Analysis of the response and toxicity of gefitinib for non-small cell lung cancer

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Abstract.

Background: Gefitinib is an oral agent that inhibits the tyrosine kinase of epidermal growth factor receptor (EGFR), which had antitumor activity in patients with previously treated non-small cell lung cancer (NSCLC). We analyzed the efficacy, toxicitiy, and overall survival time of gefitinib in patients with NSCLC.

Patients and Methods: One hundred and twenty-two patients with NSCLC who received gefitinib between 2002 and 2004 in our institutes were evaluated retrospectively.

Results: The objective response rate was 24.6%. The variables identified as significant in univariate analysis included gender and smoking habit. The median overall survival time was 14.4 months. Significant variables associated with improved survival included good performance status (PS), female, adenocarcinoma and never smoked status, and never smoked status and good PS were independent prognostic factors in multivariate analysis. Four patients (3.3%) developed interstitial pneumonitis associated with gefitinib.

Conclusion: Gefitinib showed favorable anti-tumor activity in females, never smokers and adenocarcinoma.

Introduction

Lung cancer is one of the most common fatal malignancies, and the incidence of this type of cancer is increasing worldwide (1). Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all cases of lung cancer. The current standard of care for patients with locally advanced or metastatic NSCLC is systemic chemotherapy with a two-drug combination regimen that includes a platinum based chemotherapy (2). Although platinum-based chemotherapy offers modest efficacy and survival advantage over best supportive care (BSC) alone for chemotherapy naive patients with advanced NSCLC, the overall 5-year survival rate after diagnosis remains at 10-15% due to frequent recurrence and metastasis of the NSCLC (1-4). Moreover, docetaxel is currently approved as the second-line chemotherapy on the basis of randomized trials in patients who failed on previous chemotherapy (5, 6). The objective response rates of docetaxel are only 5-10% associated with a modest survival improvement. No agent rhas produced a tumor response in more than 5% of patients in the third-line treatment setting. In addition, elderly patients with poor performance status (PS) or patients with complications can not receive standard chemotherapy due to the toxicity associated with anticancer drugs. Thus, there is need for new therapies with novel mechanisms of action that are well tolerated, effective, and convenient.

The epidermal growth factor receptor (EGFR) is a type I family of transmembrane glycoproteins and regulates the growth of both epithelial or nonepithelial cell types. EGFR is highly expressed in NSCLC and the association between EGFR expression and poor patient prognosis has been extensively documented (7, 8). Because activation of EGFR enhances the processes

responsible for tumor growth and progression, including the promotion of proliferation, angiogenesis, and invasion/metastasis and inhibition of apoptosis, EGFR is a rational molecule target for antitumor therapy and many strategies who are currently being developed (9, 10).

Gefitinib (Iressa^{R}, ZD1839; AstraZeneca, Wilmington, DE) is an oral inhibitor of the intracellular tyrosine kinase domain of EGFR, and block signal transduction pathways implicated in the proliferation and survival of cancer cells (11, 12). In the phase I trials, gefitinib was generally tolerated and confirmed partial responses or survival prolongation were seen in some patients (13, 14). Subsequently, two phase II trials, IDEAL 1 and IDEAL 2, confirmed that response occurred in 12% to 18% in previously treated NSCLC patients receiving 250 mg/day gefitinib, and that gefitinib showed significant antitumor activity (15, 16). However, some patients who received gefitinib developed severe acute interstitial pneumonitis as a severe adverse event and more detailed investigation has been thought to be required (17).

In the present study, we retrospectively analyzed response rates, survival time, and toxicity in patients with NSCLC at our institutes who were given 250 mg/day gefitinib. In addition, we compared the relationship between response or survival time and clinical features.

Patients and Methods

Patients and treatment. Between July 2002 and March 2004, 122 patients with histologically or cytologically confirmed NSCLC received 250 mg/day gefitinib

orally at our institutes, Hokkaido University Hospital, National Hospital Organization Hokkaido Cancer Center, Sapporo City General Hospital, and Fukushima Medical University Hospital. Those records were analyzed retrospectively. The histopathological classification was based on WHO criteria for histopathological classification (18) and Tumor-Node-Metastasis (TNM) was determined based on the American Joint Committee on Cancer guidelines (19). Patients, who had recurrent or refractory disease after surgery, radiotherapy or prior systemic chemotherapy or who could not tolerate standard systemic chemotherapy in the judgment of a physician, were included. Patients continued treatment until disease progression, no efficacy, intolerable toxicity, or withdrawal of consent. Patients received no systemic anticancer treatment during treatment with gefitinib.

