Comparison of Adverse Events of Erlotinib with those of Gefitinib in Patients with Non-small Cell Lung Cancer: A Case-control Study in a Japanese Population

TOMOHIRO SUZUMURA, TATSUO KIMURA, SHINZOH KUDOH, KANAKO UMEKAWA, MISATO NAGATA, HIDENORI TANAKA, SHIGEKI MITSUOKA, NARUO YOSHIMURA, YUKIMI KIRA, and KAZUTO HIRATA

TOMOHIRO SUZUMURA, TATSUO KIMURA, SHINZOH KUDOH et al. Comparison of Adverse Events of Erlotinib with those of Gefitinib in Patients with Non-small Cell Lung Cancer: A Case-control Study in a Japanese Population. Osaka City Medical Journal. 2012, 58, 25-34

Osaka City Med. J. Vol. 58, 25-34, 2012

Comparison of Adverse Events of Erlotinib with those of Gefitinib in Patients with Non-small Cell Lung Cancer: A Case-control Study in a Japanese Population

Tomohiro Suzumura[1)], Tatsuo Kimura[1)], Shinzoh Kudoh[1)], Kanako Umekawa[1)], Misato Nagata[1)], Hidenori Tanaka[1)], Shigeki Mitsuoka[1)], Naruo Yoshimura[1)], Yukimi Kira[2)], and Kazuto Hirata[1)]

Departments of Respiratory Medicine[1)] and Central Laboratory[2)], Osaka City University, Graduate School of Medicine

Abstract

Background

Rash, liver dysfunction, and diarrhea are known as adverse events of erlotinib and gefitinib. However, clinical trials with gefitinib have reported different adverse events compared to those with erlotinib. In an *in vitro* study, cytochrome P450 (CYP) 2D6 was shown to be involved in the metabolism of gefitinib and not of erlotinib. It has been hypothesized that gefitinib therapy results in different adverse events compared to erlotinib therapy.

Methods

The frequency of each adverse event was evaluated in a case-control study on Japanese patients who were treated with gefitinib or erlotinib. The CYP2D6 phenotype was categorized into 2 groups according to functional or reduced metabolic levels. In addition, we evaluated the odds ratio (OR) of adverse events with each factor, including CYP2D6 activities as well as treatment types.

Results

A total of 112 patients received gefitinib therapy, 74 patients received erlotinib therapy, and 17 patients received erlotinib and gefitinib sequentially. The OR of developing rash with gefitinib versus erlotinib treatment was 0.38 (95% confidence interval [CI], 0.15-0.86). The OR of developing diarrhea with gefitinib versus erlotinib treatment was 0.46 (95% CI, 0.22-0.94). The OR of developing liver dysfunction with gefitinib versus erlotinib treatment was 3.30 (95% CI, 1.59-7.22). Reduced function of CYP2D6 was not associated with an increased risk of any adverse events in both gefitinib and erlotinib cohorts.

Received December 9, 2011; accepted January 5, 2012.
Correspondence to: Tomohiro Suzumura, MD.
Department of Respiratory Medicine, Osaka City University, Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan
Tel: +81-6-6645-3803; Fax: +81-6-6646-6808
E-mail: tsuzumura@msic.med.osaka-cu.ac.jp

Conclusions

Erlotinib had higher rate of rash and diarrhea than gefitinib. Liver dysfunction occurred significantly more often in the gefitinib group than in the erlotinib group.

Key Words: Non-small cell lung cancer; Gefitinib; Erlotinib; Adverse events

Introduction

Compared to cytotoxic agents, gefitinib and erlotinib are orally available epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) that prolong survival, have few hematological adverse events, and improve the quality of life in non-small cell lung cancer (NSCLC) patients with *EGFR*-active gene mutations[1-6]. The common adverse events that occur with gefitinib and erlotinib therapy are rash, liver dysfunction and diarrhea[1-5,7-10]. Recent clinical phase Ⅲ trials have revealed that gefitinib therapy results in a higher frequency of drug-induced liver dysfunction in Asian patients compared to erlotinib therapy[1-4,11,12].

