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Early or Late Gefitinib, Which is Better for Survival? - Retrospective Analysis of 228 Korean Patients with Advanced or Metastatic NSCLC

Dong Gun Kim, Min Kyoung Kim, Sung Hwa Bae[2], Sung Ae Koh, Sung Woo Park, Hyun Je Kim, Myung Jin Kim, Hyo Jin Jang, Kyung Hee Lee, Kwan Ho Lee[1], Jin Hong Chung[1], Kyung Chul Shin[1], Hun Mo Ryoo[2], Myung Soo Hyun

Division of Oncology, [1]Division of Pulmonology, Department of Internal Medicine, College of Medicine, Yeungnam University, Daegu, Republic of Korea
[2]Division of Oncology, Department of Internal Medicine, School of Medicine, Catholic University of Daegu, Republic of Korea

－Abstract－

Background : The optimal timing of treatment with EGFR-tyrosine kinase inhibitors (EGFR-TKI) in NSCLC patients has not yet been determined.

Methods : We separated 228 patients with advanced /metastatic NSCLC treated with gefitinib into an early gefitinib group (patients who received gefitinib as first- or second-line treatment) and a delayed gefitinib group (patients who received gefitinib as third or fourth-line treatment) and attempted to determine whether the timing of gefitinib treatment affected clinical outcomes.

Results : Median overall survival (OS), progression free survival (PFS), and median OS from first-line treatment of advanced/metastatic disease (OSt) for 111 patients in the early gefitinib group were 6.2 months, 3.3 months, and 11.6 months. However, median OS, PFS, and OSt for 84 patients in the delayed gefitinib group were 7.8 months, 2.3 months, and 22.7 months. No differences in OS and PFS were observed between the 2 groups. However, OSt was significantly longer in the delayed gefitnib group. Timing of gefitinib therapy was one of the independent predictors of OSt. Hb $\geq$ 10 g/dl, and having never smoked, and ECOG performance status $\leq$1 were independent predictors of better PFS.

Corresponding Author : Min Kyoung Kim, 317-1, Daemyeong-dong, Namgu, Division of Oncology, Department of Internal Medicine, College of Medicine, Yeungnam University, Daegu, Republic of Korea Tel: (053) 620-4683, Fax: (053) 654-8386, E-mail: kmk21c@med.yu.ac.kr

Conclusion : Deferral of gefitinib therapy in patients with advanced or metastatic NSCLC may be preferable if they are able to tolerate chemotherapy.

Key Words : Tyrosine kinase inhibitor, Gefitinib, Non-small cell lung cancer

Introduction

The discovery that signaling by epidermal growth factor receptor (EGFR) is important in tumorigenesis prompted efforts to target this receptor in anticancer therapy, leading to the development of inhibitors of EGFR tyrosine kinase activity.[1] Based on results of phase II trials, gefitinib (ZD1839, Iressa™) was the first tyrosine kinase inhibitor approved for use as salvage therapy in patients with advanced non-small cell lung cancer (NSCLC).[2,3] Although the Iressa Survival of Evaluation in Lung Cancer (ISEL) trial showed that gefitinib did not significantly improve overall survival (OS) compared with placebo, we found that gefitinib was associated with impressive responses and survival benefits in a subgroup of patients.[4] Erlotinib (OSI774, Tarceva™), another EGFR tyrosine kinase inhibitor, has also shown significant antitumor activity and improved survival in NSCLC patients who failed first- or second-line chemotherapy.[5,6]

The unique mechanism of action of EGFR tyrosine kinase inhibitors leads to distinct patterns of response and toxicity in NSCLC patients. Since dramatic responses are seen in only a fraction of patients, investigators have attempted to identify pretreatment characteristics associated with sensitivity to gefitinib. Adenocarcinoma or bronchioloalveolar carcinoma histology, female gender and no smoking history have been found to predict better response to treatment with EGFR tyrosine kinase inhibitors.[2,3,5-7]

Several recent phase II trials have shown that single agent erlotinib or gefitinib as first-line therapy in patients with advanced or metastatic NSCLC was associated with response rates of 24.5% to 33.3%.[8,9] Front line treatment with gefitinib showed a response rate >50%, with higher rates associated with favorable clinicopathologic factors.[10,11] Gefitinib has become a promising first-line treatment agent in Asian patients with NSCLC.

