DOI: 10.4046/trd.2011.71.1.15
ISSN: 1738-3536(Print)/2005-6184(Online)
Tuberc Respir Dis 2011;71:15-23

Original Article

Comparison of Therapeutic Efficacy of Gefitinib and Erlotinib in Patients with Squamous Cell Lung Cancer

Hong-Joon Shin, M.D.[1], Tae-Ok Kim, M.D.[1], Hyun-Wook Kang, M.D.[1], Su-Young Chi, M.D.[1], Hee-Jung Ban, M.D.[1], Soo-Ok Kim, M.D.[2], Yong-Soo Kwon, M.D.[1], In-Jae Oh, M.D.[1], Kyu-Sik Kim, M.D.[1], Yu-Il Kim, M.D.[1], Sung-Chul Lim, M.D.[1], Young-Chul Kim, M.D.[1]

Department of Internal Medicine, [1]Chonnam National University Medical School, [2]Seonam University College of Medicine, Gwangju, Korea

Background: Gefitinib and erlotinib are useful, molecular targeted agents in patients with non-small-cell lung cancer (NSCLC) who failed previous chemotherapy. We compared the efficacy and toxicity of two drugs in patients with squamous cell lung cancer, most of whom are male smokers.

Methods: We retrospectively reviewed the clinical information on patients with NSCLC who were treated with gefitinib or erlotinib treatment at Chonnam National University Hwasun Hospital between July 2002 and November 2009. The overall response rate (ORR), overall survival (OS) and progression-free survival (PFS) were compared between the two drugs.

Results: A total of 182 (100 gefitinib vs. 82 erlotinib) of 584 patients treated by targeted agents had squamous histology. Of the 182 patients, 167 (91.7%) were male and 159 (87.4%) were smokers. The ORR and disease control rate (DCR) were 4.9% and 40.6%, and there was no significant difference between gefitinib and erlotinib (ORR, 5.0% vs 4.8%; p=0.970; DCR, 40.0% vs 41.4%; p=0.439). The median OS in the gefitinib group was 12.1 months, and that in the erlotinib was 12.7 months (hazard ratio [HR], 1.282; 95% confidence interval [CI], 0.771～2.134; p=0.339). The median PFS for the gefitinib group was 1.40 months, compared with 1.37 months for the erlotinib group (HR, 1.092; 95% CI, 0.809～1.474; p=0.564). Skin rash ≥grade 3 was more common in erlotinib (12.2%) than gefitinib (1.0%, p=0.003) groups.

Conclusion: This retrospective study showed that the two drugs appear to have similar antitumor efficacy and toxicity except for skin rash.

Key Words: Carcinoma, Squamous Cell; gefitinib; erlotinib; Treatment Outcome

Introduction

With the clinical application of targeted agents in patients with lung cancer, unlike conventional chemotherapy, the toxicity and side effects have been improved. Epidermal growth factor receptor - tyrosine kinase inhibitors (EGFR-TKIs) are targeted agents that are frequently used in patients with non-small-cell lung cancer (NSCLC). Gefitinib and erlotinib are two representative EGFR-TKIs which have shown a higher treatment response in Asian, women, non-smokers and adenocarcinoma histology[1,2]. Although two drugs are usually used as the second-line and third-line treatment regimens, they can be chosen as the first-line agents particularly in patients with EGFR-mutation positive non-squamous cell carcinoma[3,4]. Comparative studies have reported the efficacy of two types of EGFR-TKIs[5-8], but there are not a great number of studies that have compared between gefitinib and erlotinib in patients with squamous cell carcinoma.

Given the above background, we conducted this study to compare the treatment efficacy and toxicity be-

Address for correspondence: **In-Jae Oh, M.D.**
Lung and Esophageal Cancer Clinic, Chonnam National University Hwasun Hospital, 160, Ilsim-ri, Hwasun-eup, Hwasun 519-763, Korea
Phone: 82-61-379-7617, Fax: 82-61-379-7619
E-mail: droij@chonnam.ac.kr
Received: May 7, 2011
Accepted: Jun. 14, 2011

tween gefitinib and erlotinib in patients with squamous cell carcinoma. And we also attempted to examine the difference in the prognostic indicator associated with each drug.