Recent *in vitro* studies have reported different metabolic profiles of gefitinib and erlotinib for human cytochrome P450 (CYP) enzymes[13-15]. CYP3A4, 3A5, and 1A1 metabolize both erlotinib and gefitinib. However, CYP2D6 was involved in the metabolism of gefitinib and not of erlotinib. Asians have a high frequency of the reduced function of the alleles that range from 43% to 47%[16-19].

It has been hypothesized that gefitinib therapy results in different adverse events compared to erlotinib therapy. To test this, we conducted a case-control study to evaluate the adverse events of treatment with gefitinib and erlotinib. CYP2D6 phenotypes were determined from the *CYP2D6* genotype using real-time polymerase chain reaction (PCR) methods, which are able to determine single nucleotide polymorphisms (SNPs).

Methods

Study subjects and data collection

Patients with advanced NSCLC who were treated with either gefitinib or erlotinib between May 2007 and February 2011 in Osaka City University Hospital and its collaborating hospitals were recruited for this study. This study protocol was approved by the ethics committee of Osaka City University (approval number, 1700).

The frequency of each adverse event was evaluated in a case-control study that was comprised of Japanese patients treated with gefitinib or erlotinib, during the period that the patients received EGFR-TKI therapy. The participation rate among the cases was 100%. The controls were selected from the patients treated with EGFR-TKI therapy in the same hospital during the same period because hospital controls are more motivated and are more easily accessible in order to obtain DNA samples. All living participants were provided written informed consents. Formalin-fixed and paraffin-embedded tissues or blood samples (when tissues were not available) were collected. If the patients were dead, formalin-fixed and paraffin-embedded tissues were collected by permission of the ethics committee.

Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). We defined liver dysfunction as one or more events of increased levels of aspartate aminotransferase (AST), alanine aminotransferase

(ALT), or blood bilirubin. The frequency and severity of three major non-hematological toxicities including rash, diarrhea, and liver dysfunction, were evaluated.

Genotyping Methods

Genomic DNA was extracted from peripheral blood or formalin-fixed and paraffin-embedded tissue using a QIAGEN QIAamp® DNA Blood Mini Kit (QIAGEN K.K., Tokyo, Japan) and a QIAGEN QIAamp® DNA FFPE Tissue Kit (QIAGEN K.K.) according to the manufacturer's instructions. Extracted DNA samples were stored at −80℃ before examination. The DNA concentration was determined by optical density at 260 nm (Nano Drop® ND-1000, Thermo Fisher Scientific, Inc., Wilmington, DE, USA). In order to determine the *CYP2D6* polymorphisms, 4 SNPs of the *CYP2D6* gene, including rs1065852 (100C>T), rs5030865 (1758G>A), rs16947 (2850C>T), and rs1135840 (4180G>C), were measured by real-time PCR methods in order to evaluate the 5 mutated alleles, *CYP2D6*1*, **2*, **10*, **14A*, and **14B*. Genotyping was performed by Taqman® Drug Metabolism Genotyping Assays™ (Applied Biosystems Japan Ltd., Tokyo, Japan) according to the manufacturer's instructions. The following reagents were used for amplification in 10 μL: 4.5 μL of DNA (around 50 ng), 0.5 μL of each *CYP2D6* primer and probe mixture (20×), and 5 μL of GTXexpress™ Master Mix. The thermal cycling conditions consisted of the first 20 seconds at 95℃ and 40 cycles at 95℃ for 15 seconds and 60℃ for 1 minute. Primers and probes were supplied by Applied Biosystems Japan Ltd as Drug Metabolism Genotyping Assays™. The assays IDs were C__11484460_40 for rs1065852, C_30634117D_30 for rs5030865, C__27102425_10 for rs16947, and C__27102414_10 for rs1135840. All assays were conducted in 96-well plates. Plates were read on the Applied Biosystems 7500 Real-time PCR system using the Sequence Detection System Software (Applied Biosystems Japan Ltd.).

