About 70-80% of lung cancer patients are already at advanced stage when diagnosed due to lack of effective early diagnostic tool. They have lost the opportunity of radical surgical therapy. In recent years, new chemotherapy agents targeting advanced NSCLC have reached a plateau of efficacy. Molecular targeted therapy is increasingly becoming the focus of interest.

Molecular targeted therapy is to address the tumor-specific target by blocking receptor and signal transduction pathway so as to specifically inhibit the growth of tumor cells. This therapeutic approach is realized by taking advantage of the molecular biological difference between tumor and normal cells. Gefitinib is an orally effective epidermal growth factor receptor (EGFR), tyrosine kinase inhibitor (TKI). It can compete with ATP for the ATP-binding site in tyrosine kinase domain to inhibit the phosphorylation of tyrosine kinase. This will lead to blocking of the signal transduction pathway of tumor cells, and inhibition of tumor cell growth and metastases. Gefitinib is the first molecular targeted therapy used to treat advanced NSCLC. Its efficacy in a non-smoking Asian female adenocarcinoma patient has been confirmed in several international multi-center clinical trials. Gefitinib is appraised as “God’s gift to oriental people”.

The therapeutic effect of Gefitinib on bone and brain metastases of NSCLC has been reported (Ceresoli et al., 2004). However, the effect is not confirmed in large sample multi-center studies. The divergence of gefitinib efficacy between primary lesion and metastatic lesion is not reported in the literature available. In this report, we analyzed the phenomenon of divergent efficacy of gefitinib between primary lesion and metastatic lesion in the treatment of 4 advanced NSCLC patients in Beijing Military Area General Hospital. The characteristics, potential mechanism and strategy of this divergence phenomenon in TKI treatment of lung cancer were also discussed.

*Corresponding author: E-mail: proffzhang@163.com

Table 1. Clinical data of 4 NSCLC patients.

Patients	Age (years old)	Gender	Smoking	TKI-response	Divergence phenomenon organ
Case 1	74	Male	No	Partial response	Bone
Case 2	54	Male	No	Partial response	Bone
Case 3	67	Female	No	Partial response	Brain
Case 4	51	Male	No	Partial response	Brain

PATIENTS AND METHODS

The clinical data of 13 NSCLC adenocarcinoma patients treated with gefitinib during January 2006 and December 31, 2009 were retrospectively reviewed. There were 9 males and 4 females with mean age of 64.61years old (range 45-77). Two patients were smokers. The other 11 patients had no smoking history. Seven patients received prior chemotherapy. Six patients did not receive prior chemotherapy. The best response evaluation identified no patient with complete response (CR), 6 (46.15%) partial response (PR), 6 (46.15%) stable disease (SD) and 1 (7.7%) progressive disease. The disease control rate was 92.30%.

RESULTS

Divergent efficacy between primary lesion (control) and metastatic lesion (progression) was found in 4 patients after disease control for some time. These patients accounted for 33.33% of the responders. All these 4 patients were non-smokers. Two of the four patients had their primary lung lesion and pre-existing bone metastases effectively controlled, but developed new metastatic bone lesions. One patient continued gefitinib therapy and benefited from the treatment for more than 15 months. One patient had effectively controlled the lung disease, but the brain metastasis showed progressive disease. It is unfortunate that this patient did not receive whole body bone scanning after treatment to evaluate the efficacy for bone metastases. One patient had effectively controlled the lung lesion and pre-existing bone metastases, but developed new metastatic bone lesions and progression of brain metastasis. Clinical details of these 4 NSCLC patients are presented in (Table 1).