Efficacy. We assessed objective tumor response as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) by repeat radiographic imaging in accordance with the Response Evaluation Criteria in Solid Tumors Group (RECIST) guidelines (20). Disease control was defined as CR, PR, or SD. Patient responses were defined as Unknown if they died of progressive disease or they stopped gefitinib due to adverse events within 10 days. The responses of patients in whom efficacy could not be assessed due to short duration of observation were also defined as Unknown. Tumor dimensions were assessed every 4 weeks by radiographic examinations. PR was sustained for 4 weeks or longer and SD was sustained for 8 weeks or longer.

Toxicity. Toxicity was evaluated based on the National Cancer Institute Common Toxicity Criteria, version 2, every 2 weeks or 4 weeks.

Overall survival. Overall survival was defined as the period from the date of start of gefitinib to the date of tumor related death. Living patients at data cutoff were censored at the last date that patients were confirmed to be alive.

Statistical analysis. The associations between response and patient characteristics were statistically analyzed using Fisher's exact test as appropriate using Statview software (version 5.0; SAS Institute, CA, USA). Those variables that were significant in the univariate analysis were included in a multivariable Logistic regression analysis. The progression free survival curves and survival curves were estimated by the Kaplan-Meier method for estimation and the log-rank test for comparing the characteristics of patients. Those variables that were significant in the univariate analysis were included in a multivariable Cox proportional hazard model. Values of $P < 0.05$ were considered to indicate statistical significance and all tests were two tailed.

Results

Patients. We assessed 122 patients (66 males and 56 females) who received 250 mg/day gefitinib. Table I shows the baseline patient characteristics. The most common tumor histology was adenocarcinoma, including 1 patient with bronchioloalveolar carcinoma. The median PS of all patients was 1 (range 0 - 4),

the median number of chemotherapy regimens was 2 (range, 0 - 4), and the median duration of treatment for all 122 patients who consented to taking gefitinib was 2.6 months (range, 0 - 21.7 months).

Efficacy. The best overall tumor responses are shown in Table II. PR was observed in 30 patients (24.6%), SD in 35 patients (28.7%) and PD in 47 patients (38.5%). No CR was achieved. In 10 patients, tumor response could not be determined. Three patients died of progressive diseases within 10 days of gefitinib administration, 2 patients ceased gefitinib due to adverse events (diarrhea and nausea) within 10 days, and in 5 patients efficacy could not be defined due to the short duration of observation. The objective response rate was 24.6% and disease control rate was 53.3%.

Female patients showed a higher response rate (37.5%) than male patients (13.6%) ($P<0.01$) and those who had never smoked showed a higher response rate (41.7%) than current or former smokers (13.5%) ($P<0.01$) (Table III). Although the tumor response in patients with adenocarcinoma tended to be higher than that in patients with other histological types, in the univariate analysis, no statistical difference was observed (30% vs. 12%, $P=0.1$). Furthermore, no statistical differences were observed between tumor response and gender or smoking habit in the multivariate analysis, although the never smoked group tended to show favorable tumor response (odds ratio of 2.5, 95% CI, 0.89 to 7.21; $P=0.08$) (data not shown). On the other hand, there were 20 patients who had no previous chemotherapy before treatment with gefitinib. PR was observed in 5 patients (25.0%), SD was observed in 7 patients (35.0%), and PD was observed in 6

patients (30.0%) (Table III).

The duration of treatment for patients with PR or SD who consented to take gefitinib was 7.6 months (range, 1 ~ 21.7 months) and 18 patients were treated with gefitinib for more than 10 months (data not shown). Although five of 18 patients with long duration of treatment stopped gefitinib due to progression of disease and one patient stopped gefitinib due to adverse event, the remaining patients still had PR or SD at the data cut off and treatment with gefitinib is continued.