CYP2D6 phenotype

The metabolizing functions of CYP2D6 are generally categorized into 4 groups: ultra-rapid metabolizer (UM), extensive metabolizer (EM), intermediate metabolizer (IM), and poor metabolizer (PM)[20]. UM and EM result in normal or better function, and IM and PM result in reduced function. *CYP2D6* alleles were assigned based on the determination of the appropriate key mutations. *CYP2D6*1* and **2* have normal activity, **10* and **14B* have impaired activity, and **5* and **14A* have no activity[21,22]. Alleles containing additional copies of functional *CYP2D6* genes were categorized as UM. EM included a combination of one or two functional alleles, such as *CYP2D6*1* or **2*, the IM phenotype included two impaired alleles, and the PM phenotype included two non-functional alleles. In this study, the CYP2D6 phenotype was categorized into 2 groups according to the metabolic levels: functional (UM and EM) or reduced groups (IM and PM). Unknown phenotypes that had a combination of impaired and undetermined alleles or that had two undetermined alleles were excluded.

Statistical Analysis

Comparisons of patient characteristics between those treated with gefitinib or erlotinib were performed using Fisher's exact tests. Next, we identified the risk factors for the adverse events. Treatment, gender, age, stage, and CYP2D6 activity were selected and estimated in a multivariate analysis in order to adjust for its potential confounding effects for rash, diarrhea, and liver dysfunction. Unconditional logistic regressions were used to compute the odds ratios

(ORs) and their 95% confidence intervals (CIs). All analyses were two-sided, and p values less than 0.05 were considered statistically significant. The statistical analyses were performed with JMP 9 software (SAS Institute, Inc., Cary, NC, USA) and the software R version 2.10.0 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

The Consolidated Standards of Reporting Trials (CONSORT) diagram of this study is illustrated in Figure 1. A total of 169 patients with advanced NSCLC who were treated with gefitinib or erlotinib were enrolled in the study. Among them, 17 patients who were treated with gefitinib also were treated with erlotinib at different periods. DNA samples were collected from 148 patients, including 99 patients who received gefitinib and 66 patients who received erlotinib. We did not obtain DNA samples from 21 patients because of screen failure. Genomic DNA was extracted from 99 samples, including 16 blood samples and 83 tissues, in the gefitinib group and from 66 samples, including 10 blood samples and 56 tissues, in the erlotinib group.

The distributions of the patient characteristics among the study subjects are summarized in Table 1. Comparisons of the gefitinib and erlotinib groups that are representative of the cohort indicated that the gefitinib group had a lower rate of non-adenocarcinoma patients (gefitinib group, 0%; erlotinib group, 9.8%; p=0.003), and a higher rate of active *EGFR* mutation-positive patients (gefitinib group, 73.7%; erlotinib group, 60.6%; p<0.001). There were no significant