Case 1: A 74-year-old male patient without smoking history complained of unexplained movement disorder and pain in his left leg 2 months before his admission. CT scan before admission showed lump the diameter of about 2.5 cm in left lower lung field with surrounding short spikes. The 4^{th} and 11^{th} thoracic vertebrae were destroyed. Whole body bone scanning showed abnormal concentration at 9 to 12 thoracic vertebrae and 2, 3, and 5^{th} lumbar vertebrae, as well as multiple ribs. Fiberoptic bronchoscopy revealed mild bronchial stenosis in lower lobe of left lung. Biopsy did not identify cancer cell. CT-guided puncture and biopsy reported adenocarcinoma. Tumor marker CEA was 54.74 ng/ml; CA153, 123.20 U/ml. Diagnosis was lung adenocarcinoma of left lower lobe complicated with bone metastasis. Treatment with oral gefitinib (Iressa, AstraZeneca, 0.25 g) 250 mg once daily was started since October 2007.

Bisphosphonate zoledronic acid was administered intravenously once every month. Evaluation 1 month later reported normal movement of left leg without pain. Tumor markers were significantly reduced. Chest CT revealed that the lump in left lower lobe was apparently shrunk. The efficacy was defined as partial response. Chest CT at 6 months since treatment showed stable lesion in left lung. Tumor markers remained at normal range. New metastatic lesions were found in thoracic vertebrae. Brain metastasis was found another six months later and received radiotherapy. The patient continued his gefitinib therapy constantly with stable primary lung disease until dieing of relapse of brain metastasis 1 year later.

Case 2: A 54-year-old male patient without smoking history reported unexplained cough, and bloody sputum. Chest CT revealed wedge solid density in upper lobe of left lung. The internal density was heterogeneous. Bronchial was blocked in upper lobe of left lung. Central type cancer was considered in left lung. Metastasis was not excluded due to the nodules on right upper lung field. Fiberoptic bronchoscopy revealed neoplasm blocking the opening of left upper lobe, lung cancer in left upper lobe. Biopsy did not identify cancer tissue. Left upper lobe was excised. Post-operative pathological examination showed central type large cell lung cancer in left upper lobe. Mucus was found in partial cytoplasm, which was characterized by adenoid differentiation. No cancerous involvement was found in bronchial end and pleura. About 1/3 of hilar lymph nodes had metastases. Lymph nodes metastasis at anterior mediastinum and other sites showed 0/9. Two cycles of chemotherapy with vinorelbine plus cisplatin regimen were given post operation.

Repeat chest CT found multiple nodules and pieces of shadow in both lungs. Tumor marker CA125 was 77.44 U/ml, signifying progressive disease. Chemotherapy was stopped. Oral gefitinib (Iressa, AstraZeneca, 0.25 g) of 250 mg once daily was started. Chest CT one moth later revealed that the pieces of shadow were reduced in both lungs. Tumor marker was reduced to normal range. Repeat examination 2 month later showed that the nodules were reduced in both lungs. Five months later, chest CT revealed stable disease in both lungs. Tumor marker remained within normal range. Whole body bone scanning revealed active metabolism of bone mineral at right sacroiliac joint, suggesting new lesion.

Case 3: A 67-year-old female patient without smoking history fainted suddenly when bathing at her home. Chest and cranial CT identified space occupying disease in left upper lung and right brain. Tumor markers CEA, CA153, CA125, and CA199 increased to various degrees. SCC was higher than 20× Upper Normal Limit (UNL). Clinical diagnosis was left lung cancer with brain metastasis. Transdermal puncture of left lung tumor and pathological examination reported adenocarcinoma. Whole cranial radiotherapy and enhanced radiotherapy targeting local brain lesion were administered. Chemotherapy with gemcitabine plus carboplatin regimen was initiated immediately before the end of radiotherapy for 2 cycles. Grade III myelosuppression developed after chemotherapy. Her efficacy was defined as partial response. The patient and her family asked to stop chemotherapy. The patient was treated with traditional Chinese medicines for more than 2 months after discharge. Then she had pains in her right shoulder. Whole body bone scanning revealed multiple bone metastases. Chest CT suggested apparent expansion of left lung lesion compared with the status at end of chemotherapy.