To date, however, the guideline for optimal timing of gefitinib is still to be determined. Because EGFR-TKI is oral agent with minimal toxicity, it may be better for survival to be given after patients have exhausted chemotherapy. In contrast, because the response is usually achieved within a month and the response is mostly dramatic, early gefitinib therapy may improve overall survival. We have therefore analyzed the effects of timing of gefitinib treatment on

outcomes in Korean patients with advanced NSCLC.

Materials and Methods

Patients and gefitinib treatment

Eligibility criteria of this study are as follows; patients with pathologically confirmed stage IIIB (with pleural effusion or pericardial effusion) or IV NSCLC; at least one bidimensionally measurable or radiographically assessable lesion; adequate renal, hepatic and bone marrow function; patients who did not receive concurrent chemotherapy, radiotherapy or other experimental agents.

Between February 2002 to August 2007, 228 patients with advanced/metastatic or recurrent NSCLC were treated with gefitinib monotherapy at two tertiary hospitals. Thirty-three patients were excluded from the analysis because they did not satisfy the inclusion criteria, or missing pertinent data was missing. The remaining 195 patients were included in this analysis (67 patients from the Hospital of Catholic University of Daegu and 128 patients from Yeungnam University Hospital).

Treatment and response assessment

Patients were treated with 250 mg daily oral dose of gefitinib for 4 weeks and treatment was continued until the disease progression, development of unacceptable toxicity, or patient's refusal. Chest radiograph was obtained every 1 month and CT scan was performed every two months or if disease progression was suspected. Treatment related toxicities were graded according to National Institute of Health Common Toxicity Criteria Version 2.0. Objective tumor responses were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria and required confirmation with at least two scans obtained 30 days apart.

Statistical analysis

Baseline characteristics were compared using Student's t-test, the χ^2 test, or Fisher's exact test, where appropriate. Survival time was calculated from the date of start of gefitinib (OS) or the date of start of first-line treatment of advanced/metastatic or recurrent disease (OSt) to the date of death of any cause. Progression free survival (PFS) was defined as the time from the start of gefitinib to the date of first observation of relapse or death due to any cause. Survival analysis was performed by the Kaplan-Meier method, and differences between the curves were analyzed using the log-rank test. All statistical tests were two-sided, with significance defined as $p<0.05$. Analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA) and SigmaPlot version 9.0 (Systat Software, Inc. San Jose, CA, USA).

Results

Patient characteristics

The baseline characteristics of the patients are shown in Table 1. All 195 patients were Korean with a median age of 62 years (range 29-86). Eighty-four patients (43%) were never-smokers and 81 patients (42%) were female. The most common histological subtype was adenocarcinoma (67%). Forty-five patients (23%) received gefitinib as first-line therapy. Seven patients (3.6%) received gefitinib as forth-line therapy. Of the 150 patients who had history of prior chemotherapy, 137 patients (91.3%) received platinum based doublet as a first line chemotherapy and best response were CR in 2 patients (1.0%) and PR in 60 patients (30.8%) with an overall response rate of 31.8%. To determine the impact of gefitinib timing, we separated patients into an early gefitinib group (patients that received gefitinib as first- or second-line treatment) and a delayed gefitinib group (patients who received gefitinib as third- or fourth-line treatment). The early gefitinib group was older and (in comparison to the delayed gefitinib group) included more women, never-smokers, and patients with adenocarcinoma histology, stage IV/recurrent disease, and brain metastasis at diagnosis (Table 1).

Objective tumor response to gefitinib and its determinants

Of 195 patients with measurable disease, 2 (1%) achieved complete response (CR), 41 patients (21%) achieved partial response (PR), and 85 patients (44%) had stable disease (SD), showing an overall response rate of 22% (95% CI 16.2-27.8). Univariate analysis showed that gender, smoking history, tumor histology, timing of gefitinib and Hb level at start of gefitinib therapy were significantly associated with response to gefitinib (Table 2). As women and non smokers strongly overlapped (of 81 women, 72 were non-smokers), the statistical analysis was unstable if both factors were analyzed simultaneously, and we therefore excluded gender from multivariate analysis. We found that smoking history (p=0.003, relative risk [RR] 3.41, 95% CI 1.52-7.64) and Hb level at start of gefitinib treatment p=0.026, RR 4.24, 95% CI 1.19-15.16) were significant predictors of response to gefitinib. In addition, patients with adenocarcinoma histology tended to show a favorable response (p=0.084, RR 0.39, 95% CI 0.13-1.14).