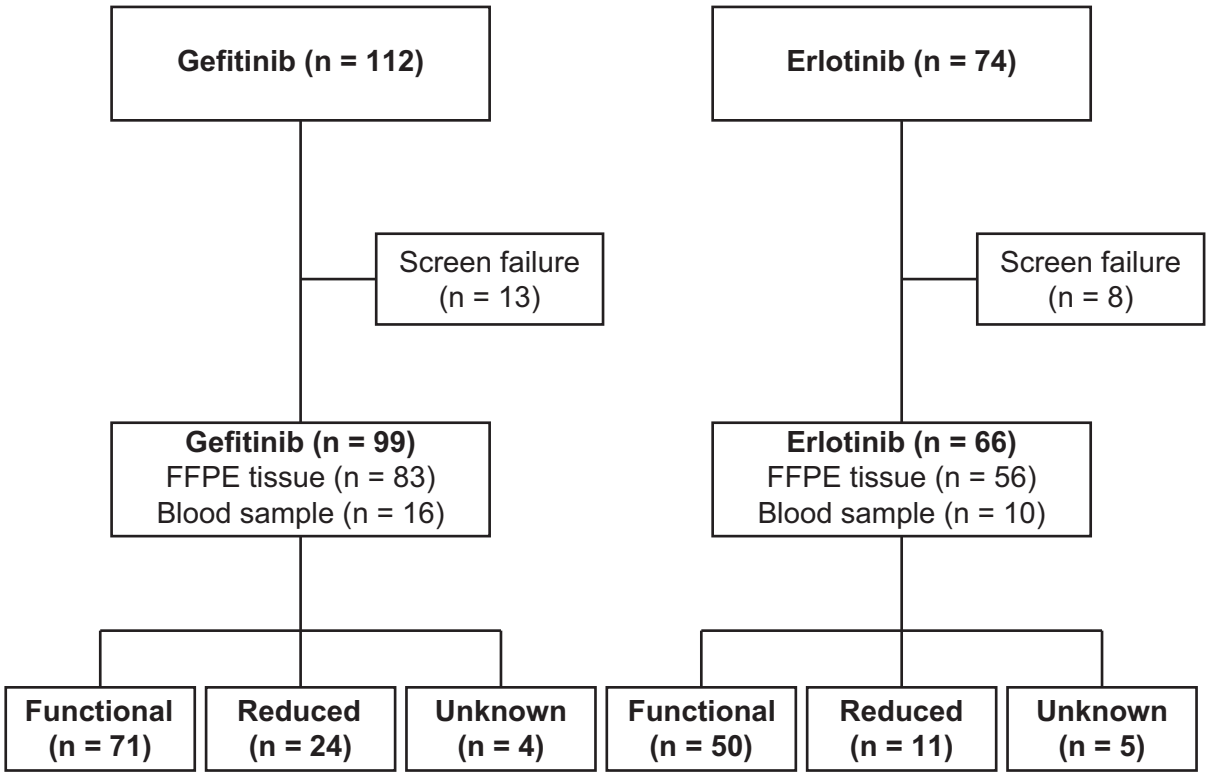

Figure 1. CONSORT diagram. This diagram shows the patient distributions according to gefitinib or erlotinib therapy. Seventeen patients received erlotinib and gefitinib sequentially. Among them, 12 patients are functional, 4 patients are reduced, and one patient is unknown phenotype. FFPE, formalin-fixed paraffin-embedded.

Table 1. Patient characteristics of gefitinib and erlotinib with functional or reduced CYP2D6 activity

Characteristics	Gefitinib (n=95)	Erlotinib (n=61)	p value
Median age (range)	68 (34-90)	64 (34-86)	0.18
70 or older	44	21	
under 70	51	40	
Gender			0.24
Male	60	32	
Female	35	29	
Histology			
Adenocarcinoma	95	55	0.003
Squamous cell carcinoma	0	5	
Large cell carcinoma	0	1	
Smoking status			0.33
Ever smoker	43	33	
Never smoker	52	28	
ECOG performance status			0.06
0	19	6	
1	61	50	
2 - 4	15	5	
EGFR mutation status			<0.001
Positive	70	37	
Negative	2	15	
Unknown	23	9	
Stage			0.44
Ⅰ-ⅢB	24	12	
Ⅳ	71	49	
HCV antibody			0.14
Positive	5	4	
Negative	84	57	
Unknown	6	0	
HBs antigen			0.08
Positive	1	0	
Negative	88	61	
Unknown	6	0	
Pretreatment LFT			0.58
normal	67	46	
abnormal	28	15	
CYP2D6 activity			0.33
functional	71	50	
reduced	24	11	

ECOG, Eastern Cooperative Oncology Group; EGFR, Epidermal Growth Factor Receptor; HCV, hepatitis C virus; HBs, hepatitis B surface; LFT, liver function test; and CYP2D6, cytochrome P450 2D6.

differences between the gefitinib and erlotinib groups in terms of age, sex ratio, smoking status, Eastern Cooperative Oncology Group performance status, stages, infection with the hepatitis B or C virus, CYP2D6 functions, or pretreatment liver function tests.

Adverse events

In the gefitinib treatment group, the rate of all grades and grade 3 or 4 of rash were 70.5% and 3.2%, those of diarrhea were 24.2% and 2.1%, and those of liver dysfunction were 45.3% and

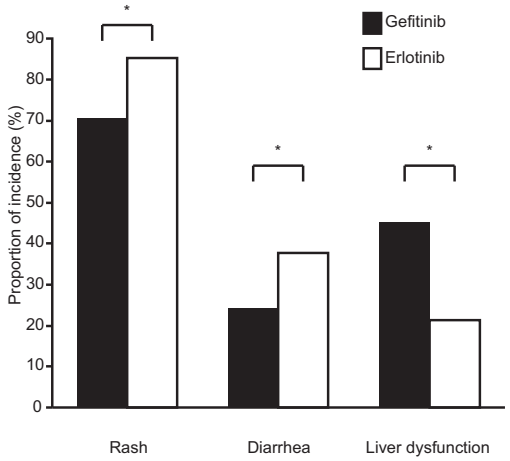

Figure 2. Comparison of adverse events between gefitinib and erlotinib groups. Liver dysfunction of all grades occurred significantly more often in the gefitinib group than in the erlotinib group (p=0.001). Rash and diarrhea occurred significantly more often in the erlotinib group than in the gefitinib group (p=0.02, 0.03, respectively). *p<0.05 by logistic regression model.