Tumor markers CEA and CA153 increased significantly. Oral gefitinib (Iressa, AstraZeneca, 0.25 g) of 250 mg once daily was started. Bisphosphonate zoledronic acid was infused intravenously once every month. The pain in her right shoulder was relieved after oral treatment. Repeat examination after taking gefitinib for 5 months found that the lesion in left lung was reduced. Tumor markers were gradually returned to normal range. After taking Iressa for about 6 months, the patient began to develop dizziness and unsteady walking. Her symptoms were progressive. Cranial MR showed patches of irregular abnormal signals at right temporo-occipital region and left frontoparietal region. Low or intermediate T1/T2 signal was reported. Patches of finger-like edema were seen. Right brain ventricle became deformed and smaller due to compression. Left ventricle was expanded. Mid-line structure was shifted to left. Chest CT showed no change of lung lesion. Tumor markers remained at normal range. Gamma knife therapy for brain metastasis failed. The patient died of intestinal obstruction 3 months later.

Case 4: A 51-year-old male patient without smoking history received chest X-ray examination due to dry cough. Shadow was found in the right upper lung on chest film. Chest CT suggested place occupying disease in right upper lung, lung cancer potential. Fiberoptic bronchoscopy and pathological examination revealed a few cancer cells in tracheal lavage. The cell type was not identified. The patient did not agree to receive surgical therapy. He was treated with 2 cycles of vinorelbine plus cisplatin regimen. His cough was improved after chemotherapy. Subsequently he was treated with traditional Chinese medicine for 3 months. His cough aggravated with blood sputum. Repeat chest CT revealed apparent expansion of right lung lesion, complicated with right pleural effusion, pericardial effusion, multiple metastatic lesions in thoracic vertebrae and ribs. PET-CT revealed very active metabolism in right upper lung nodules, bronchial stenosis of left upper lobe due to compression, local obstructive inflammatory change in right lung, metastases to lymph nodes at right root of the neck and mediastinum region 7, multiple bone metastases, involving cervical vertebrae, scapulae, thoracic vertebrae, ribs, lumbar vertebrae, and pelvis. Tumor markers CEA, CA125, SCC and Cyfra211 increased significantly. The patient was retreated with vinorelbine plus cisplatin regimen for 1 cycle. His cough and sputum were not improved after chemotherapy. Pain in his right flank became more severe. Local radiotherapy was administered for cervical and thoracic vertebrae and ribs. Meanwhile, oral gefitinib (Iressa, AstraZeneca, 0.25 g) was given 250 mg once daily.

Bisphosphonate zoledronic acid was infused intravenously once every month. His cough, sputum and pain were greatly improved after treatment for 5 days. Three weeks later, repeat chest CT revealed apparent reduction of right lung lesion. Pleural effusion was absorbed. The above-listed tumor markers were decreased to various degrees. His efficacy was rated as partial response. After treatment for 3 months, the patient had dizziness, dramatic headache, blurred vision, and projectile vomiting induced by agitation due to business conflict. His symptoms were intermittent and progressive, and developed mania, delirium, visual and auditory hallucination. PET-CT showed that the lesion in right upper lobe was shrunk and metabolism was reduced. Lymph nodes were reduced with lower metabolism. The pre-existing lesions of multiple metastases responded to treatment, but new lesion developed. No place-occupying disease was identified in brain scan. Enhanced cranial MR showed diffuse thickening of meninges, and multiple nodules with enhancement in cerebral parenchyma, which was consistent with meningeal and cerebral metastases of lung cancer. Whole cranial radiotherapy was given for one time. The symptoms were not improved. The patient was discharged.