Survival. In all 122 patients, the median overall survival was 14.4 months. The 1-year survival rate was 50% (Figure 1). Female patients had significantly better survival compared to male patients ($P<0.01$) (Figure 2A). Survival of those who had never smoked was significantly longer than that of current or former smokers ($P<0.01$) (Figure 2B). Patients with adenocarcinoma had significantly better survival than patients with non-adenocarcinomas ($P<0.01$) (Figure 2C). The survival of patients with PS 0 to 2 was prolonged significantly longer compared to that of patients with PS 3 to 4 ($P<0.01$) (data not shown).

A multivariate analysis was carried out using the Cox hazard proportional model with significant prognostic factors identified in the univariate analyses (Table IV). Never smoked ($P<0.05$) and good PS (PS 0 to 2) ($P<0.01$) remained independent significant prognostic factors statistically, and female patients tended to have better survival in the multivariate analysis ($P=0.07$).

Toxicity. Most treated patients were assessable for toxicity (Table V). The main

toxicity was Grade 1 or 2 rash, seen in 52.5% patients. Grade 1 or 2 pruritis and diarrhea were seen in 27.9% and 24.6%, respectively. Of the 122, 4.1% of patients and 2.5% of patients developed Grade 3 anorexia and rash, respectively. In addition, 8 patients (6.6%) stopped gefitinib due to diarrhea, nail change, nausea, anorexia, or elevated transaminases.

Four patients developed gefitinib-related interstitial pneumonitis. Two of them were complicated with interstitial pneumonitis, and one with radiation pneumonitis prior to gefitinib, although their pulmonary diseases were clinically stable. Three of the 4 were males. One patient recovered by stopping gefitinib and 2 patients recovered by stopping gefitinib and beginning steorid treatment. However, one patient died from progression of interstitial pneumonitis despite of steroid treatment (Table VI).

Discussion

In the present analysis, we retrospectively analyzed the efficacy of 250mg/day gefitinib for patients with NSCLC. The objective response rate was 24.6% of the total patient population. Two phase II trials of gefitinib in patients with pretreated advanced NSCLC (IDEAL 1 and IDEAL 2) demonstrated antitumor activity (objective response rates, 11.8% to 18.4%) (15, 16), whereas the response rates were higher for Japanese patients (27.5%) than non-Japanese patients (10.4%) (15). The response rate in the present analysis was comparable to that of Japanese patients in IDEAL 1. The median survival was 14.4 months in the present analysis. In IDEAL1 and IDEAL 2, median survival was 7.6 months and 7

months, respectively. Subset analysis of data from the Japanese patients in IDEAL 1 showed that median survival was 414 days, which is comparable to the present data (21).

We also analyzed the association between sensitivity to gefitinib and patients characteristics. In the present analysis, gender and smoking habit were associated with favorable tumor response, and four factors were associated with improved survival in patients receiving gefitinib; females, never smoked, adenocarcinoma and good PS in the univariate analysis. Among them, smoking habit was predictive of tumor response in the multivariate analysis, although no statistical difference was observed (P=0.08). In addition, good PS (PS 0 to 2) and never smoked remained independent prognostic factors and female patients tended to have better survival in the multivariate analysis. Previously, multivariate analysis of all patients in IDEAL 1 revealed that PS, gender, histology, and prior immuno/hormonal therapy were significant prognostic factors associated with objective tumor response (15). Subset analysis of data from Japanese patients in IDEAL 1 showed that survival was longer in patients with adenocarcinoma, those with symptom improvement, or female patients in the univariate analysis, but not in the multivariate analysis (21). Moreover, Janne, *et al.* reported that significant independent prognostic factors associated with improved survival were females, good PS, and adenocarcinoma (22). Our results are almost comparable to these results and confirmed the result of subset analysis of Japanese patients in IDEAL 1.

Miller, *et al.* reported that bronchioloalveolar carcinoma was a more significant prognostic factor for gefitinib sensitivity than adenocarcinoma (23). We had only

one patient with bronchioloalveolar carcinoma, who showed an objective response. In the present analysis, most of the patients were diagnosed by small specimens of trasnbronchial lung biopsy, by which it was difficult to definitely diagnose bronchioloalveolar carcinoma, and we were unable to analyze the association between tumor response and bronchioloalveolar carcinoma

The present analysis included 20 patients with no previous chemotherapy. Among them, 5 patients showed a tumor response (25%), which was almost compatible with that in patients with previous chemotherapy (24.5%) in the present analysis. In addition, median survival of patients with no previous chemoteherapy was 8.6 months. There are few reports about the efficacy of gefitinib monotherapy as first-line therapy. Argiris, *et al.* reported that 25 patients who were unfit or refused chemotherapy received 250mg oral gefitinib daily as first-line therapy for the treatment of NSCLC, and 4 of the 22 evaluable patients (18%) had an objective response (24). The median time to progression was 2.2 months, median survival was 12.6 months and 1-year survival was 52% (24). The present results were compatible with former analysis and suggested that gefitinib was effective as first-line therapy. Gefitinib monotherapy should undergo further evaluation as first-line therapy in advanced NSCLC.