Materials and Methods

1. Patients

Of patients who were diagnosed with stage III or IV NSCLC and then treated with gefitinib or erlotinib at Chonnam National University Hwasun Hospital during a period ranging from July of 2002 to November of 2009, those with a diagnosis of squamous cell carcinoma were enrolled in the current study.

2. Methods

Through a retrospective analysis of the medical records, we reviewed the sex, age, smoking history, stage, Eastern Cooperative Oncology Group (ECOG) performance status and a past history of taking prior chemotherapeutic agents. In the gefitinib treatment group, gefitinib 250 mg was orally administered once daily. In the erlotinib treatment group, erlotinib 150 mg was orally administered once daily. The dose reduction due to toxicity and the selection of drugs were based on the judgment of investigators.

Within the first 4～8 weeks following the treatment with EGFR-TKIs, a chest computed tomography (CT) was performed. The tumor response was evaluated based on the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1[9]. A complete response (CR) is defined as the disappearance of all target lesions. A partial response (PR) is defined as at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. A progressive disease (PD) is defined as at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. A stable disease (SD) is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, and it is also referred to as cases in which the lesions were persistently present for more than eight weeks. A follow-up chest CT was performed at a 4- to 8-week interval until the lesions were evaluated as the PD.

The toxicity of two drugs was evaluated in accordance with the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0[10].

3. Statistical analysis

Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA), where a p-value of <0.05 was considered statistically significant. A comparison of the continuous variables was made using Student t-test. Besides, the best response rate (RR) and the disease control rate (DCR) were analyzed using a Chi-square test. The overall survival (OS) and the progression-free survival (PFS) were defined as the length of days elapsed since the gefitinib or erlotinib were first administered. Following a Kaplan-Meier survival analysis, a log-rank test was performed to compare between the two survival curves. In this study, factors affecting the survival of patients were analyzed using a Cox regression model.

Results

1. The patient characteristics

During a period ranging from July of 2002 to November of 2009, a total of 584 patients with NSCLC were treated with either gefitinib or erlotinib. Of these, there were 182 patients (31%) with squamous cell carcinoma. There were 100 patients (55%) of the gefitinib treatment group and 82 patients (45%) of the erlotinib treatment group (Table 1). The median age was 65 years old (range, 41～81) and there were 167 male patients (92%). There were 159 smokers (87%). In 171 patients (94%), gefitinib or erlotinib were used as more than third-line treatment. Prior chemotherapeutic agents were based on taxane in 128 patients (70%). There were no significant differences in the age, the types of prior chemotherapeutic agents and the stages between two treatment group. But there were significant differ-

ences in the sex, smoking history and the frequency of prior chemotherapy between the two groups. In the erlotinib treatment group, the proportion of male patients and smokers was significantly higher.

2. A comparison of the RR and the DCR

Of 182 study patients, except for 10 patients (6%) who were cannot be evaluated, there were no patients who achieved a CR in the remaining 172 ones. There

Table 1. Baseline characteristics in the treatment patients

Variables	All (n=182)	Gefitinib (n=100)	Erlotinib (n=82)	p-value
Age*, yr	65 (41～48)	65 (41～81)	65 (41～81)	0.602
Male	167 (91.8)	87 (87.0)	80 (97.6)	0.013
Smoking				0.012
Never-smoker	17 (9.3)	14 (14.0)	3 (3.7)	
Current or ever smoker	159 (87.4)	85 (85.0)	74 (90.2)	
Unknown	6 (3.3)	1 (1.0)	5 (6.1)	
ECOG-performance status				0.104
0～1	155 (85.2)	86 (86.0)	69 (84.1)	
≥2	23 (12.6)	10 (10.0)	13 (15.9)	
Unknown	4 (2.2)	4 (4.0)	0 (0.0)	
Stage at diagnosis				0.165
≤IIIA	38 (20.9)	24 (24.0)	14 (17.1)	
IIIB	71 (39.0)	42 (42.0)	29 (35.4)	
IV	73 (40.1)	34 (34.0)	39 (47.6)	
Numbers of prior chemotherapy				0.001
<2	11 (6.0)	11 (11.0)	0 (0.0)	
≥2	171 (94.0)	89 (89.0)	82 (100.0)	
Regimens of prior chemotherapy				0.269
Taxane-based	128 (70.3)	71 (71.0)	57 (69.5)	
Gemcitabine-based	45 (24.7)	22 (22.0)	23 (28.0)	
EGFR mutation				0.134
Positive	2 (1.1)	2 (2.0)	0 (0.0)	
Negative	15 (8.2)	11 (11.0)	4 (4.9)	
Unknown	165 (90.7)	87 (87.0)	78 (95.1)	

Vales are presented as number (%) unless otherwise indicated.
*Presented as median (range).
ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor.