Survival after gefitinib treatment and prognostic factors

At a median follow-up of 17.4 months (range 4.5-53.2) for surviving patients, the median OS from gefitinib was 6.7 months (95% CI 5.0-8.5) and the median PFS was 2.7 months (95% CI 2.2-3.2). Median OS was 20.2 months (95% CI 12.1-28.3) for responders, 6.7 months (95% CI 4.8-8.6) for

Table 1. Patient characteristics according to the timing of gefitinib treatment

Parameters	Total (n=195)	Timing of gefitinib treatment		*p* value
		Early gefitinib (1st/2nd-line, n=111)	Delayed gefitinib (3rd/4th-line, n=84)	
Age				<0.001
> 65 years	121	52	69	
≤ 65 years	74	59	15	
Gender				<0.001
Male	114	51	63	
Female	81	60	21	
Smoking				0.001
Non smoker	84	59	25	
Smoker	111	52	59	
ECOG PS at initial diagnosis*				0.061
0, 1	155	93	72	
≥ 2	40	28	12	
Stage at initial diagnosis*				0.014
IIIB	48	20	28	
IV/recurrent	147	91	56	
Tumor histology				<0.001
Adenocarcinoma	130	88	42	
Other NSCLC	65	23	42	
History of surgery				0.728
Yes	35	19	16	
No	160	92	68	
Brain metastasis at diagnosis				0.024
Yes	14	12	2	
No	181	99	82	
Liver metastasis at diagnosis				0.686
Yes	8	4	4	
No	187	107	80	
Hb level at diagnosis*				0.587
< 10 g/dL	14	7	7	
≥ 10 g/dL	177	102	75	
Missing	4	2	2	
Response to first-line treatment†				0.006
CR/ PR	76	34	42	
SD/ PD/ NA	119	77	42	
ECOG PS at start of gefitinib				0.006
0, 1	52	38	14	
≥ 2	143	73	70	
Stage at start of gefitinib therapy				0.855
IIIB	20	11	9	
IV/recurrent	175	100	75	
Brain metastasis at start of gefitinib				0.277
Yes	42	27	15	
No	153	84	69	
Liver metastasis at start of gefitinib				0.170
Yes	17	7	10	
No	178	104	74	
Hb level at start of gefitinib therapy				0.088
< 10 g/dL	40	18	22	
≥ 10 g/dL	155	93	62	

* Initial diagnosis of advanced or metastatic/recurrent disease.
† Including response to gefitinib treatment in patients who received gefitinib as a first line treatment.
ECOG PS: Eastern Cooperative Oncology Group Performance Score, NSCLC: non-small cell lung cancer, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, NA: not available.

Table 2. Predictive factors associated with an objective response as determined by univariate analysis

Parameters	Total	Responder (n=43)	Response rate(%)	*p* value
Age				0.058
> 65 years	121	32	26.4	
≤ 65 years	74	11	14.9	
Gender				<0.001
Male	114	14	12.3	
Female	81	29	35.8	
Smoking				<0.001
Non smoker	84	31	36.9	
Smoker	111	12	10.8	
Timing of gefitinib treatment				0.009
Early (1st /2nd line)	111	32	28.8	
Delayed (3rd/4th line)	84	11	13.1	
Tumor histology				0.001
Adenocarcinoma	130	38	29.2	
Other NSCLC	65	5	7.7	
History of surgery				0.899
Yes	35	8	22.9	
No	160	35	21.9	
ECOG PS at start of gefitinib				0.835
0, 1	52	12	23.1	
≥ 2	143	31	26.7	
Stage at start of gefitinib				0.737
IIIB	20	5	25.0	
IV/recurrent	175	38	21.7	
Brain metastasis at start of gefitinib				0.116
Yes	42	13	31.0	
No	153	30	19.6	
Liver metastasis at start of gefitinib				0.347
Yes	17	3	17.6	
No	178	40	22.7	
Hb level at start of gefitinib				0.011
< 10 g/dL	40	3	7.5	
≥ 10 g/dL	155	40	25.8	

ECOG PS: Eastern Cooperative Oncology Group Performance Score, NSCLC: non-small cell lung cancer.

patients with stable disease and 2.6 months (95 %CI 1.5-3.6) for patients with disease progression while receiving gefitinib. Univariate analysis showed that smoking status, Hb level at start of gefitinib treatment, tumor histology, gender, ECOG performance status, timing of gefitinib therapy, and history of surgery were significantly

Table 3. Prognostic factors associated with PFS as determined by univariate analysis