Table 2. Characteristics of confirmed cases in each adverse event

Characteristics	Cases			Total (n=156)
	Rash (n=119)	Diarrhea (n=46)	Liver dysfunction (n=56)	
Treatment				
Gefitinib	67	23	43	95
Erlotinib	52	23	13	61
Median age	67	66.5	68	67
(range)	(34-90)	(47-86)	(34-90)	(34-90)
70 or older	52	20	22	65
under 70	67	26	34	91
Gender				
Male	49	14	22	64
Female	70	32	34	92
Histology				
Adenocarcinoma	113	45	56	150
Squamous cell carcinoma	5	1	0	5
Large cell carcinoma	1	0	0	1
Smoking status				
Ever smoker	58	19	24	76
Never smoker	61	27	32	80
ECOG performance status				
0	21	2	11	25
1	88	39	38	111
2 - 4	10	5	7	20
EGFR mutation status				
Positive	82	27	43	107
Negative	15	9	2	17
Unknown	22	10	11	32
Stage				
Ⅰ-ⅢB	29	10	11	36
Ⅳ	90	36	45	120
CYP2D6 activity				
functional	93	33	44	121
reduced	26	13	12	35

ECOG, Eastern Cooperative Oncology Group; EGFR, Epidermal Growth Factor Receptor; and CYP2D6, cytochrome P450 2D6.

15.8%, respectively. In the erlotinib treatment group, the rate of all grades and grade 3 or 4 of rash were 85.3% and 8.2%, those of diarrhea were 37.7% and 0%, and those of liver dysfunction were 21.3% and 4.9%, respectively. Figure 2 shows the frequencies and severities of rash, diarrhea, and liver dysfunction. Two interstitial lung disease (ILD) patients were observed only in the gefitinib group, and ILD related death was observed in one patient.

Case and control subjects

The frequency of each adverse event was evaluated. Table 2 shows the characteristics of the cases and controls with rash, diarrhea, and liver dysfunction. In the overall cohort data, 119 cases (76.3%) of rash, 46 cases (29.5%) of diarrhea, and 56 cases (35.9%) of liver dysfunction were observed. Because controls were selected from the patients treated with EGFR-TKI therapy, there were no significant differences in the characteristics, except for the treatment between each case and control.

The ORs for the risk factors of adverse events from the final logistic regression model are shown in Figure 3. The OR of developing rash with gefitinib versus erlotinib treatment was 0.38 (95% CI, 0.15-0.86). The OR of developing diarrhea with gefitinib versus erlotinib treatment was 0.46 (95% CI, 0.22-0.94). The OR of developing liver dysfunction with gefitinib versus erlotinib treatment was 3.30 (95% CI, 1.59-7.22). There were no risk factors aside from treatment that

