의학석사 학위논문

Gefitinib-induced Interstitial Lung Disease in Korean Lung Cancer Patients

제피티닙 치료를 받은 한국의 폐암 환자에서 발생한 약제유발 간질성 폐렴

2014년 2월

서울대학교 대학원

임상의과학과

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2013년 10월

서울대학교 대학원

임상의과학과

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범승훈의 의학석사 학위논문을 인준함

2013년 12월

위원장 _____(인)

부위원장 _____(인)

위원 _____(인)

Gefitinib-induced Interstitial Lung Disease in Korean Lung Cancer Patients

by

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A thesis submitted to the department of Clinical Medical Sciences in partial fulfillment of the requirements for the degree of Master of Science in Clinical Medical Sciences at the Seoul National University College of Medicine, Seoul, Korea

December, 2013

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ABSTRACT

Background

Gefitinib is effective in the treatment of advanced non-small cell lung cancer (NSCLC), especially in patients harboring an epidermal growth factor receptor (EGFR) gene mutation. Interstitial lung disease (ILD) is a serious adverse effect of gefitinib, but its incidence and risk factors are not clearly defined yet. We examined the incidence and clinical characteristics of drug-induced ILD in Korean NSCLC patients treated with gefitinib.

Patients and methods

A retrospective cohort study was performed in NSCLC patients who started gefitinib treatment at Seoul National University Hospital from January 2002 through December 2011. Patients who developed new abnormal radiologic findings with respiratory symptoms after gefitinib treatment were defined as having possible adverse pulmonary reactions. The patients' medical records were reviewed independently by investigators to identify the causes of pulmonary toxicities. Multivariate logistic regression analyses were performed to identify independent predictive factors for gefitinib-induced ILD.

Results

Among the 1,114 patients evaluated, 128 (11.5%) patients developed pulmonary adverse reactions after taking gefitinib. An infectious complication occurred in 98 (8.8%) patients and 15 (1.3%) patients developed ILD. Nine (60.0%) of the 15 patients with gefitinib-induced ILD experienced a fatal clinical course that met the Common Terminology Criteria for

Adverse Events (CTCAE) grade 4 (n = 3) or grade 5 (n = 6). Twelve (80.0%) of 15 patients developed ILD in the first 8 weeks of gefitinib administration. In multivariate analysis, a lower serum albumin level at the time of gefitinib initiation was significantly associated with the development of gefitinib-induced ILD (odds ratio = 0.46; 95% confidence interval: 0.22 – 0.98, P = 0.045).

Conclusions

The incidence of gefitinib-induced ILD in Korean NSCLC patients was similar to that reported worldwide, but lower than values reported for other Asian populations. ILD is usually a life-threatening adverse effect of gefitinib and the development of ILD should be monitored closely, particularly among patients with a low serum albumin level.

Key words: gefitinib, interstitial lung disease, pulmonary toxicity, adverse event, lung cancer

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INTRODUCTION

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors are well-established treatments for advanced non-small cell lung cancer (NSCLC) in many countries. They are generally well tolerated and not associated with the side effects typical of cytotoxic chemotherapy.

Gefititinib (Iressa®, AstraZeneca, London, U.K.) is an orally administered, reversible tyrosine kinase inhibitor of EGFR (1). In 2002 it was approved for the treatment of inoperable or recurrent NSCLC based on the results of two large-scale multicenter phase II studies that showed favorable responses and low toxicities (2, 3). The Iressa Pan-Asia Study (IPASS) found that gefitinib produced longer progression-free survival compared to carboplatin plus paclitaxel in patients with advanced pulmonary adenocarcinoma harboring EGFR mutations (4). A more recent phase III trial, conducted in metastatic NSCLC patients with mutated EGFR, confirmed these findings (5).

Common adverse events associated with gefitinib treatment are diarrhea, skin rashes, and nausea, but most of these adverse events are mild in severity and manageable (4, 6). However, since the first report of gefitinib-induced interstitial lung disease (ILD) from Japan (7), ILD associated with molecularly targeted agents has warranted considerable attention. The incidence of ILD during gefitinib treatment was not infrequent and varied among different ethnicities. The incidence of gefitinib-induced ILD was approximately 1% in worldwide populations (8), while the frequency of ILD in the Japanese series was reported to be much higher than that in the rest of the world (9). The incidence in other Asian populations, besides Japanese, remains uncertain. In Korean patients, one prospective study reported that 2 (1.3%) of 159 patients developed ILD during gefitinib treatment (10).

Gefitinib-induced ILD is often life-threatening; its mortality is approximately 30-40% (11).

However, investigation of predictive and prognostic factors for gefitinib-induced ILD is limited; therefore, these factors are not clearly defined yet. Even less is known about the mechanisms of developing ILD.

In this study, we aimed to determine the incidence of gefitinib-induced ILD in a large Korean population and describe the major clinical findings. Also we evaluated possible risk factors and prognostic factors for gefitinib-induced ILD. Furthermore, we analyzed the association between clinical factors and the development of adverse pulmonary reactions related to gefitinib.

PATIENTS AND METHODS

Study populations

A retrospective cohort study was performed with histology proven NSCLC patients who were treated with gefitinib at Seoul National University Hospital from January 2002 through December 2011. Patient clinical data, including medical records, radiographic findings and laboratory results were reviewed. This study protocol was approved by the Institutional Review Board (IRB) of the Seoul National University Hospital (IRB protocol number: H 1308-047-511).