DISCUSSION AND CONCLUSION

The phenomenon of divergent efficacy indicates the following situation when evaluating the efficacy of tumor treatment: inconsistent change of lesion size at the same or different sites; or apparent reduction of pre-existing lesions, but new lesion develops in any site. Divergent efficacy is occasionally seen in the patients receiving chemotherapy. Gefitinib is a small molecular selective EGFR-TKI. Its efficacy for NSCLC has been confirmed in several international multi-center clinical trials. NCCN guidelines of the US and Chinese NSCLC guideline have included gefitinib as standard treatment of NSCLC. Bone and brain metastasis is the common metastatic site of

advanced NSCLC. Some case reports suggest that gefitinib is effective for bone and brain metastases of NSCLC.

It is reported in the literature that about 10 to 77% of intra-cerebral lesions of NSCLC respond to gefitinib. The disease control rate of gefitinib ranged from 27 to 100%. The inconsistent results may reflect the fact that most of the studies are retrospective. And the studies have included various pathological types of diseases (Ceresoli et al., 2004; Namba et al., 2004; Wu et al., 2007; Wang et al., 2006; Hotta et al., 2004; Chiu et al., 2005). A prospective study in Veterans General Hospital of Chinese Taipei showed that 21 patients had both intracranial evaluable lesions and extra-cranial evaluable lesions. Of these patients, 17 (81.0%) responded to gefitinib in both intra- and extra-cranial lesions (Chiu et al., 2005). A retrospective study in the US reported that of the 21 patients who responded to gefitinib treatment, 7 had central nervous system recurrence (brain metastases in 5 patients, meninges metastases in 2 patients) after response for some time.

However, lung disease was still controlled in 4 (71.43%) of these 7 patients. The median time to brain metastasis was 13 months (3 to 29 months). The details of these 4 patients were not described in the report. However, from the range of time to brain metastasis provided, it can be seen that brain metastasis was not only seen in the patients with longer response. At least one patient had brain metastasis after treatment for 3 months (Omuro et al., 2005). Two cases (2/11) of this series had progressive brain metastatic disease while the primary lesion was effectively controlled. The incidence is lower than that reported in the literature. The brain metastasis in the 2 patients occurred within 6 months after gefitinib treatment. This may be related to the fact that some patients of this series were still on treatment and not reached study endpoint.

About 20 to 40% of NSCLC patients develop bone metastasis. The common symptoms of bone metastasis include bone pain, pathological fracture, and spinal compression symptoms. The symptoms of bone metastasis may have great impact on patients' quality of life. Some case report has shown the potential activity of gefitinib on bone metastasis (Satoh et al., 2009), even though its effect on bone metastasis was not described in the clinical trials of treating NSCLC patients. Its effect is mainly reflected in promoting sclerosis of osteolytic lesion and relieving bone pain, or even leading to complete remission of bone metastatic lesions (Zampa et al., 2008). It has been shown that gefitinib can significantly inhibit the production of osteolytic factors by stromal cells in bone marrow, such as macrophage colony-stimulating factor (Normanno et al., 2005). In addition, gefitinib can also reduce the activity of uPA and MMP-9 in prostate cancer cells, and so significantly impair its ability to form metastatic bone lesions (Angelucci et al., 2006). Authors of this report did not see the report of controlled lung disease and progressive bone metastasis in gefitinib-treated NSCLC patients.

The above-stated 4 patients indicate that efficacy divergence is not only seen in brain metastasis, but also in bone metastasis, or both. The mechanism underlying this phenomenon may be related to the following aspects.

Firstly, the interactions between tumors stem cell and tumor micro-environment (or niche): More and more clinical and experimental evidence demonstrated that most tumors are originated from tumor stem cell. This cell type has the ability of self renewal, and unlimited proliferation. It can produce various proliferative and differentiated cells in the tumor tissues to form tumor *in vivo* and *in vitro.* Stem cell niche is a micro-environment where stem cells live. The niche is in organs or tissues to keep stem cells self-renew and avoid differentiation. The niche is composed of niche cells, extracellular matrix and soluble factors originating from niche cells. Niche cells are the main component. The niche varies with different tissues. The maintenance of stem cell features is closely associated with the niche of stem cells. The stem cell and its niche interact with each other directly or indirectly. The interaction between tumor stem cell and its niche lasts the whole process of tumor genesis, development, and metastasis. Therefore, the cytobiological features and external niches may be different for primary lesion and metastatic lesion, which may have effect on the treatment response (Wu et al., 2008). Unfortunately, the primary lesion and metastatic lesion were not excised for further comparison in the above reported patients. The answers to whether the cytobiological features of primary lung cancer is completely the same as that in the bone or brain metastatic lesions in NSCLC patients, where is the difference between the niche form primary tumor and that for the metastatic tumors, may be helpful for characterizing the underlying mechanism of this divergent phenomenon.