Table 2. Response to gefitinib and erlotinib according to RECIST version 1.1

Variables	All (n=182)	Gefitinib (n=100)	Erlotinib (n=82)	p-value
Response				
Complete response	0 (0)	0 (0)	0 (0)	
Partial response	9 (4.9)	5 (5.0)	4 (4.9)	
Stable disease	65 (35.7)	35 (35.0)	30 (36.6)	
Progressive disease	98 (53.8)	52 (52.0)	46 (56.1)	
Not evaluable	10 (5.5)	8 (8.0)	2 (2.4)	
Disease control rate	74 (40.7)	40 (40.0)	34 (41.4)	0.439
Response rate	9 (4.9)	5 (5.0)	4 (4.8)	0.970

Values are presented as number (%).
RECIST: response evaluation criteria in solid tumor.

were 9 patients (5%) who achieved a PR, 65 patients (35%) who had a SD and 98 patients (54%) who had a PD. These results indicate that the DCR was 40.7% and the RR was 4.9%. Besides, there were no significant differences in the RR (5.0% vs. 4.8%, p=0.970) and the DCR (40.0% vs. 41.4%, p=0.439) between two group (Table 2). The period of the use of each drug was found to be 1.2 months (range, 0.2～22.2) in the gefitinib treatment group and 1.4 months (range, 0.1～8.1) in the erlotinib treatment group. But this difference reached no statistical significance (p=0.873). The number of patients who received the additional chemotherapy following the treatment with EGFR TKIs was 50 in the gefitinib treatment group and 52 in the erlotinib treatment group. But this difference reached no statistical significance (p=0.070).

3. A comparison of the OS and the PFS

The median survival was 1.2 months (95% confidence interval [CI], 10.0～14.2) in the gefitinib treatment group and 12.7 months (95% CI, 11.6～13.7) in the erlotinib treatment group. But this difference reached no statistical significance (hazard ratio [HR]=1.282; 95% CI, 0.771～2.134; p=0.339) (Figure 1A). The median value of PFS was 1.40 months (95% CI, 0.86～1.94) in the gefitinib treatment group and 1.37 months (95% CI, 1.26～1.48) in the erlotinib treatment group. But this difference reached no statistical significance (HR, 1.092; 95% CI, 0.809～1.474; p=0.564) (Figure 1B).

In the variables which were predicted to affect the survival rate of study patients, the relative risk was calculated using a Cox proportional hazard model. This showed that the survival was not associated with the sex, smoking history, ECOG performance status, stage and the frequency of prior chemotherapy. It was also observed that the age of 60 years or older (HR, 2.178; 95% CI, 1.279～3.707; p=0.004) affected the survival rate. Following an analysis where other variables were controlled, the difference between the two drugs (gefitinib and erlotinib) was not statistically significant independent variable (HR, 1.376; 95% CI, 0.810～2.336; p=0.238).

4. Adverse events

There were 66 cases (36.3%) of skin rash, 34 cases (18.7%) of decreased appetite, 19 cases (10.4%) of diarrhea and 11 cases (6.0%) of fatigue. The skin rash occurred at a higher incidence (47.6%, 39 cases) in the erlotinib treatment group (p=0.005). Besides, there were ten patients (12.2%) with skin rash of NCI-CTC grade 3 or higher in the erlotinib treatment group (p=0.003) (Table 3). But there were no cases of early termination due to the occurrence of skin rash in the erlotinib treatment group. Except for the skin rash, there