Clinical data collection

The following demographic data were abstracted: age, sex, comorbidities, smoking history, Eastern Cooperative Oncology Group (ECOG) performance status (PS), histologic type, previous anticancer treatment and concurrent pulmonary disease (e.g. pulmonary emphysema

or interstitial pneumonitis). Adverse events from gefitinib treatment were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) from the National Cancer Institute, version 4.0 and a fatal adverse event was defined as being CTCAE grade 4 or grade 5 (any experience that resulted in death). Treatment response to gefitinib was assessed according to the criteria of the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (12). We classified a patient who had partial response or complete response as a responder. Laboratory results, including complete blood cell and differential counts, chemistry tests, and oxyhemoglobin saturation measured by pulse oxymetry (SpO2) performed when gefitinib treatment began and when ILD occurred were collected. Overall survival was calculated from the initiation of gefitinib treatment to the date of death or last follow-up.

Confirmation of adverse pulmonary reaction and gefitinib-induced ILD

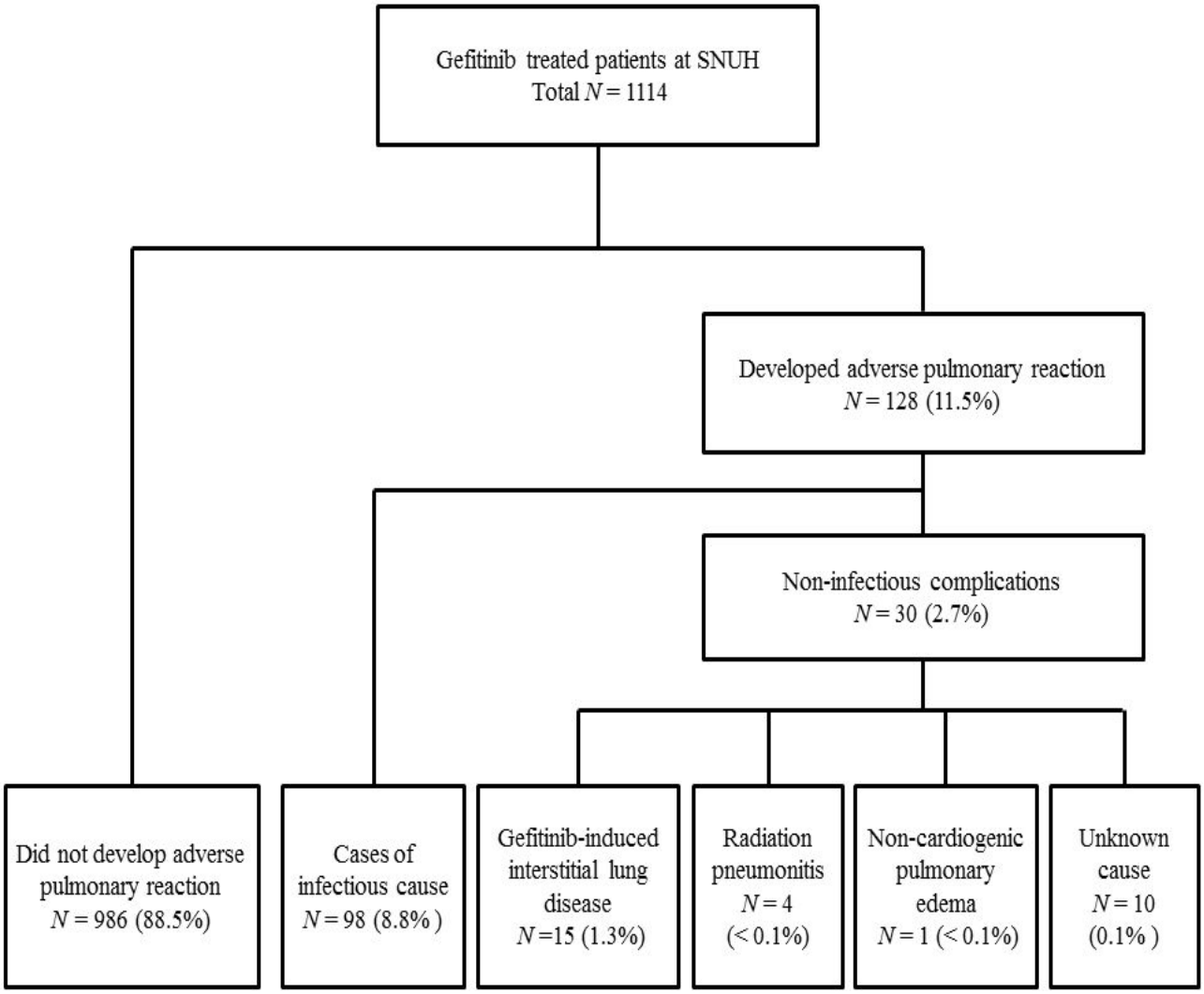
New abnormal radiologic findings with respiratory symptoms after gefitinib treatment were defined as possible adverse pulmonary reactions. To identify the cause of an adverse pulmonary reaction, two of the investigators (SH Beom and SH Sim) reviewed the data independently. If their opinions differed, regarding the cause of an adverse pulmonary reaction, another investigator (DW Kim) made the decision. Pulmonary infiltrates identified as lung cancer progression were excluded from this evaluation. Adverse pulmonary reactions were classified as non-infectious and infectious complications; the causes of non-infectious complications were categorized according to classifications described in previous studies (13, 14). The diagnosis of gefitinib-induced ILD was based on previously published, generally accepted clinical criteria (11, 15). In brief, for the diagnosis of ILD, four specific findings were required: (1) progressive dyspnea with or without cough or fever, (2) lack of evidence

of infection, (3) radiologic findings consistent with drug-induced ILD (i.e., bilateral, diffuse, or patchy interstitial and/or alveolar opacifications without evidence of marked progression of underlying lung cancer), and (4) consistent pathologic findings, if available.