Parameters	Progression free survival following gefitinib treatment		
	No.	Median months (95% CI)	*p* value
Age			0.470
> 65 years	121	2.8 (1.8-3.7)	
≤ 65 years	74	2.5 (1.7-3.3)	
Gender			0.0006
Male	114	2.3 (1.9-2.7)	
Female	81	4.9 (3.5-6.2)	
Smoking			<0.0001
Never smoker	84	5.0 (3.0-7.0)	
Smoker	111	2.1 (1.8-2.5)	
Timing of gefitinib treatment			0.020
Early (1st /2nd line)	111	3.3 (1.9-4.6)	
Delayed (3rd/4th line)	84	2.3 (2.0-2.7)	
Tumor histology			0.0001
Adenocarcinoma	130	3.7 (2.3-5.1)	
Other NSCLC	65	2.0 (1.5-2.5)	
History of surgery			0.039
Yes	35	2.5 (2.1-3.0)	
No	160	1.3 (2.2-7.1)	
ECOG PS at start of gefitinib therapy			0.015
0, 1	52	4.9 (2.4-7.3)	
≥ 2	143	2.5 (2.0-3.0)	
Stage at start of gefitinib therapy			0.746
IIIB	20	3.2 (2.3-4.0)	
IV/recurrent	175	2.6 (2.1-3.2)	
Brain metastasis at start of gefitinib			0.168
Yes	42	3.7 (1.1-6.4)	
No	153	2.5 (2.0-2.9)	
Liver metastasis at start of gefitinib			0.131
Yes	17	1.7 (0.5-2.8)	
No	178	2.8 (2.3-3.4)	
Hb level at start of gefitinib therapy			<0.0001
< 10 g/dL	40	1.8 (1.3-2.4)	
≥ 10 g/dL	155	3.2 (1.8-4.6)	

ECOG PS: Eastern Cooperative Oncology Group Performance Score, NSCLC: non-small cell lung cancer.

associated with PFS (Table 3). Multivariate analysis showed that Hb ≥10 g/dl (p< 0.001, Hazard ratio (HR) for progression or death 0.47, 95% CI 0.32-0.68), non-smoker (p=0.033;HR 0.55 95% CI 0.32-0.95), ECOG PS ≤1 (p=0.039, HR 0.69, 95% CI 0.48-0.98) and history of surgery (p=0.049, HR 0.66, 95% CI 0.44-0.10) were associated with

Table 4. Prognostic factors associated with PFS as determined by multivariate analysis

Parameters	No	Hazard ratio	95% CI	*p* value
Gender				0.88
Male	114	1.04	0.61-1.78	
Female	81			
Smoking				
Non smoker	84	0.55	0.32-0.95	0.033
Smoker	111	1		
Timing of gefitinib treatment				
Early (1st /2nd line)	111	0.97	0.70-1.36	0.973
Delayed (3rd/4th line)	84	1		
Tumor histology				
Adenocarcinoma	130	0.83	0.56-1.23	0.345
Other NSCLC	65	1		
History of surgery				
Yes	35	0.66	0.44-0.10	0.049
No	160	1		
ECOG PS at start of gefitinib				
0, 1	52	0.69	0.48-0.98	0.039
≥ 2	143	1		
Hb level at start of gefitinib				
< 10 g/dL	40	1.46	1.02-2.08	<0.001
≥ 10 g/dL	155	1		

ECOG PS: Eastern Cooperative Oncology Group Performance Score, NSCLC: non-small cell lung cancer.

better PFS (Table 4).

OSt according to the timing of gefitinib treatment

At a median follow-up of 27.1 months (range 5.9-69.4) for surviving patients, the median OS from the date of first -line treatment of advanced or metastatic/recurrent disease (OSt) was 16.8 months (95% CI 13.9-19.7), 11.6 months (95% CI 8.9-14.3) for the 111 patients in early gefitinib therapy group, and 22.7 months (95% CI 16.6-28.7) for the 84 patients in delayed gefitinib group (Table 5). Univariate analysis showed that OSt was significantly associated with response to first-line treatment, history of surgery, ECOG PS, and timing of gefitinib treatment (Table 5). Cox proportional hazard models showed that history of surgery (p<0.001), response to first-line treatment (p=0.002), smoking status (p=0.004), and timing of gefitinib treatment (p=0.011) were independent predictors of OSt. ECOG PS (p=0.078) tended to associated with OSt by multivariate analysis (Table 6).