In the present analysis, the median duration of treatment with gefitinib for patients with PR or SD was 7.6 months and many patients received gefitinib for long time. There are few precise reports on long duration of treatment with gefitinib. The present results suggested that the efficacy of gefitinib could be sustainable for long time and long duration of treatment could contribute to the prolongation of survival.

Recently, somatic mutations in the tyrosine kinase domain of the EGFR gene have been shown to correlated with clinical responsiveness to gefitinib (25, 26). Screening for such mutations in lung cancers may identify patients who will have a response to gefitinib, as does being females, having adenocarcinoma, and never having smoked. We have not yet analyzed whether the 30 patients with objective responses have specific mutations in the EGFR gene and the investigation for EGFR mutations would be definitely needed in the future study.

Major adverse events were rash, pruritis, diarrhea and anorexia, which is consistent with previous reports. Patients given gefitinib have been documented to develop severe acute interstitial pneumonitis (17). In the present analysis, four patients developed interstitial pneumonitis, and one died of interstitial pneumonitis. Three of them were complicated with prior pulmonary complications. Although the cause of interstitial pneumonitis by gefitinib is unknown, the frequency of interstitial pneumonitis in Japanese patients tends to be higher than in non-Japanese patients, and may be related to population or environmental differences.

In conclusion, gefitinib showed favorable anti-tumor activity for patients with NSCLC, particularly females, never smokers, or patients with adenocarcinoma. On the other hand, one patient died from gefitinib-related interstitial pneumonitis and closer investigation is required in patients with prior pulmonary complications.

References

1. Ginsberg RJ, Vokes EE and Raben A: Non-small cell lung cancer. In: De Vita VT, Hellmann S, Rosenberg SA (eds): Cancer: Principles and Practice of Oncology. Ed. 6, Philadelphia, Lippincott-Raven Publishers 858-910, 2001.
2. Bunn PA: Treatment of advanced non-small-cell lung cancer with two-drug combinations. J Cin Oncol *20*: 3565-3567, 2002.
3. Non-Small Cell Lung Cancer Collaborative Group: Chemotherapy in non-small cell lung cancer - A meta-analysis using updated data on individual patients from 52 randomized clinical trials. BMJ *311*: 899-909, 1995.
4. Grilli R, Oxyman AD and Julian JA: Chemotherapy for advanced non-small-cell lung cancer: how much benefit is enough? J Clin Oncol *11*: 1866-1872, 1993.
5. Shepherd FA, Fossella FV, Lynch T, Armand JP, Rigas JR and Kris MG: Docetaxel (Taxotere) shows survival and quality-of-life benefits in the second-line treatment of non-small cell lung cancer: a view of two Phase III trials. Semin Oncol *28*: 4-9, 2001.
6. Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, Kalman L, Miller V, Lee JS, Moore M, Gandara D, Karp D, Vokes E, Kris M, Kim Y, Gamza F and Hammershaimb L: Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol *18*: 2354-2362, 2000.
7. Pavelic K, Banjac Z, Pavelic J and Spavebti S: Evidence for a role of EGF receptor in the progression of human lung carcinoma. Anticancer Res *13*:

1133-1137, 1993.