Statistical analysis

Categorical clinical variables were compared using a χ^2 test or Fisher's exact test; continuous variables were compared using an independent unpaired *t* test or the Mann-Whitney *U* test if the variables were not normally distributed. Univariate analysis was performed to evaluate associations between the outcomes of gefitinib-induced ILD or adverse pulmonary reactions, and patient characteristics. Predictive factors for gefitinib-induced ILD and adverse pulmonary reaction were assessed by multivariate analysis using logistic regression models. Kaplan-Meier method was used to assess overall survival after onset of ILD in different patient groups. *P* values $\leq$ 0.05 were considered statistically significant. All statistical analyses were performed with SPSS software, version 21.0 (IBM SPSS Statistics, IBM Corp., Somers, NY).

Figure 1. Outline of patient recruitment and distribution of adverse pulmonary reactions.



RESULTS

Incidence of adverse pulmonary reaction and gefitinib-induced ILD

The medical records of the 1,114 patients who received gefitinib from January 2002 through December 2011 were reviewed and abstracted (Figure 1). Among these patients, 128 (11.5%) patients developed symptomatic pulmonary infiltrates after treatment initiation. All patients were treated with gefitinib monotherapy. An infectious pulmonary complication occurred in 98 (8.8%) patients and 30 (2.7%) patients experienced a non-infectious pulmonary complication. Fifteen patients (1.3%) with gefitinib-induced ILD were identified.

Risk factors for adverse pulmonary reaction

Univariate analysis found that poor ECOG PS (2 to 4), the coincidence of interstitial lung disease, underlying emphysema, lower hemoglobin level, higher leukocytes count and lower albumin level were associated with the development of an adverse pulmonary reaction (Table 1). Multivariate logistic regression analysis revealed that poor ECOG PS (OR= 2.07; 95% CI: 1.37-3.12; P = 0.001) and lower albumin level (OR = 0.65; 95% CI: 0.46-0.93; P = 0.017) significantly predicted an adverse pulmonary reaction (Table 2). Patients with the coincidence of ILD and underlying emphysema tended to develop adverse pulmonary reactions more frequently (P = 0.097 and P = 0.059, respectively).

Risk factors for gefitinib-induced ILD

In multivariate analysis, as well as in univariate analysis, only a lower serum albumin level was significantly associated with the development of gefitinib-induced ILD after adjusting for sex, coincidence of ILD, histologic type, creatinine and ALT level (OR = 0.46; 95% CI: 0.22-0.98; $P = 0.045$, Tables 1 and 3). Patients with the coincidence of ILD and the histologic type of non-adenocarcinoma tended to develop gefitinib-related ILD more frequently ($P = 0.124$ and $P = 0.087$, respectively). The fitness of this model was confirmed with the Hosmer-Lemeshow goodness of fitness test ($P = 0.461$).

Table 1. Univariate analysis of risk factors for adverse pulmonary reaction and gefitinib-induced interstitial lung disease (ILD).

Variable	Total	Adverse pulmonary reaction				Gefitinib-induced ILD			
	N = 1114	No (*N* = 986)	Yes (*N* = 128)	Odds ratio (95% CI)	*P*-value	No (*N* = 1099)	Yes (*N* = 15)	Odds ratio (95% CI)	*P*-value
Age, years, mean	60.34 (range, 25-91)	60.15 ± 11.40	61.82 ± 11.57	1.01 (1.00-1.03)	0.120[a]	60.33 ± 11.44	60.98 ± 10.78	1.01 (0.96-1.05)	0.828
Sex									
Female	600 (53.9)	527 (53.4)	73 (57.0)	1		589 (53.6)	11 (73.3)	1	
Male	514 (46.1)	459 (46.6)	55 (43.0)	1.16 (0.80-1.68)	0.445	510 (46.4)	4 (26.7)	2.38 (0.75-7.52)	0.139[b]
History of smoking									
No	643 (57.7)	570 (57.8)	73 (57.0)	1		633 (57.6)	10 (66.7)	1	
Yes	463 (41.6)	409 (41.5)	54 (42.2)	1.03 (0.71-1.50)	0.873	458 (41.7)	5 (33.3)	0.69 (0.24-2.04)	0.503
Unknown	8 (0.7)	7 (0.7)	1 (0.8)			8 (0.7)	0 (0.0)		
ECOG PS									
0-1	733 (65.8)	677 (68.7)	56 (43.8)	1		724 (65.9)	9 (60.0)	1	
2-4	372 (33.4)	302 (30.6)	70 (54.7)	2.80 (1.92-4.08)	<0.0001[a]	366 (33.3)	6 (40.0)	1.32 (0.47-3.73)	0.602
Unknown	9 (0.8)	7 (0.7)	2 (1.6)			9 (0.8)	0 (0.0)		
Comorbidities									
Diabetes									
No	941 (84.5)	830 (84.2)	111 (86.7)	1		929 (84.5)	12 (80.0)	1	
Yes	157 (14.1)	140 (14.2)	17 (13.3)	0.91 (0.53-1.56)	0.727	154 (14.0)	3 (20.0)	1.51 (0.42-5.41)	0.528
Unknown	16 (1.4)	16 (1.6)				16 (1.5)	0 (0.0)		
Hypertension									
No	742 (66.6)	657 (66.6)	85 (66.4)	1		730 (66.4)	12 (80.0)	1	
Yes	355 (31.9)	312 (31.6)	43 (33.6)	1.07 (0.72-1.58)	0.751	352 (32.0)	3 (20.0)	0.52 (0.15-1.85)	0.311
Unknown	17 (1.5)	17 (1.7)	0 (0.0)			17 (1.5)	0 (0.0)		
History of previous tuberculosis									
No	896 (80.4)	798 (80.9)	98 (76.6)	1		883 (80.3)	13 (86.7)	1	