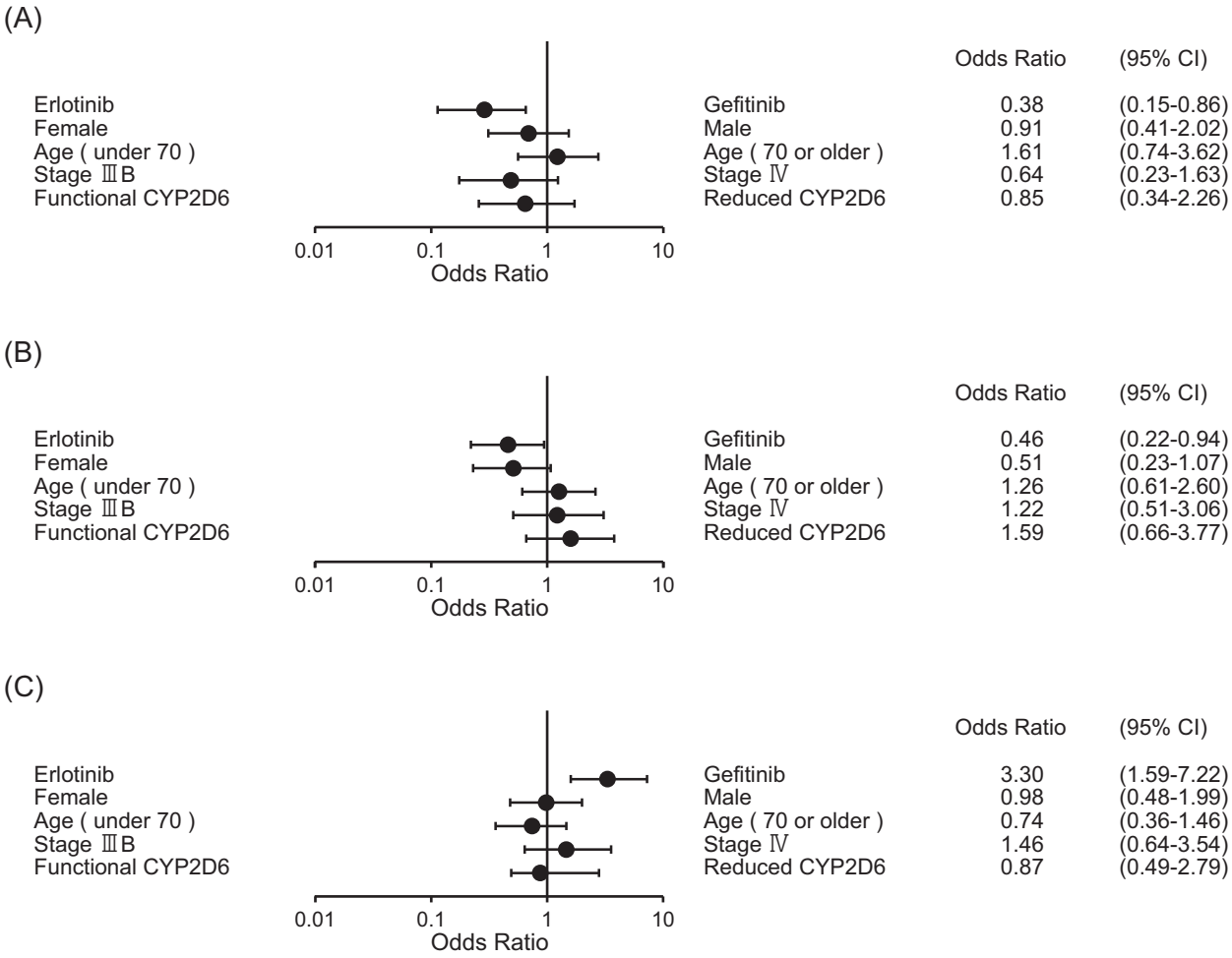

Figure 3. Odds ratio for risk factors in forest plots. Forest plots for rash (A), diarrhea (B), and liver dysfunction (C) by multiple logistic regression models. Each adverse event was divided into two groups of grade 0 or 1 to 4.

had significant effects on all grades of diarrhea and liver dysfunction.

CYP2D6 alleles, genotype and phenotype

A total of 109 patients showed genotypes that predicted normal function, 31 patients showed genotypes that predicted the reduced function, and 8 patients had unknown genotypes. The reduced function group was not associated with an increased risk of any adverse events in both of the gefitinib and erlotinib cohorts (in the gefitinib cohort with reduced versus functional CYP2D6 activity, rash: OR, 0.78 and 95% CI, 0.29-2.19; diarrhea: OR, 1.87 and 95% CI, 0.65-5.15; liver dysfunction: OR, 0.82 and 95% CI, 0.32-2.09; in the erlotinib cohort with reduced versus functional CYP2D6 activity, rash: OR, 1.9 and 95% CI, 0.30-37.39; diarrhea: OR, 1.48 and 95% CI, 0.38-5.61; liver dysfunction: OR, 0.79 and 95% CI, 0.11-3.65).

Discussion

We have demonstrated that patients treated with gefitinib had a significantly higher frequency of liver dysfunction than patients treated with erlotinib. In contrast, patients treated with erlotinib had a significantly higher frequency of rash and diarrhea than patients treated with gefitinib.