Secondly, tumor cells mutate in the new niche after metastasis and acquire resistance to gefitinib. EGFR gene is located on the short arm of human chromosome 7. It is composed of 118kb, including 28 exons. Studies demonstrate that mutation of EGFR gene is significantly associated with reduced efficacy of gefitinib in NSCLC patients. The prevalence of mutated gene is higher in female patients with adenocarcinoma. It is heterogeneous mutation and localized in the coding region of exons 19 to 21 in the ATP-binding site of EGFR tyrosine kinase. The mutation is characterized as missense due to deletion, insertion or replacement of one base or a sequence of bases (Lynch et al., 2004; Paez et al., 2004). Nearly all responders to EGFR-TKI treatment will eventually relapse. This suggests that there exists acquired resistance. As for the mechanism of acquired resistance to EGFR-TKI, the mostly studied is the missense mutation in exon T790M of EGFR gene (Inukai et al., 2006). The tumor cells develop gene mutations induced by some cytokines in the new niche after

metastasis, which leads to local resistance to EGFR-TKI therapy. This may be one of the mechanisms to explain the divergent phenomenon of gefitinib treatment in NSCLC patients.

Additionally, the blood brain barrier may affect drug distribution in central nervous system. While gefitinib is a small molecule compound, however, animal experiments demonstrate that it can not penetrate blood brain barrier. At present, as we know, no study is available on the penetration of gefitinib through human blood brain barrier. The effect of blood brain barrier on drug penetration into central nervous system may be the best explanation of the divergent phenomenon regarding controlled primary lung disease but progressive disease of brain metastasis. However, several clinical studies have shown that gefitinib is effective for pre-existing brain metastasis of lung cancer. The different clinical response reflects the need for further research on the effect of gefitinib treatment on NSCLC brain metastasis.

The divergent phenomenon of anticancer efficacy is really observed in gefitinib-treated NSCLC patients. With reference to the relevant literature, this phenomenon is especially common in the responders whose disease had been controlled for certain time. Currently, the most prevalent tumor response evaluation criteria was the response evaluation criteria in solid tumors (RECIST), which was proposed by the clinical trial groups of European EORTC, NCI of the US and Canadian NCI, and published in 2000 in Journal of the National Cancer Institute. According to RECIST criteria, progressive disease is defined as lesion progression in any site, or development of new lesion, or definitive progression of non-target lesion, during treatment. Further treatment usually follows the principle of “continue when response and change when no response”. One of the above-described 4 patients developed new bone metastasis in thoracic vertebra, but he benefited from continuing treatment. For the patients showing divergent efficacy when treated with molecular targeted therapy, how to select the subsequent treatment, whether all patients should discontinue the treatment, these issues have challenged the response evaluation criteria and treatment principles for traditional solid tumors.

It is necessary to further investigate the mechanisms responsible for the divergent efficacy of TKI in treatment of lung cancer. Multi-center and large sample size clinical trial should be designed. On the basis of such studies, the specific response evaluation criteria and treatment principles should be established for molecular targeted therapy. These efforts are more helpful for molecular targeted therapy to produce more desirable therapeutic effect. Meanwhile, these jobs will provide clues for exploring tumor origin and the mechanism of tumor metastasis.