Yes	201 (18.0)	171 (17.3)	30 (23.4)	1.43 (0.92-2.22)	0.113[a]	199 (18.1)	2 (13.3)	0.68 (0.15-3.05)	0.617
Unknown	17 (1.5)	17 (1.7)	0 (0.0)			17 (1.5)	0 (0.0)		
Interstitial lung disease									
No	1096 (98.4)	973 (98.7)	123 (96.1)	1		1082 (98.5)	14 (93.3)	1	
Yes	18 (1.6)	13 (1.3)	5 (3.9)	3.04 (1.07-8.68)	0.037[a]	17 (1.5)	1 (6.7)	4.55 (0.57-36.56)	0.155[b]
Emphysema									
No	907 (81.4)	816 (82.8)	91 (71.2)	1		894 (81.3)	13 (86.7)	1	
Yes	207 (18.6)	170 (17.2)	37 (28.9)	1.95 (1.29-2.96)	0.002[a]	205 (18.7)	2 (13.3)	0.74 (0.17-3.30)	0.692
Chronic kidney disease									
No	1040 (93.4)	918 (93.1)	122 (95.3)	1		1025 (93.3)	15 (100.0)	1	
Yes	58 (5.2)	52 (5.3)	6 (4.7)	0.87 (0.37-2.06)	0.749	58 (5.3)	0 (0.0)	0.00	0.997
Unknown	16 (1.6)	16 (1.6)	0 (0.0)			16 (1.5)	0 (0.0)		
Chronic liver disease									
No	1018 (91.4)	897 (91.0)	121 (94.5)	1		1003 (91.3)	15 (100.0)	1	
Yes	80 (7.2)	73 (7.4)	7 (5.5)	0.71 (0.32-1.58)	0.402	80 (7.3)	0 (0.0)	0.00	0.997
Unknown	16 (1.4)	16 (1.6)	0 (0.0)			16 (1.5)	0 (0.0)		
Histological type									
Adenocarcinoma	797 (71.5)	711 (72.1)	86 (67.2)	1		789 (71.8)	8 (53.3)	1	
Others	317 (28.5)	275 (27.9)	42 (32.8)	1.26 (0.85-1.87)	0.246	310 (28.2)	7 (46.7)	2.23 (0.80-6.19)	0.125[b]
Previous treatment									
Previous chest surgery									
No	905 (81.2)	802 (81.3)	103 (80.5)	1		894 (81.3)	11 (73.3)	1	
Yes	209 (18.8)	184 (18.7)	25 (19.5)	1.06 (0.66-1.69)	0.813	205 (18.7)	4 (26.7)	1.59 (0.50-5.03)	0.434
Previous thoracic radiotherapy									
No	894 (80.3)	798 (80.9)	96 (75.0)	1		881 (80.2)	13 (86.7)	1	
Yes	220 (19.7)	188 (19.1)	32 (25.0)	1.42 (0.92-2.18)	0.114[a]	218 (19.8)	2 (13.3)	0.62 (0.14-2.78)	0.534
Previous chemotherapy									
No	169 (15.2)	146 (14.8)	23 (18.0)	1		168 (15.3)	1 (6.7)	1	

Yes	945 (84.8)	840 (85.2)	105 (82.0)	0.79 (0.49-1.29)	0.349	931 (84.7)	14 (93.3)	2.53 (0.33-19.34)	0.372
Laboratory results at baseline									
Hemoglobin (g/dL)	11.84 ± 1.74	11.88 ± 1.72	11.49 ± 1.81	0.88 (0.79-0.98)	0.018[a]	11.84 ± 1.74	11.49 ± 1.25	0.89 (0.67-1.19)	0.434
Leukocytes (x 10^3/μL)	7.71 ± 3.68	7.59 ± 3.61	8.70 ± 4.10	1.07 (1.03-1.12)	0.002[a]	7.70 ± 3.66	8.45 ± 4.98	1.05 (0.93-1.17)	0.435
Creatinine (mg/dL)	0.94 ± 0.35	0.94 ± 0.31	0.93 ± 0.56	0.91 (0.51-1.62)	0.753	0.94 ± 0.35	0.81 ± 0.16	0.08 (0.01-1.10)	0.059[b]
AST (IU/L)	24.76 ± 15.42	24.84 ± 15.64	24.08 ± 13.69	1.00 (0.98-1.01)	0.598	24.81 ± 15.50	20.53 ± 6.92	0.96 (0.89-1.03)	0.251
ALT (IU/L)	24.70 ± 31.47	24.64 ± 32.05	25.15 ± 26.65	1.00 (1.00-1.01)	0.864	24.82 ± 31.65	15.60 ± 8.53	0.95 (0.89-1.01)	0.100[b]
Albumin (g/dL)	3.82 ± 0.58	3.85 ± 0.58	3.57 ± 0.57	0.49 (0.37-0.65)	<0.0001[a]	3.83 ± 0.58	3.49 ± 0.55	0.49 (0.26-0.91)	0.025[b]

Data are presented as mean ± standard deviation or *n* (%), unless otherwise stated.