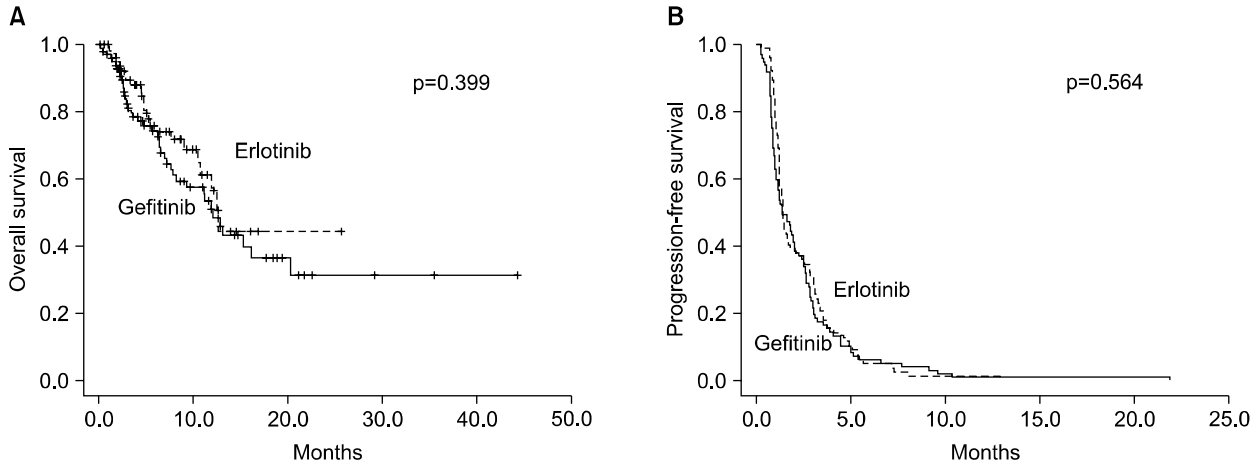

Figure 1. Survival outcomes based on gefitinib and erlotinib treated. Overall survival (A) and progression-free survival (B). Values were calculated by log-rank test.

Table 3. Adverse reactions related with gefitinib and erlotinib

Adverse reactions	Gefitinib (n=100)		Erlotinib (n=82)		p-value	
	All	Grade ≥3	All	Grade ≥3	All	Grade ≥3
Rash	27 (27.0)	1 (1.0)	39 (47.6)	10 (12.2)	0.005	0.003
Anorexia	20 (20.0)	0 (0)	14 (17.1)	0 (0)	0.704	
Diarrhea	10 (10.0)	0 (0)	9 (11.0)	0 (0)	1.000	
Fatigue	7 (7.0)	0 (0)	4 (4.9)	0 (0)	0.757	
Myalgia	0 (0)	0 (0)	3 (3.7)	0 (0)	0.090	
Anemia	3 (3.0)	0 (0)	3 (3.7)	0 (0)	1.000	
Interstitial pneumonitis	3 (3.0)	0 (0)	2 (2.4)	2 (2.4)	0.593	0.202
Neuropathy	3 (3.0)	0 (0)	1 (1.2)	0 (0)	0.628	
Weight loss	2 (2.0)	0 (0)	0 (0)	0 (0)	0.502	
Nausea	1 (1.0)	0 (0)	0 (0)	0 (0)	1.000	
Vomiting	0 (0)	0 (0)	0 (0)	0 (0)		
Elevated liver enzyme	0 (0)	0 (0)	0 (0)	0 (0)		

Values are presented as number (%).

were no significant differences in the incidence and severity of toxicities between the two groups.

In regard to the interstitial pneumonitis, three cases (3%) occurred in the gefitinib treatment group and two cases (2.4%) occurred in the erlotinib treatment group. The number of patients who were in need of intensive care unit (ICU) treatment was two each in both groups. In all the three cases of interstitial pneumonitis that occurred in the gefitinib treatment group, the symptoms were resolved following the treatment with a high-dose steroid. In two cases of interstitial pneumonitis that occurred in the erlotinib treatment group, however, the death occurred despite the steroid therapy.

Discussion

The current study is a retrospective one which disclosed that there were no significant differences in the RR and the survival between gefitinib and erlotinib following a comparison of these two drugs in a single-institution setting only in patients with squamous cell carcinoma which has been reported to show a lower RR to EGFR-TKIs. A rate of the treatment response of 4.9% seen in our study was close to 4.1% seen in patients with non-adenocarcinoma, which has been reported on the BR21[1], a large-scale phase III study evaluating erlotinib. In regard to the toxicities of each drug, the incidence of skin rash was significantly higher in the erlotinib treatment group.