REFERENCES

Angelucci A, Gravina GL, Rucci N, Millimaggi D, Festuccia C, Muzi P, Teti A, Vicentini C, Bologna M (2006). Suppression of EGF-R signaling reduces the incidence of prostate cancer metastasis in nude mice. Endocr. Relat. Cancer, 13(1): 197-210.

Ceresoli GL, Cappuzzo F, Gregorc V, Bartolini S, Crinò L, Villa E (2004). Gefitinib in patients with brain metastasis from non small-cell lung cancer: a prospective trial. Ann. Oncol., 15(7): 1042-1047.

Chiu CH, Tsai CM, Chen YM, Chiang SC, Liou JL, Perng RP (2005). Gefitinib is active in patients with brain metastases from non small cell lung cancer and response is related to skin toxicity. Lung Cancer, 47(1): 129-138.

Inukai M, Toyooka S, Ito S, Asano H, Ichihara S, Soh J, Suehisa H, Ouchida M, Aoe K, Aoe M, Kiura K, Shimizu N, Date H (2006). Presence of epidermal growth factor receptor gene T790 M mutation as a minor clone in non small cell lung cancer. Cancer Res., 66(16): 7854-7858.

Hotta K, Kiura K, Ueoka H, Tabata M, Fujiwara K, Kozuki T, Okada T, Hisamoto A, Tanimoto M (2004). Effect of gefitinib ('Iressa', ZD1839) on brain metastases in patients with advanced non small-cell lung cancer. Lung Cancer, 46(2): 255-261.

Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J, Haber DA (2004). Activating mutations in the epidermal growth factor receptor underlying responsiveness of non small-cell lung cancer to gefitinib. N. Engl. J. Med., 350(21): 2129-2139.

Namba Y, Kijima T, Yokota S, Niinaka M, Kawamura S, Iwasaki T, Takeda Y, Kimura H, Okada T, Yamaguchi T, Nakagawa M, Okumura Y, Maeda H, Ito M (2004). Gefitinib in patients with brain metastasis from non small-cell lung cancer: review of 15 clinical cases. Clin. Lung Cancer, 6(2): 123-128.

Normanno N, De Luca A, Aldinucci D, Maiello MR, Mancino M, D'Antonio A, De Filippi R, Pinto A (2005). Gefitinib inhibits the ability of human bone marrow stromal cells to induce osteoclast differentiation: implications for the pathogenesis and treatment of bone metastasis. Endocr. Relat. Cancer, 12(2): 471-82

Omuro AM, Kris MG, Miller VA, Franceschi E, Shah N, Milton DT, Abrey LE (2005). High incidence of disease recurrence in the brain and lepotomeninges in patients with non small cell lung carcinoma after response to gefitinib. Cancer, 103(11): 2344-2348.

Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnson BE, Meyerson M (2004). EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. Science, 304(5676): 1497-1500.

Satoh H, Ishikawa H, Ohara G, Kikuchi N, Sekizawa K(2009). Prolonged response to gefitinib in bone metastasis. Med. Oncol., 26(1):101-2

Wang Y, Wang Y, Wang B (2006). Preliminary results of gefitinib in treatment of NSCLC brain metastases. Chin. J. Lung. Cancer, 9(5): 447-451.

Wu C, Li LY, Wang MZ, Zhang L, Zhang XT, Zhong W, Wang SL, Wang HZ (2007). Gefitinib in the treatment of advanced non small cell lung cancer with brain metastasis. Zhonghua. Zhong. Liu. Za. Zhi., 29(12): 943-945.

Wu YY, Huang Q, Dong J, Lan Q (2008). Correlation of stem cell niche to genesis and development of tumor stem cells. Cancer, 27(1): 109-112.

Zampa G, Moscato M, Brannigan BW, Morabito A, Bell DW, Normanno N (2008). Prolonged control of bone metastases in non small-cell lung cancer patients treated with gefitinib. Lung Cancer, 60(3): 452-454