[a] and [b] Data used for multivariate analysis of risk factors for adverse pulmonary reaction and gefitinib-induced ILD.

Table 2. Multivariate analysis of risk factors for adverse pulmonary reaction.

Variables	Adjusted odds ratio	95% CI	*P* value
Age (years) [a]	1.00	0.99-1.02	0.810
ECOG PS			
2-4 vs. 0-1	2.07	1.37-3.12	0.001
History of previous tuberculosis	1.27	0.79-2.02	0.322
Interstitial lung disease	2.59	0.84-7.97	0.097
Emphysema	1.54	0.98-2.42	0.059
Previous thoracic radiotherapy	1.11	0.70-1.76	0.653
Hemoglobin (g/dL)[b]	0.98	0.87-1.10	0.714
Leukocytes (x 10^3/μL)[c]	1.03	0.98-1.08	0.247
Albumin (g/dL)[d]	0.65	0.46-0.93	0.017

[a] (*x* + 1 years vs. *x* years).

[b] (*x* + 1 g/dL vs. *x* g/dL).

[c] (*x* + 1 x 10^3/μL vs. *x* x 10^3/μL).

[d] (*x* + 1 g/dL vs. *x* g/dL).

Table 3. Multivariate analysis of risk factors for gefitinib-induced interstitial lung disease.

Variables	Adjusted odds ratio	95% CI	*P* value
Sex (male)	2.85	0.72-11.34	0.137
Interstitial lung disease	5.50	0.63-48.35	0.124
Others vs. adenocarcinoma	2.57	0.87-7.61	0.087
Creatinine (mg/dL)[a]	0.26	0.01-4.59	0.356
ALT (IU/L)[b]	0.96	0.90-1.01	0.137
Albumin (g/dL)[c]	0.46	0.22-0.98	0.045

[a] (*x* + 1 mg/dL vs. *x* mg/dL).

[b] (*x* + 1 IU/L vs. *x* IU/L).

[c] (*x* + 1 g/dL vs. *x* g/dL).

Clinical characteristics of gefitinib-induced ILD

Clinical and laboratory findings of gefitinib-induced ILD are summarized in Table 4. The median time interval from the start of gefitinib administration to onset of ILD was 29.0 days (range: 3-1953 days). In 12 (80.0%) patients, ILD occurred during the first 8 weeks of gefitinib treatment. Gefitinib was used as first-line treatment in only one patent (6.7%). In 3 (20.0%) patients, the computed tomography (CT) findings at the time of ILD diagnosis revealed combined lung cancer progression. ILD developed in 3 (20.0%) patients who responded to gefitinib treatment. The most common clinical presentation of gefitinib-induced ILD was dyspnea (100%), followed by cough (60.0%). Two (13.3%) patients presented with fever at the onset of ILD. Severe hypoxemia was found and the mean SpO2 was 80.47% on room air. Leukocytosis and elevated level of C-reactive protein (CRP) were common; mean leukocytes count was 13.14 x $10^3/\mu L$ and mean CRP level was 12.01 mg/dL. No patient presented with eosinophilia at the time of ILD diagnosis. The mean albumin level was 3.03 g/dL, which was much lower than the mean albumin level of 3.49 g/dL before gefitinib administration. In 2 (13.3%) patients, nosocomial pneumonia occurred during treatment of ILD.

Table 4. Clinical features and outcomes of gefitinib-induced interstitial lung disease (ILD).

Variables	Total	Non-Fatal	Fatal	*P* value
	N = 15	*N* = 6	*N* = 9	
Clinical findings				
Age, mean (years)	60.98 ± 10.78	61.39 ± 10.80	60.70 ± 11.41	0.908
Sex (male/female)	11 (73.3) / 4 (26.7)	3 (50.0) / 3 (50.0)	8 (88.9) / 1 (11.1)	0.235
Current or Ex-smoker	5 (33.3)	4 (66.7)	1 (11.1)	0.089
ECOG PS (≥ 2)	6 (40.0)	2 (33.3)	4 (44.4)	1.000
Emphysematous lung	2 (13.3)	1 (16.7)	1 (11.1)	1.000
Previous treatment				
Chest surgery	4 (26.7)	1 (16.7)	3 (33.3)	0.604
Thoracic radiotherapy	2 (13.3)	1 (16.7)	1 (11.1)	1.000
Chemotherapy	14 (93.3)	6 (100.0)	8 (88.9)	1.000
Combined lung cancer progression	3 (20.0)	1 (16.7)	2 (22.2)	1.000
Responder to gefitinib	3 (20.0)	2 (33.3)	1 (11.1)	0.525
Onset of symptoms after gefitinib therapy, median (days)	29.00 ± 14.81 (range, 3-1953)	54.00 ± 23.27	10.00 ± 2.24	0.024
≤ 8 weeks	12 (80.0)	3 (50.0)	9 (100.0)	0.044
> 8 weeks	3 (20.0)	3 (50.0)	0 (0.0)	
Symptoms				
Dyspnea	15 (100.0)	6 (100.0)	9 (100.0)	1.000
Cough	9 (60.0)	4 (66.7)	5 (55.6)	1.000
Chest discomfort	2 (13.3)	0 (0.0)	2 (22.2)	0.486
Fever > 38.0 ℃	2 (13.3)	0 (0.0)	2 (22.2)	0.486
SpO2 (%) (*n* = 13)	80.47 ± 20.32	96.75 ± 2.06	73.23 ± 20.65	0.009
Laboratory findings at the time of ILD onset				
Leukocytes (x 10^3/μL)	13.14 ± 8.63	9.08 ± 2.35	15.84 ± 10.32	0.143
Eosinophil percentage	2.52 ± 2.60	3.05 ± 2.53	2.17 ± 2.74	0.539
Hemoglobin (g/dL)	10.79 ± 1.95	11.17 ± 2.61	10.53 ± 1.48	0.557
CRP (mg/dL) (*n* = 13)	12.01 ± 8.78	7.72 ± 10.31	13.92 ± 7.91	0.257
Albumin (g/dL)	3.03 ± 0.56	3.55 ± 0.45	2.69 ± 0.31	0.001
Treatment				
Cessation of gefitinib treatment	15 (100.0)	6 (100.0)	9 (100.0)	1.000
Interval from onset of symptoms to cessation of gefitinib (days)	8.21 ± 8.12	10.80 ± 7.66	6.78 ± 8.44	0.388
Administration of corticosteroids	12 (80.0)	4 (66.7)	8 (88.9)	0.525
Methylprednisolone dose (mg/kg/d)	1.01 ± 0.53	0.65 ± 0.34	1.20 ± 0.52	0.088
Duration of corticosteroids treatment (days)	34.08 ± 34.24	61.50 ± 45.86	20.38 ± 17.22	0.170