Survival outcome of 75 never smokers with adenocarcinoma histology

Table 5. Prognostic factors associated with OSt as determined by univariate analysis

Parameters	Overall survival from first-line treatment (OSt)		
	No.	Median, months (95% CI)	*p* value
Age			0.102
> 65 years	121	17.9 (14.9-20.9)	
≤ 65 years	74	16.0 (9.6-22.5)	
Gender			0.502
Male	114	16.0 (12.1-20.0)	
Female	81	17.9 (14.2-21.6)	
Smoking			0.098
Non smoker	84	19.2 (10.7-27.7)	
Smoker	111	14.0 (9.5-18.5)	
ECOG PS at initial diagnosis*			0.005
0, 1	155	18.4 (15.9-20.9)	
≥ 2	40	10.9 (4.5-17.2)	
Stage at initial diagnosis*			0.050
IIIB	48	23.2 (14.8-31.7)	
IV/recurrent	147	14.3 (10.4-18.1)	
Timing of gefitinib treatment			0.008
Early (1st /2nd line)	111	11.6 (8.9-14.3)	
Delayed (3rd/4th line)	84	22.7 (16.6-28.7)	
Tumor histology			0.547
Adenocarcinoma	130	17.5 (14.6-20.3)	
Other NSCLC	65	14.6 (8.0-21.1)	
History of surgery			0.005
Yes	35	24.9 (17.4-32.4)	
No	160	14.7 (11.0-18.4)	
Brain metastasis at diagnosis*			0.847
Yes	14	16.5 (10.7-22.3)	
No	181	16.8 (13.6-19.9)	
Liver metastasis at diagnosis*			0.802
Yes	8	11.6 (5.9-17.3)	
No	187	17.0 (14.0-19.9)	
Response to first line treatment†			0.001
CR/ PR	80	25.1 (18.1-32.0)	
SD/ PD/ NA	110	11.6 (8.5-14.8)	
Hb level at initial diagnosis*			0.737
< 10 g/dL	14	14.3 (7.8-20.7)	
≥ 10 g/dL	177	17.0 (13.9-20.1)	
Missing	4		

* Initial diagnosis of advanced or metastatic/recurrent disease.
† Including response to gefitinib treatment in patients who received gefitinib as a first line treatment.
ECOG PS: Eastern Cooperative Oncology Group Performance Score, NSCLC: non-small cell lung cancer, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, NA: not available.

Table 6. Prognostic factors associated with overall survival from first-line treatment of advanced/metastatic or recurrent disease (OSt) as determined by multivariate analysis

Parameters	No of patients	Hazard ratio	95% CI	*p* value
Stage at initial diagnosis*				0.226
IIIB	48	0.79	0.54-1.16	
IV/recurrent	147	1		
Smoking				
Non smoker	84	0.61	0.43-0.86	0.004
Smoker	111	1		
ECOG PS at initial diagnosis*				
0, 1	155	0.69	0.46-1.04	0.078
≥ 2	40	1		
Timing of gefitinib treatment				
Early (1st /2nd line)	111	1.60	1.11-2.30	0.011
Delayed (3rd/4th line)	84	1		
History of surgery				
Yes	35	0.46	0.28-0.68	<0.001
No	160	1		
Response to first line treatment†				
CR/ PR	76	0.58	0.41-0.82	0.002
SD/ PD/ NA	119	1		

* Initial diagnosis of advanced or metastatic/recurrent disease.
† Including response to gefitinib treatment in patients who received gefitinib as a first line treatment.
ECOG PS: Eastern Cooperative Oncology Group Performance Score, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, NA: not available.

Of the 75 never smokers with adenocarcinoma histology, 53 (71%) were treated with gefitinib as first or second line therapy and 22 (29%) as third or greater line therapy. The median OS in these 75 patients was 12.9 months (95% CI 6.8-19.0) and the median PFS was 5.9 months (95% CI 3.8-8.0). Median OS and PFS for patients in early gefitinib group were 12.9 months (95% CI 5.0-20.8) and 7.9 months (95% CI 4.1-11.7), respectively. Median OS and PFS for patients in delayed gefitinib group were 12.7 months (95% CI 3.1-22.2) and 3.3 months (95% CI 0.7-5.9), respectively. Timing of gefitinib treatment had no effect on OS (p=0.70) or PFS (p=0.17). Median OSt in these 75 patients was 24.3 months (95% CI 16.2-32.4), 19.7 months (95% CI 10.7-28.7) for patients in early gefitinib group, and 25.5 months (95% CI 8.0-43.1) for patients in delayed gefitinib group (p=0.27).