8. Fujino S, Enokibori T, Tezuka N, Asada Y, Inoue S, Kato H and Mori A: A comparison of epidermal growth factor receptor levels and other prognostic parameters in non-small cell lung cancer. Eur J Cancer *32A*: 2070-2074, 1996.
9. Baselga J: New technologies in epidermal growth factor receptor-targeted cancer therapy. Signal *1*: 12-21, 2000.
10. Wells A: The epidermal growth factor receptor (EGFR): A new target in cancer therapy. Signal *1*: 4-11, 2000.
11. Woodburn JR: The epidermal growth factor receptor and its inhibition in cancer therapy. Pharmacol Ther *82*: 241-250, 1999.
12. Lawrence DS and Niu J: Protein kinase inhibitors: the tyrosine-specific protein kinases. Pharmacol Ther *77*: 81-114, 1998.
13. Herbst RS, Maddox AM, Rothenberg ML, Small EJ, Rubin EH, Baselga J, Rojo F, Hong WK, Swaisland H, Averbuch SD, Ochs J and LoRusso PM: Selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 is generally well-tolerated and has activity in non-small-cell lung cancer and other solid tumors: results of a phase I trial. J Clin Oncol *20*: 3815-3825, 2002.
14. Baselga J, Rischin D, Ranson M, Calvert H, Raymond E, Kieback DG, Kaye SB, Gianni L, Harris A, Bjork T, Averbuch SD, Feyereislova A, Swaisland H, Rojo F and Albanell J: Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types. J Clin Oncol *20*: 4292-4302, 2002.
15. Fukuoka M, Yano S, Giaccone G, Tamura T, Nakagawa K, Douillard JY,

Nishikawa Y, Vansteenkiste J, Kufoh S, Rischin D, Eek R, Horai T, Noda K, Takata I, Smit E, Averbuch S, Macleod A, Feyereislova A, Dong RP and Baselga J: Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. J Clin Oncol *21*: 2237-2246, 2003.

16. Kris MG, Natale RB, Herbst RS, Lynch TJ Jr, Prager D, Belani CP, Schiller JH, Kelly K, Spiridonidis H, Sandler A, Albain KS, Cella D, Wolf MK, Averbuch SD, Ochs JJ and Kay AC: Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer. JAMA *290*: 2149-2158, 2003.
17. Inoue A, Saijo Y, Maemondo M, Gomi K, Tokue Y, Kimura Y, Ebina M, Kikuchi T, Moriya T and Nukiwa T: Severe acute interstitial pneumonia and gefitinib. Lancet *361*: 137-139, 2003.
18. Histological typing of lung and pleural tumors, Ed 3. International histological classification of tumours, World Health Orgnization. Geneva 1999.
19. American Joint Committee on Cancer. Lung. In Beahrs OH, Henson DE, Hutter RVP, Kennedy BJ (eds). Manual for Staging of Cancer. Philadelphia Lippincott 115-122, 1992.
20. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst *92*: 205-216, 2000.
21. Nishiwaki Y, Yano S, Tamura T, Nakagawa K, Kudoh S, Horai T, Noda K, Takata I, Watanabe K, Saka H, Takeda K, Imamura F, Matsui K, Katakami N,

Yokoyama A, Sawa Y, Takada M, Kiura K, Sugiura T, Fukuoka M and Uchida H: Subset analysis of data in the Japanese patients with NSCLC from IDEAL 1 study on gefitinib. Jpn J Cancer Chemother *31*: 567-573, 2004.

22. Janne PA, Gurubhagavatula S, Yeap BY, Lucca J, Ostler P, Skarlin AT, Fidias P, Lynch TJ and Johnson BE: Outcomes of patients with advanced non-small cell lung cancer treated with gefitinib (ZD1839, 'Iressa') on an expanded access study. Lung Cancer *44*: 221-230., 2004
23. Miller VA, Kris MG, Shah N, Patel J, Azzoli C, Gomez J, Krug LM, Pao W, Rizvi N, Pizzo B, Tyson L, Venkatraman E, Ben-Porat L, Memoli N, Zakowski M, Rusch V and Heelan RT: Bronchioloalveolar pathologic subtype and smoking history predict sensitivity to gefitinib in advanced non-small-cell lung cancer. J Clin Oncol *22*: 1103-1109, 2004.
24. Argiris A and Mittal N: Gefitinib as first-line, compassionate use therapy in patients with advanced non-small-cell lung cancer. Lung Cancer *43*: 317-322, 2004.
25. Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnson BE and Meyerson M: EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science *304*: 1497-1500, 2004.
26. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J and Haber DA: Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med *350*: 129-39, 2004.

Figure Legends

Figure 1. Kaplan-Meier method of overall survival in all-122 patients. Median survival time was 14.4 months.