Interval from symptom onset to start of corticosteroids (days)	6.58 ± 3.99	10.25 ± 4.50	4.75 ± 2.19	0.087
Coadministration of antibiotics	12 (80.0)	4 (66.7)	8 (88.9)	0.525
Clinical course				
Combined nosocomial pneumonia	2 (13.3)	0 (0.0)	2 (22.2)	0.486
ILD-related death	6 (40.0)	0 (0.0)	6 (66.7)	0.028
Median survival time after ILD onset (weeks)	5.93 ± 1.08	13.40 ± 6.03	5.17 ± 2.93	0.199
Subsequent chemotherapy after ILD				0.314
Cytotoxic chemotherapy	2 (13.3)	1 (20.0)	1 (11.1)	
Erlotinib	1 (6.7)	1 (20.0)	0 (0.0)	

Data are presented as mean ± standard deviation or *n* (%), unless otherwise stated.

Treatment and outcomes of gefitinib-induced ILD

Treatment and outcomes of gefitinib-induced ILD are summarized in Table 4. Gefitinib was immediately discontinued when ILD was clinically suspected in all patients. None of these patients were rechallenged with gefitinib. Twelve (80.0%) patients received systemic corticosteroids for gefitinib-induced ILD; the mean dose was equivalent to 1.01 mg/kg/d methylprednisolone initially and then was gradually tapered off. Among 15 patients with gefitinib-induced ILD, 9 (60.0%) patients had a fatal clinical course and 6 (40.0%) patients died directly from ILD. The median survival time from onset of ILD was 5.93 weeks.

We compared the clinical and laboratory variables of the fatal and nonfatal cases of ILD and found that patients in the fatal group developed ILD after a shorter median length of gefitinib administration and had lower mean SpO2 and lower albumin level at the time of ILD development than did the non-fatal group (Table 4). However, the fatal and non-fatal groups did not differ significantly in underlying comorbidities, pulmonary disease, types of previous cancer treatment, time interval from onset of ILD to cessation of gefitinib or administration of corticosteroids and methylprednisolone dosage.

Table 5. Reported incidence, mortality and risk factors of gefitinib-induced interstitial lung disease (ILD) in Japanese [11, 15-20] and Taiwanese [22] studies.

Year	Study group	No. patients	No. cases of ILD (%)	No. ILD death (mortality, %)	Risk factors
2004	National Cancer Center, Japan [16]	112	6 (5.4)	4 (66.7)	preexisting pulmonary fibrosis
2005	Okayama Lung Cancer Study Group [17]	330	15 (4.5)	8 (53.3)	preexisting pulmonary fibrosis, poor PS, prior thoracic irradiation
2006	West Japan Thoracic Oncology Group [15]	1,976	70 (3.5)	31 (44.3)	preexisting pulmonary fibrosis, male, smoker
2007	AstraZeneca [11]	1,482	59 (4.0)	- (31.6)	preexisting chronic ILD, poor PS, smoker, older age (>55 years), recent NSCLC diagnosis, reduced normal lung on computed tomography scan, concurrent cardiac disease
2009	Japan-Multinational Trial Organization [18]	526	17 (3.2)	7 (41.2)	no risk factors found
2010	Okayama Lung Cancer Study Group [19]	330	8 (2.4)	5 (62.5)	preexisting pulmonary fibrosis, poor PS
2013	NEJ 002 and WJTOG 3405 trials [20]	201 (EGFR mutation positive)	10 (5.0)	2 (20.0)	smoking
2013	Chang et al [22]	1,080	25 (2.3)	10 (40.0)	not evaluated
2013	This study	1,114	15 (1.3)	6 (40.0)	low albumin level

DISCUSSION

Gefitinib is an effective therapy for treating NSCLC, especially in certain groups, such as females, Asian populations, adenocarcinoma, never smokers and patients with specific EGFR mutations (4, 6). Gefitinib is recognized as a relatively safe oral agent, and most common toxicities associated with its use are mild and self-limiting diseases, including skin toxicities and diarrhea (8). However, the development of ILD during gefitinib treatment is a well-documented drug-related toxicity that sometimes has serious consequences. In 2003, an FDA analysis of 50,000 patients who received gefitinib reported a 1% worldwide incidence of ILD (8). Notably, the incidence of ILD in Japanese populations was reported to range between 2.4 and 5.4% in clinical trials (11, 15-20). In other Asian studies, the incidence of ILD also exceeds the global incidence; in Taiwanese patients it was reported as 5.8% (Shih et al (21)) and 2.3% (Chang et al (22)). However, the incidence of ILD in our study was 1.3%, a finding consistent with a previous clinical trial of Korean patients (10) and similar to values reported worldwide. It is a much lower incidence than those reported in other Asian populations, including studies of Japanese and Taiwanese patients (Table 5).