Almost all of the patients received properly supportive care in their treatment. The adverse events were generally controlled, except for ILD. In our study, gefitinib treatment showed different adverse events compared to those of erlotinib treatment. In general, erlotinib was associated with more toxicity and less tolerability than gefitinib because the dose of erlotinib was nearly equal to the maximum tolerated dose, whereas the dose of gefitinib was nearly equal to the minimum active dose. However, the gefitinib group had a high frequency of liver dysfunction. In the gefitinib group, the rate of liver dysfunction of all grades in our study was 45.3%, including 19.0% of grade 1, 10.5% of grade 2, 14.7% of grade 3, and 1.1% of grade 4. In the erlotinib group, the rate of liver dysfunction in our study was 21.3%, including 8.2% of grade 1, 8.2% of grade 2, 4.9% of grade 3, and 0% of grade 4. With respect to gefitinib therapy, Maemondo et al reported a rate of 55% of all grades of increased levels of aminotransferase elevation, and a rate of grade 3 or 4 was 21.5% in a Japanese cohort[2]. Mitsudomi et al reported a rate of 70.1% of all grades and a rate of 16.1% of grade 3 or 4[12]. With respect to erlotinib therapy, an Asian report of a multicenter, open-label, and randomized phase Ⅲ study showed a rate of 37% for all grades of increased levels of ALT, and a rate of 4% of grade 3 or 4[23]. Our results were similar to those found in previous gefitinib and erlotinib phase Ⅲ clinical trials in Japanese and Asian subjects. There have been few reports that have compared the safety between gefitinib and erlotinib. Togashi's report of adverse events showed that liver function test abnormalities did not differ between the gefitinib and erlotinib groups[9]. The findings of this study showed a very low frequency of liver dysfunction with gefitinib therapy compared to previous Japanese phase Ⅲ reports[2,3,12]. This could possibly be due to the fact that both Togashi's and our report were retrospective studies and the criteria for dose reduction or discontinuation were not defined. Early discontinuation of gefitinib may occur.

CYP2D6 metabolizes many clinically important drugs, including antidepressants, neuroleptics, beta blockers, anti-arrhythmics, and anti-cancer agents. In breast cancer patients who were treated with tamoxifen, the CYP2D6 phenotype was associated with survival[24] and with the concentration of the active tamoxifen metabolite, endoxifen[25]. However, in our study,

the subjects with CYP2D6 reduced function were not associated with an increased risk of any adverse events in both the gefitinib and erlotinib cohorts. One of the reasons was that our study was too small to have enough power to detect the association with CYP2D6 activity and any adverse events including liver dysfunction.

We are always faced with the disparity in selecting these drugs in clinical practice. In previous reports, erlotinib has been shown to prolong survival in unselected and in the *EGFR* wild-type patients with NSCLC after first-line or second-line chemotherapy[6,26]. These are the reasons why the erlotinib group had a significantly higher population of non-adenocarcinoma patients than the gefitinib group, and the gefitinib group had a higher population of *EGFR* mutation-positive patients than the erlotinib group.

The limitations of this study include that the number of patients was too small to have enough power to detect significant differences of the adverse events between CYP2D6 phenotypes. We could not separate the UM cohort from the EM cohort. Because UM consists of *CYP2D6*1* or **2*, this group was included with EM in this study. The blood concentrations of gefitinib and erlotinib and the metabolites of gefitinib and erlotinib were not measured. The relationship between these concentrations and reduced CYP2D6 activity remains to be elucidated.

We conclude that patients treated with gefitinib had a significantly higher frequency of liver dysfunction than patients treated with erlotinib. In contrast, patients treated with erlotinib had a significantly higher frequency of rash and diarrhea than patients treated with gefitinib. Further clinical studies that consist of prospective investigations in a large patient population with pharmacokinetics/pharmacodynamics analyses and that include detailed information on CYP2D6 phenotype and activity as well as CYP2D6 genotypes should be conducted.

Acknowledgements

The authors thank Ms. Matsuyama, Ms. Nakai, and Ms. Tsuji for their secretarial assistance.