According to the guidelines of The National Comprehensive Cancer Network (NCCN)[3], the EGFR-TKIs are recommended as the second-line or third-line treatment regimen for patients with NSCLC whose ECOG performance status was 0-3. Based on the results of recent clinical trials[11-14], however, the use of erlotinib has been accredited as the first-line treatment regimen for patients with the EGFR-mutation positive non-squamous cell carcinoma. Besides, it has also been accredited as a maintenance therapeutic agent for patients who achieved a SD or PR after first-line chemotherapy. As described here, the indications of erlotinib have been gradually extended[4].

The EGFR mutation test is of clinical use in predicting the treatment response to the EGFR-TKIs. But there are no available clinical data reporting that the selection of optimal treatment regimen based on the EGFR analysis has improved the survival rate. It is not therefore recommended for all the patients with NSCLC but only for those with non-squamous cell carcinoma in whom the EGFR mutation is known to be prevalent[3,4].

It has been reported that the EGFR mutation is more prevalent in women, non-smokers, Asian people and

patients with adenocarcinoma histology. According to a study of the Spanish Lung Cancer Group, where the EGFR mutation positive patients were treated with erlotinib, the EGFR mutation was present in 30% of male patients, 26% of smokers and 9% of patients with non-adenocarcinoma[15]. It can therefore be inferred that the presence of EGFR mutation cannot be predicted solely based on the clinical characteristics. According to the NCCN guidelines, the incidence of EGFR mutation was 3.6% in patients with squamous cell carcinoma[16] and this is a relatively lower value, so the EGFR mutation test is not recommended for these patients. However, other some studies[17-19] have reported that the EGFR test is useful in patients with squamous cell carcinoma because the incidence of EGFR mutation is 5～15% and this is a relatively higher value. According to a pooled analysis of 33 patients with the EGFR mutation positive non-adenocarcinoma, who were treated with gefitinib, the treatment outcomes of patients with the EGFR mutation positive squamous cell carcinoma were poorer (RR, 30%; DCR, 67～70%; the median value of PFS, 3.1 months) as compared with those of patients with the EGFR mutation positive adenocarcinoma (RR, 66%; DCR, 92～93%; the median value of PFS, 9.4 months)[19]. It could also be shown that some patients with squamous cell carcinoma had a substantial degree of treatment response. In our study, the EGFR mutation test was performed for 17 patients (9.0%). All the two patients with the EGFR mutation were found to receive the gefitinib treatment. Accordingly, there are some limitations in interpreting the results of the current study. Gefitinib treatment could be continuously done for 19 months in the patient with exon 19 deletion. In the patient with exon 20 point mutation, however, the treatment could be done for a month. Due to the death because of the brain metastasis, the treatment response could not be assessed in this patient.

According to an early-stage, large-scale phase III study[1,2], there were significant differences in the treatment outcomes between the two targeted agents. To explain this, it has been argued that erlotinib is prescribed at a dose as closely to the maximal tolerated dose as possible[20,21]. Besides, it has also been argued that the clearance of erlotinib is relatively lower in an in vivo setting because erlotinib is less sensitive to cytochrome P450 metabolism as compared with gefitinib[22]. According to clinical trials which directly compared between these two drugs, however, there were no significant differences[6,8]. In Taiwan, there were contradictory reports that erlotinib has an excellent profile of the DCR, the PFS and the OS[23]. Further studies are therefore warranted to examine the difference in the treatment effect between the two drugs. Because most of the studies have enrolled patients with adenocarcinoma, there are few studies which have been conducted only in patients with squamous cell carcinoma. On a theoretical basis, erlotinib would be more favorable for the treatment of squamous cell carcinoma, where the number of smokers is relatively greater, because it is less sensitive to cytochrome P450 metabolism. In our study, there was no significant difference in the anti-cancer effect between the two drugs. As shown in the clinical characteristics at baseline (Table 1), however, due to the limitation of the health insurance coverage in Korea, the proportion of cases in which the drugs were administered to women and non-smokers and as the second-line treatment regimen was relatively higher in the gefitinib treatment group. This might restrict the interpretation of the results of the current study.