Risk factors for ILD have been identified in several Japanese studies (Table 5), but the findings from the reported studies are inconsistent; thus, risk factors for ILD are not clearly defined yet. In the present study, we also attempted to identify risk factors for ILD in gefitinib-treated NSCLC patients by collecting all possible risk factors including laboratory results as well as clinical factors that were evaluated in previous studies. Unlike the results from previous studies, a lower serum albumin level was identified as the only risk factor for developing gefitinib-induced ILD. A smaller Japanese study evaluated the association

between ILD and several laboratory values including albumin level, but did not find a significant association (18).

The mechanism by which gefitinib may cause ILD is unclear. However, decreased EGFR phosphorylation resulting in a decrease regenerative epithelial proliferation could augment pulmonary fibrosis (23, 24). According to the results of our study, hypoalbuminemia revealed a significant association with the development of gefitinib-induced ILD. Notably, the albumin level at the time of ILD development was further decreased compared to that before gefitinib administration (mean, 3.03 and 3.49 g/dL, respectively). A similar phenomenon occurs with methotrexate therapy. Methotrexate is a commonly prescribed an antineoplastic agent and an immune modulating compound; its pulmonary toxicities have been well described. Hypoalbuminemia is a known predisposing factor for methotrexate-induced pulmonary toxicity (either before or during therapy) (25, 26). It has been suggested as a hypothesis that a lower degree of protein binding of methotrexate and higher levels of free methotrexate resulted from hypoalbuminemia could enhance drug-induced pulmonary toxicity in methotrexate-treated patients (26). However, it is difficult to demonstrate the causality between hypoalbuminemia and the development of gefitinib-induced ILD clearly from the results in our study. Hypoalbuminemia is widely accepted as marker for illness severity (27) and malnutrition (28). Furthermore, in various malignant diseases, serum albumin which is thought to reflect the systemic inflammatory response has been implemented in the parameters of the Glasgow Prognostic Score, used to estimate to cancer prognosis (29). We found that hypoalbuminemia might be an important surrogate marker for predicting gefitinib-induced ILD.

Another possible predisposing factor for gefitinib-induced ILD is ethnic differences in

susceptibility to ILD. Notably, the incidence of gefitinib-induced ILD in Japanese patients was higher than the incidence found in our study; the incidence in our study was similar to values reported in worldwide populations. Forsythe and Faulkner have suggested that the reason for the observed difference in susceptibility to ILD may be related to population or environmental differences or differences in diagnostic or clinical practice (30). For other drug treatment, a higher incidence of ILD has been noted in Japan than elsewhere (31). In fact, the frequency of coincidence with interstitial pneumonitis before gefitinib treatment was much higher (5.0-13.6%) (15-19) than that observed in our Korean population (1.6%). Of note, comorbid interstitial pneumonitis was found to be a major risk factor for gefitinib-induced ILD in several Japanese studies.

We also investigated risk factors for adverse pulmonary reactions besides gefitinib-induced ILD. Multivariate analysis showed that poor PS and lower serum albumin level were independently associated with the development of adverse pulmonary reactions. In addition, we found that patients with the coincidence of ILD and underlying emphysema tended to develop adverse pulmonary reactions more frequently. The majority of adverse pulmonary events had an infectious cause (76.6%). Infection is a very common cause of pulmonary infiltrates and respiratory failure in lung cancer patients (32, 33). Poor PS is a well-known major risk factor for bacterial pneumonia in lung cancer patients as well as in the general population (33, 34).

Low albumin level is a strong risk factor for patients who are re-admitted with pneumonia after hospital discharge (35, 36). Low albumin level, as a marker of poor nutritional status, is also an important risk factor for pneumonia in general populations (37-39). Recently, Kang et

al reported that lower albumin level could be a risk factor for adverse pulmonary events in cancer patients treated with monoclonal antibodies (14).

Chronic obstructive pulmonary disease (COPD) and structural lung disease, such as ILD, are not only predisposing factors for pneumonia in general populations (40), but also risk factors for pneumonia in lung cancer patients (33).

Gefitinib-induced ILD usually occurs during the first 3 months of treatment, the median time to onset was actually 24 to 42 days (8). In our study, the median time to development of ILD was 29 days and 80.0% of ILD cases presented within the first 8 weeks of starting gefitinib treatment. The main manifestations of gefitinib-induced ILD were dyspnea (100.0%) and cough (60.0%), sequentially, while only 2 patients (13.3%) presented with fever, a commonly recognized sign of infectious pneumonia.

The prognosis for gefitinib-induced ILD was also quite consistent with other studies (Table 5). In the present study, among patients diagnosed with ILD, 6 patients had an ILD related death (mortality: 40.0%). Treatment of gefitinib-induced ILD is largely supportive, including supplemental oxygen, empirical antibiotics and mechanical ventilation. Immediate discontinuation of the drug is strongly recommended and systemic corticosteroids are usually prescribed, although no controlled trials have been conducted to evaluate their efficacy (9).