Discussion

Prolonged survival is the ultimate goal of anticancer therapy and an important outcome in evaluating the effects of first line treatment for NSCLC. EGFR tyrosine kinase

inhibitors have been found to enhance patient survival. We analyzed survival in 195 NSCLC patients who received gefitinib, 111 as first- or second-line treatment and 84 as third- or fourth-line treatment. We found that delayed gefitinib therapy mighy confer a greater survival benefit than early gefitinib therapy.

First- line gefitinib treatment of unselected Japanese patients with NSCLC showed a 30% response rate and a median OS of 13.9 months.[8] In subsets of selected patients, first-line gefitinib has shown more dramatic responses and mild toxicity. A response rate of 69% and 33 weeks of the median PFS have been reported for Korean never smokers with advanced or metastatic adenocarcinoma.[11] Patients harboring EGFR mutations had an overall response rate to first-line gefitinib of 75% and a median PFS of 9.7 months.[12] These results suggested that gefitinib may be effective as first-line treatment for patients with clinicopathologic predictors of gefitinib sensitivity.[13]

To date, however, there have been no randomized studies of optimal strategies to incorporate EGFR-TKI. Patients with clinical predictors of gefitinib sensitivity, including women and never-smokers, also have longer survival times in response to chemotherapy.[14-17] suggesting that the effectiveness of first-line gefitinib on survival may have been overestimated. In addition, patients with poor performance status at progression to first-line treatment may not have the opportunity for additional chemotherapy but may be able to take gefitinib. For example, of 53 chemotherapy-naïve patients with progressive disease who were treated with first-line gefitinib, only 9 (17%) could receive salvage chemotherapy with a platinum-based regimen.[10] Moreover, studies reporting that first-line gefitinib therapy was associated with longer survival should have compared overall lung cancer survival instead of PFS in assessing the impact of gefitinib timing on survival.13 In this context, we sought to demonstrate the effects of timing of gefitinib treatment on the outcome of patients with NSCLC. We found that the OSt of the early gefitinib group of patients was shorter than for the delayed gefitinib group of patients, whereas OS and PFS were similar for the 2 groups, and the timing of gefitinib also did not affect survival in never-smokers with adenocarcinoma. Although the response rate was slightly higher in the early gefitinib group, these patients may have been selected according to previously known favorable prognostic factors, and timing of gefitinib (early vs delayed) may have lost significance during multivariate analysis for prediction of response. These results suggest that early gefitinib treatment may not be indicated in unselected patients if chemotherapy is possible. The value of first-line gefitinib in patients with factors predicting favorable responses should be determined in prospective

randomized clinical trials, which should also evaluate overall quality of life.

Unexpectedly and interestingly, anemia (Hb <10 g/dL) had an unfavorable effect on response and survival after gefitinib therapy. An inverse correlation between anemia and effect of chemotherapy has been reported in both palliative and adjuvant chemotherapy for lung cancer.[18-20] To the best of our knowledge, this is the first study reporting associations between anemia and lower response and poorer PFS to gefitinib treatment. Although a low hemoglobin level has been associated with a small distribution volume and short half-life in patients treated with another tyrosine kinase inhibitor, imatinib, additional studies of the association between anemia and resistance to gefitinib are needed. Tumor size or volume has been reported to be prognostic in patients with NSCLC.[21-23] We found that history of surgery was an independent prognostic factor for survival, but history of surgery may be associated with small tumor volume.

This study had several important limitations, including its retrospective design. In addition, there may have been selection bias, in that patients who could not be treated with gefitinib after chemotherapy were excluded. The patients in the delayed gefitinib treatment group may have been selected from a subgroup of patients who benefited from previous chemotherapy. However, patients with a history of prior chemotherapy had an overall response rate to first line chemotherapy of 31.8%, comparable to results of previous prospective phase III studies of platinum-based chemotherapy.[24-26] As the use of gefitinib has minimal adverse events, physicians have administered this agent to patients with poor performance who failed chemotherapy. Indeed, we found that 83.3% of patients in the delayed gefitinib group had ECOG PS >2 at the start of gefitinib treatment. Moreover, the OSt between 2 groups was significantly different after adjusting for other confounding variables such as age, stage, ECOG PS, and response to first-line treatment. We therefore consider these results clinically meaningful despite the inevitable limitations.

In conclusion, the findings presented here suggest that it may be better to defer gefitinib therapy in patients with advanced or metastatic NSCLC if patients are able to tolerate chemotherapy. Prospective studies are warranted to evaluate the optimal strategy of gefitinib in the treatment of NSCLC.

Conflict of interest

The authors report no conflicts of interest.

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