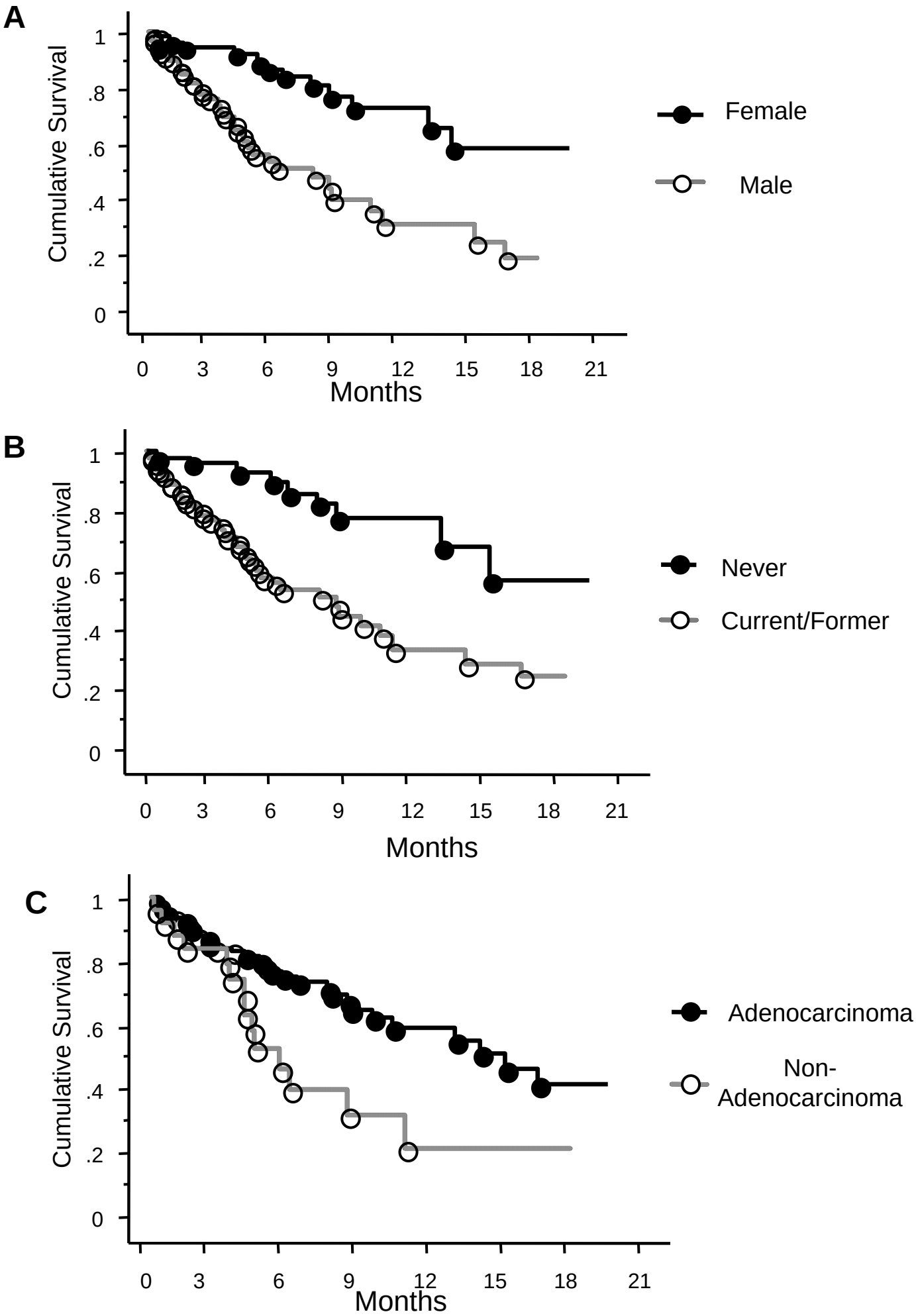
Figure 2. Kaplan-Meier method of overall survival according to each patient characteristics. (a) Overall survival is shown separately on the basis of gender. (b) Overall survival is shown separately on the basis of never having smoked and current/former smokers. (c) Overall survival is shown separately on the basis of patients with adenocarcinoma and non-adenocarcinoma. The survival differences in each category are statistically different ($P<0.01$).