According to other studies where a greater number of patients with adenocarcinoma were enrolled, the RR to EGFR-TKI was approximately 40%. In our study, however, the RR was 4.9% and the DCR was 40.6%, being relatively lower. This might be not only because the rate of the expression of the EGFR mutation was significantly lower in patients with squamous cell carcinoma as compared with those with adenocarcinoma but also because the proportion of male patients and smokers was significantly higher. Because the EGFR mutation test was not sufficiently done in this study, however, its significance as a prognostic indicator for treatment response could not be identified. In addition, it has also been reported that the histologic types of adenocarcinoma are prognostic indicators for the survival follow-

ing the treatment with EGFR-TKI[8,24]. In our study, however, additional prognostic indicators for patient survival could not be found.

The adverse events occured at a similar incidence between two groups. Skin rash and diarrhea are the most frequently reported ones, and interstitial pneumonitis might be fatal although rare[1,2,25]. The skin rash might be associated with the EGFR inhibitory reaction on the skin rather than the allergic reaction. It has been reported that the skin rash is associated with the treatment response to erlotinib. But there were contradictory reports in gefitinib treatment[26]. In the current study, the incidence and severity of skin rash were significantly higher in the erlotinib group as compared with the gefitinib group. This might be because erlotinib is prescribed at a dose, as closely to the maximal tolerated dose as possible, as compared with gefitinib. Except for the skin rash, there was no significant difference in the incidence of other side effects between the two groups. In regard to the incidence of interstitial pneumonitis, there were three cases (3%) in the gefitinib treatment group and two cases (2.4%) in the erlotinib treatment group. There were two patients each of both groups who were in need of the ICU treatment. Two cases occurring in the gefitinib treatment group, composed of male and female patients each, were improved with the medical treatments including steroid therapy. Two male patients of the erlotinib treatment group were all found to die. The incidence of interstitial pneumonitis due to EGFR-TKIs has been reported to be 1.2～5.7% and the mortality has been reported to be approximately 0.3%[1,2,27,28]. As the risk factors of developing EGFR-TKIs-associated interstitial pneumonitis, male patient, smoking history, irradiation, the concurrent presence of interstitial lung disease and the poor ECOG performance status have been reported[28-30]. In our study, however, there were no significant differences in the risk factors between the two groups.

In summary, although there are some limitations in analyzing the results of the current study, the RR of EGFR-TKIs treatment was 5% and the DCR was approximately 40% in patients with squamous cell carcinoma. These values were relatively lower than those seen in patients with adenocarcinoma. Besides, there were no significant differences in the RR, the PFS and the OS between gefitinib and erlotinib. Most of the toxicities had occurred at a similar incidence, but the skin rash occurred at a higher incidence in the erlotinib treatment group.

References

1. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005; 353:123-32.
2. Thatcher N, Chang A, Parikh P, Rodrigues Pereira J, Ciuleanu T, von Pawel J, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 2005;366:1527-37.
3. National Comprehensive Cancer Network (NCCN). National Comprehensive Cancer Network: your best resource in the fight against cancer [Homepage]. Fort Washington, PA: NCCN; c2011 [cited 2011 July 20]. Available from: http://www.nccn.org/index.asp.
4. 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.
5. Emery IF, Battelli C, Auclair PL, Carrier K, Hayes DM. Response to gefitinib and erlotinib in non-small cell lung cancer: a restrospective study. BMC Cancer 2009; 9:333.
6. Kim ST, Lee J, Kim JH, Won YW, Sun JM, Yun J, et al. Comparison of gefitinib versus erlotinib in patients with nonsmall cell lung cancer who failed previous chemotherapy. Cancer 2010;116:3025-33.
7. Hong J, Kyung SY, Lee SP, Park JW, Jung SH, Lee JI, et al. Pemetrexed versus gefitinib versus erlotinib in previously treated patients with non-small cell lung cancer. Korean J Intern Med 2010;25:294-300.
8. Lee JH, Lee KE, Ryu YJ, Chun EM, Chang JH. Comparison of gefitinib and erlotinib for patients with advanced non-small-cell lung cancer. Tuberc Respir Dis 2009;66:280-7.
9. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation cri-