We investigated the association between clinical factors at the time of onset and fatality from gefitinib-induced ILD. In this study, the treatment for gefitinib-induced ILD was not significantly different between the fatal and non-fatal groups. When ILD was suspected clinically, gefitinib was discontinued immediately in all patients. The time interval from onset of symptoms to cessation of gefitinib was similar between both groups. Among the 15

patients who developed ILD, 12 (80.0%) patients were treated with corticosteroids. The median dose of corticosteroids at the time of onset of ILD, treatment duration and the time interval from ILD onset to administration of corticosteroids were not significantly associated with the prognosis of ILD. No patient was rechallenged with gefitinib after recovery from ILD. In univariate analysis, patients with fatal ILD were more likely to develop ILD within a shorter interval, to have lower SpO2 and lower serum albumin compared to those with non-fatal ILD. Although not confirmed by multivariate analysis, due to small sample size, ILD with abrupt onset after gefitinib treatment and severe pneumonitis requiring high O2 demand might have a poor prognosis despite appropriate treatment. Also low albumin level might be a prognostic factor as well as a predictive factor. Further investigation of possible prognostic factors, including comorbidities, is warranted.

This is the first study that evaluated predictive factors for gefitinib-induced ILD, as well as adverse pulmonary reaction, and also examined prognostic factors for ILD with the same data set in Korean patients treated with gefitinib. However, this study had several limitations. Our study was conducted retrospectively. Another concern was misdiagnosis of ILD, but we believe that the independent review of clinical data by investigators minimized this problem in the present study. The diagnosis of ILD is a critical component of this study. It was based on CT findings and clinical characteristics, and biopsies - generally considered the gold standard for ILD diagnosis - were not performed in all cases. This same diagnostic problem was reported in a large prospective study (11). Nevertheless the clinical features of gefitinib-induced ILD found in our study were similar to those previously reported.

In conclusion, the incidence of gefitinib-induced ILD in Korean NSCLC patients was similar to that of worldwide reports but lower than values reported for other Asian

populations. This study found that poor PS and lower albumin level were predictive factors for adverse pulmonary reactions caused by gefitinib. Hypoalbuminemia was the only risk factor for gefitinib-induced ILD. ILD is a serious adverse effect and clinicians should be alert for the possibility of gefitinib-induced ILD, particularly among patients with a low serum albumin level.

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국문 초록

배경

제피티닙(gefitinib)은 진행성 비소세포폐암 환자, 특히 표피 성장 인자 수용체(epidermal growth factor receptor, EGFR) 유전자 돌연변이가 있는 비소세포폐암 환자에서의 효과가 널리 알려진 약제이다. 약제유발 간질성 폐렴은 심각한 결과를 초래할 수 있는 제피티닙의 특이 부작용 이다. 하지만 약제유발 간질성 폐렴의 정확한 발생률과 위험 인자는 아직 명확히 밝혀지지 않았다. 본 연구는 제피티닙 치료를 받은 한국의 비소세포폐암 환자에서 약제유발 간질성 폐렴의 발생률과 임상적인 특징을 조사하였다.

환자 및 연구 방법

2002년 1월부터 2011년 12월까지 서울대학교병원에서 제피티닙을 투여 받은 비소세포폐암 환자를 대상으로 한 후향적 코호트 연구를 수행하였다. 제피티닙 치료 중 새롭게 발생한 비정상적인 영상 소견을 보이고, 호흡기 증상을 동반하였던 환자를 가능성이 있는 호흡기 부작용 환자로 정의하였다. 상기 환자들의 의무기록 및 영상 소견을 분석하였고, 호흡기 부작용의 원인을 감별하기 위해 연구자들에 의한 독립적인 조사를 수행하였다. 제피티닙유발 간질성 폐렴의 독립적인 위험인자를 밝히기 위해 다변량 로지스틱 회귀 분석을 시행하였다.

결과

총 1114명의 환자 중 128명(11.5%)의 환자에서 호흡기 부작용이 발생하였다. 감염에 의한 합병증이 98명(8.8%)의 환자에서 발생하였고, 15명(1.3%)의 환자에서 제피티닙유발 간질성 폐렴이 발병한 것으로 추정되었다. 15명의 제피티닙유발 간질성 폐렴 환자 중에 9명(60%)의 환자는 치명적인 임상 경과를 경험하였다. 치명적인 증례란 미국 국립암연구소 이상반응 표준 용어 기준 (NCI Common terminology criteria for adverse events) 4등급에 해당하는 경우(3명, 20%)와 사망에 이르게 된 증례(6명, 40%)으로 구성되었다. 15명의 환자 중 12명(80%)에서 제피티닙 투약 후 첫 8주 이내에 간질성 폐렴이 발생하였다. 다변량 분석을 통해 낮은 혈장 알부민 수치가 약제 유발성 폐렴의 발생과 통계적으로 유의한 상관관계를 보였다 (odds ratio = 0.46; 95% confidence interval: 0.22 – 0.98, P = 0.045).

결론

한국인 비소세포폐암 환자에서 제피티닙유발 간질성 폐렴의 발생률은 전세계적으로 보고되는 수치와 비슷하였으나, 다른 아시아 지역에서 보고된 빈도에 비해서는 낮았다. 간질성 폐렴은 제피티닙 치료를 받는 환자에서 대개 생명을 위협하는 심각한 부작용이며, 제피티닙 치료를 받는 환자, 특히 혈장 알부민 수치가 낮은 환자는 간질성 폐렴의 발생에 대해 주의 깊게 감시되어야 한다.

주요어: 제피티닙, 간질성 폐렴, 호흡기 독성, 약제 부작용, 폐암

학번: 2011-21992