Table Ⅰ. *Patient characteristics*

Characteristics	No. of patients	%
Number of patients	122	
Gender		
Male	66	54
Female	56	46
Age, Years		
Median	64	
Range	31-84	
Performance status		
0	15	12.3
1	70	57.4
2	23	18.8
3	8	6.6
4	6	4.9
Stage		
I~II	4	3.3
IIIA	6	4.9
IIIB	15	12.3
IV	76	62.3
Recurrence after surgery	21	17.2
Tumor histology		
Adenocaricinoma[a]	97	79.5
Squamous cell carcinoma	18	14.8
Large-cell carcinoma	3	2.5
Other NSCLC	4	3.2
Previous chemotehrapy		
0 regimen	20	16.4
1 regimen	40	32.8
2 regimens	39	31.9
More than 3 regimens	23	18.9
Surgery	31	25.4
Radiation	15	12.3
Smoking habit		
Never	48	39.3
Current	23	18.9
Former	51	41.8

[a]One patient with bronchiolar carcinoma was included in this group.

Figure 2


A
Cumulative Survival
1
.8
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.4
.2
0
0
3
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9
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Male
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Cumulative Survival
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Cumulative Survival
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12
15
18
21
Months
Adenocarcinoma
Non-
Adenocarcinoma

Table Ⅱ. *Best overall objective responses*

Response	Number of patients	(%)
Complete response (CR)	0	0
Partial response (PR)	30	24.6
Stable Disease (SD)	35	28.7
Progressive Disease (PD)	47	38.5
Unknown[a]	10	8.2

[a]No conclusion was achieved about best overall tumor response due to the short duration of observation, death from progressive disease within 10 days, or cessation of gefitinib by adverse events within 10 days.

Table Ⅲ. ***Univariate analysis of characteristics associated with response to gefitinib***

Characteristics	Number of patients[a]	(%)	P
Gender			
Male	9/66	13.6	<0.01[b]
Female	21/56	37.5	
Age			
75<	24/102	23.5	
75≧	6/20	30	0.54[c]
Tumor histology			
Adenocarcinoma	27/97	30	
Non-Adenocarcinoma	3/25	12	0.1[b]
Smoking habit			
Never	20/48	41.7	
Current / Former	10/74	13.5	<0.01[b]
Number of previous chemotherapy regimens			
0	5/20	25.0	
1	12/40	30	
2-4	13/62	20.9	0.63[b]
Performance status			
0-2	28/108	27.5	
3-4	2/14	14.3	0.34[b]

[a]The number of patients who showed PR/ the number of total patients.
[b]Fishire's exact test and [c] t test

Table Ⅳ. *Multivariable analysis[a] of features associated with improved survival*

Characteristics	Odds Ratio	95% CI	P
Gender			
Male	0.46		
Female	1	0.20 to 1.08	0.07
Smoking habit			
Never	2.59		
Current/Former	1	0.90 to 7.31	0.046
Histology			
Non-adenocarcinoma	0.46		
Adenocarcinoma	1	0.37 to 1.32	0.27
Performance status			
3-4	0.18		
0-2	1	0.08 to 0.37	<0.0001

[a]Cox hazard analysis

Table Ⅴ. *Treatment related toxicity*

	Grade 1/2	Grade 3	Grade 4
Rash	52.5	2.5	0
Pruritus	27.9	0.8	0
Diarrhea	24.6	0.8	0
Anorexia	13.1	4.1	0
Dry Skin	14.8	0.8	0
Nail Changes	8	0	0
Dehydration	2.5	1.6	0
GOT or GPT[a]	5.7	0.8	0
Intersitial Pnuemonitis	2.5	0	0.8

[a]Elevated liver transaminase

Table Ⅵ. ***Characteristics of patients with Interstitial pneumonitis***

No	Age	Gender	History	Smoking habit	PS	No. of former Chmotherapy	Prior Pulmonary Complications	Length (day)	Adverse Effect	Current Status
1	74	M	SCC[a]	Yes	1	0	Interstitial pneumonitis	47	Rash Diarrhea	Death[c]
2	74	M	Ad[b]	No	1	2	Interstitial pneumonitis	24	No	Ceased
3	70	M	Ad[b]	Yes	1	2	Radiation Pneumonitis	52	Rash Pruritus Nail changes Dry Skin	Ceased
4	76	F	Ad[b]	No	1	1	No	71	Rash Pruritus Nail changes Dry Skin Daiarrhea	Ceased

[a]Squamous cell carcinoma
[b]Adenocarcinoma
[c]Possibly therapy related death

Figure 1