teria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
10. National Cancer Institute (NCI). Cancer therapy evaluation program: common terminology criteria for adverse events (CTCAE) version 3.0. Bethesda, MD: NCI; 2006 [cited 2011 July 20]. Available from: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf.
11. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
12. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380-8.
13. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, 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.
14. Zhou C, Wung YI, Chen G, Feng J, Liu X, Wang C, et al. Efficacy results from the randomised phase III OPTIMAL (CTONG 0802) study comparing first-line erlotinib versus carboplatin plus gemcitabine, in chinese advanced non-small-cell lung cancer patients with EGFR activating mutations. Presented at European Society of Medical Oncology (ESMO) Congress; 2010 Oct 8-12; Milan, Italy.
15. Massuti B, Morán T, Porta R, Queralt C, Cardenal F, Mayo C, et al. Multicenter prospective trial of customized erlotinib for advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) mutations: final results of the Spanish Lung Cancer Group (SLCG) trial. J Clin Oncol 2009; 27(Suppl 15):8023.
16. Forbes SA, Bhamra G, Bamford S, Dawson E, Kok C, Clements J, et al. The catalogue of somatic mutations in cancer (COSMIC). Curr Protoc Hum Genet 2008; Chapter 10:Unit 10.11.
17. Miyamae Y, Shimizu K, Hirato J, Araki T, Tanaka K, Ogawa H, et al. Significance of epidermal growth factor receptor gene mutations in squamous cell lung carcinoma. Oncol Rep 2011;25:921-8.
18. Park SH, Ha SY, Lee JI, Lee H, Sim H, Kim YS, et al. Epidermal growth factor receptor mutations and the clinical outcome in male smokers with wquamous cell carcinoma of lung. J Korean Med Sci 2009;24:448-52.
19. Shukuya T, Takahashi T, Kaira R, Ono A, Nakamura Y, Tsuya A, et al. Efficacy of gefitinib for non-adenocarcinoma non-small-cell lung cancer patients harboring epidermal growth factor receptor mutations: a pooled analysis of published reports. Cancer Sci 2011; 102:1032-7.
20. Baselga J, Rischin D, Ranson M, Calvert H, Raymond E, Kieback DG, et al. Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types. J Clin Oncol 2002;20:4292-302.
21. Hidalgo M, Siu LL, Nemunaitis J, Rizzo J, Hammond LA, Takimoto C, et al. Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. J Clin Oncol 2001;19:3267-79.
22. Li J, Zhao M, He P, Hidalgo M, Baker SD. Differential metabolism of gefitinib and erlotinib by human cytochrome P450 enzymes. Clin Cancer Res 2007;13: 3731-7.
23. Fan WC, Yu CJ, Tsai CM, Huang MS, Lai CL, Hsia TC, et al. Different efficacies of erlotinib and gefitinib in taiwanese patients with advanced non-small cell lung cancer: a retrospective multicenter study. J Thorac Oncol 2011;6:148-55.
24. Wu YL, Zhong WZ, Li LY, Zhang XT, Zhang L, Zhou CC, et al. Epidermal growth factor receptor mutations and their correlation with gefitinib therapy in patients with non-small cell lung cancer: a meta-analysis based on updated individual patient data from six medical centers in mainland China. J Thorac Oncol 2007;2: 430-9.
25. Kim ES, Hirsh V, Mok T, Socinski MA, Gervais R, Wu YL, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet 2008;372:1809-18.
26. Emery IF, Battelli C, Auclair PL, Carrier K, Hayes DM. Response to gefitinib and erlotinib in Non-small cell lung cancer: a restrospective study. BMC Cancer 2009; 9:333.
27. Maruyama R, Nishiwaki Y, Tamura T, Yamamoto N, Tsuboi M, Nakagawa K, et al. Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. J Clin Oncol 2008;26:4244-52.
28. Ando M, Okamoto I, Yamamoto N, Takeda K, Tamura K, Seto T, et al. Predictive factors for interstitial lung disease, antitumor response, and survival in non-small-

cell lung cancer patients treated with gefitinib. J Clin Oncol 2006;24:2549-56.
29. Inoue A, Saijo Y, Maemondo M, Gomi K, Tokue Y, Kimura Y, et al. Severe acute interstitial pneumonia and gefitinib. Lancet 2003;361:137-9.
30. Hotta K, Kiura K, Takigawa N, Yoshioka H, Harita S, Kuyama S, et al. Comparison of the incidence and pattern of interstitial lung disease during erlotinib and gefitinib treatment in Japanese Patients with non-small cell lung cancer: the Okayama Lung Cancer Study Group experience. J Thorac Oncol 2010;5:179-84.