References

1. 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;372:1809-1818.
2. 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;362:2380-2388.
3. 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;26:4244-4252.
4. 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;361:947-957.
5. 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;366:1527-1537.
6. 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;353:123-132.
7. 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;5:179-184.
8. Lee JH, Jo YR, Park HS, Ryu YJ, Chun EM, Chang JH. Comparison of gefitinib and erlotinib for Korean

patients with advanced non-small cell lung cancer. J Thorac Oncol 2009;4:S692.
9. Togashi Y, Masago K, Fujita S, Hatachi Y, Fukuhara A, Nagai H, et al. Differences in adverse events between 250 mg daily gefitinib and 150 mg daily erlotinib in Japanese patients with non-small cell lung cancer. Lung Cancer 2011;74:98-102.
10. Uhm JE, Sun JM, Lee SH, Kong JH, Yun JA, Lee SM, et al. Comparison of erlotinib (Tarceva (TM)) versus gefitinib (Iressa (R)) as the second line therapy for the treatment of advanced non-small cell lung cancer patients: a randomized phase Ⅱ trial. J Thorac Oncol 2009;4:S292.
11. 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;24:2549-2556.
12. 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;11:121-128.
13. Kijima T, Shimizu T, Nonen S, Furukawa M, Otani Y, Minami T, et al. Safe and successful treatment with erlotinib after gefitinib-induced hepatotoxicity: difference in metabolism as a possible mechanism. J Clin Oncol 2011;29:E588-E590.
14. 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;13:3731-3737.
15. McKillop D, McCormick AD, Millar A, Miles GS, Phillips PJ, Hutchison M. Cytochrome P450-dependent metabolism of gefitinib. Xenobiotica 2005;35:39-50.
16. Johansson I, Oscarson M, Yue QY, Bertilsson L, Sjöqvist F, Ingelman-Sundberg M. Genetic analysis of the Chinese cytochrome P4502D locus: characterization of variant CYP2D6 genes present in subjects with diminished capacity for debrisoquine hydroxylation. Mol Pharmacol 1994;46:452-459.
17. Tateishi T, Chida M, Ariyoshi N, Mizorogi Y, Kamataki T, Kobayashi S. Analysis of the CYP2D6 gene in relation to dextromethorphan O-demethylation capacity in a Japanese population. Clin Pharmacol Ther 1999;65:570-575.
18. Kubota T, Yamaura Y, Ohkawa N, Hara H, Chiba K. Frequencies of CYP2D6 mutant alleles in a normal Japanese population and metabolic activity of dextromethorphan O-demethylation in different CYP2D6 genotypes. Br J Clin Pharmacol 2000;50:31-34.
19. Nishida Y, Fukuda T, Yamamoto I, Azuma J. CYP2D6 genotypes in a Japanese population: low frequencies of CYP2D6 gene duplication but high frequency of CYP2D6*10. Pharmacogenetics 2000;10:567-570.
20. Bradford LD. CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. Pharmacogenomics 2002;3:229-243.
21. Sim SC. CYP2D6 allele nomenclature. 2011; Available from: http://www.cypalleles.ki.se/cyp2d6.htm.
22. Johansson I, Lundqvist E, Bertilsson L, Dahl ML, Sjöqvist F, Ingelman-Sundberg M. Inherited amplification of an active gene in the cytochrome P450 CYP2D locus as a cause of ultrarapid metabolism of debrisoquine. Proc Natl Acad Sci U S A 1993;90:11825-11829.
23. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, 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;12:735-742.
24. Abraham JE, Maranian MJ, Driver KE, Platte R, Kalmyrzaev B, Baynes C, et al. CYP2D6 gene variants: association with breast cancer specific survival in a cohort of breast cancer patients from the United Kingdom treated with adjuvant tamoxifen. Breast Cancer Res 2010;12:R64.
25. Irvin WJ Jr, Walko CM, Weck KE, Ibrahim JG, Chiu WK, Dees EC, et al. Genotype-guided tamoxifen dosing increases active metabolite exposure in women with reduced CYP2D6 metabolism: a multicenter study. J Clin Oncol 2011;29:3232-3239.
26. Zhu CQ, da Cunha Santos G, Ding K, Sakurada A, Cutz JC, Liu N, et al. Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol 2008;26:4268-4275.