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First-Line Gefitinib Treatment for Patients with Advanced Non-small Cell Lung Cancer with Poor Performance Status

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Background: Best supportive care only is recommended for patients with advanced non-small cell lung cancer (NSCLC) with poor performance status (PS) of Eastern Cooperative Oncology Group 3 or 4. Recently, the possibility of using epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor therapy has been reported for poor PS patients harboring *EGFR* mutations.

Methods: We retrospectively analyzed 74 patients with advanced NSCLC who were treated with first-line gefitinib during hospitalization for Eastern Cooperative Oncology Group PS 3 or 4. All patients were classified according to three clinical parameters: smoking history, gender, and histology type.

Results: The median age was 64 years (range, 35–86 years). The proportions of females, never smokers, and adenocarcinoma were 51.4%, 54.1%, and 78.4%, respectively. An overall response rate, median progression-free survival (PFS), and median overall survival (OS) was 27.0%, 32 days (95% confidence interval [CI], 22–48 days), and 61 days (95% CI, 7–115 days), respectively. Female gender, never smoking, and adenocarcinoma histology were strong predictors of tumor response. Never smoking and adenocarcinoma were independent predictors of better PFS but not of OS. Seven patients experienced treatment-related adverse effects of grade 3 to 4, which included anorexia ($n = 2$), pneumonitis ($n = 4$), and elevated liver enzymes ($n = 1$). Never-smoker females with adenocarcinoma exhibited a response rate of 50.0%, median PFS of 130 days (95% CI, 51–209 days), and median OS of 236 days (95% CI, 150–322 days).

Conclusions: Gefitinib may provide clinical benefits for patients with NSCLC with poor PS who were selected according to clinically favorable parameters.

Key Words: Non-small cell lung cancer, Performance status, Chemotherapy, Epidermal growth factor receptor.

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Poor performance status (PS) is a widely accepted indicator of poor survival outcomes in advanced non-small cell lung cancer (NSCLC).[1,2] Patients with poor PS constitute a significant proportion of the lung cancer population followed in daily oncology practice. In a large population-based registry, the prevalence of patients with an Eastern Cooperative Oncology Group (ECOG) PS 3 or 4 was estimated to represent 12% of all lung cancer patients.[3] However, best supportive care is the only recommended first treatment available for these patients.[4] Moreover, patients with NSCLC with poor PS are excluded from prospective clinical trials for anticancer therapy.

Gefitinib (IRESSA, AstraZeneca) is a molecular-targeted drug that reversibly blocks the tyrosine kinase domain of the epidermal growth factor receptor (EGFR). Several clinical trials have demonstrated that this drug is well tolerated and has clinical benefits in a subset of patients of East Asian descent, female gender, never-smoking history, adenocarcinoma histologic type, and *EGFR* mutations.[5–8] Recently, based on its favorable safety profile, this drug has been evaluated in elderly patients or those with poor PS.[9,10] However, a previous placebo-controlled randomized phase II trial of Goss et al.[9] found no improvement in response rate, progression-free survival (PFS), or overall survival (OS) after treatment with gefitinib in 201 chemonaïve patients with advanced NSCLC with an ECOG PS 2 or 3. Nevertheless, this earlier study noted that gefitinib significantly improves PFS compared with placebo in patients with *EGFR* fluorescent in situ hybridization-positive tumors. Furthermore, Inoue et al.[10] showed that in patients with NSCLC with *EGFR* mutation-positive tumors, gefitinib treatment resulted in a long median OS of 17.8 months, despite poor PS (i.e., ECOG 3 or 4). In this genetically selected group, the response rate was 66% and the median PFS was 6.5 months, which is better than that reported in the literature.[10] The results of these previous studies suggest that gefitinib may be an effective therapy for selected populations with good predictors, even for patients with poor performance.

Although activating *EGFR* mutations have been known to be the strongest biologic predictors of the sensitivity of EGFR tyrosine kinase inhibitors,[11–17] screening for the presence of *EGFR* mutations, especially in patients with poor PS, has several practical limitations, including difficulty in obtaining sufficient tissue samples for the test, time delay, and cost. Thus, for these patients, other clinicopathological pa-

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rameters will be more useful in clinical practice than *EGFR* mutations. We have accumulated clinical experience regarding the usefulness of clinical predictors of gefitinib treatment in patients who were unfit for chemotherapy because of poor PS. Based on this experience, we retrospectively investigated the efficacy of gefitinib in chemonaïve patients with advanced NSCLC with an ECOG PS of 3 or 4 by focusing on the role of clinical predictors in the identification of responders without genetic testing.

PATIENTS AND METHODS

Patients and Data Collection

Using a pharmacy disposition record, we first identified 220 patients with NSCLC who received gefitinib as inpatients at the National Cancer Center Hospital (Goyang, Republic of Korea) between July 2003 and March 2009. We assumed that patients with poor PS would have started the treatment in the inpatient setting. As shown in Figure 1, we used medical record reviews to generate the list of patients who met the following criteria: (1) histologically or cytologically confirmed recurrent or metastatic NSCLC, (2) no prior chemotherapy, and (3) ECOG PS of 3 or 4 affected by the disease, which was prospectively documented. Seventy-four patients were too ill to be treated with standard chemotherapy and received gefitinib as a first-line treatment for advanced NSCLC during their hospitalization. Subsequently, we reviewed medical records and radiographic images to assess clinicopathological characteristics, tumor response, and survival outcomes using a predesigned data collection format.

Treatment and Evaluation

Patients received 250 mg of gefitinib once daily in a 4-week cycle until the onset of disease progression, intolerable toxicity, or patient refusal. Imaging studies were performed according to clinical needs. Tumor response was assessed at 2 to 4 weeks after the first treatment using chest x-ray and every 8 weeks using computed tomography and other imaging techniques. Tumor response was determined in accordance with the guideline established by the Response Evaluation Criteria in Solid Tumor (RECIST) committee.[18] We used the same tumor assessment method in a given patient for response evaluation. Toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

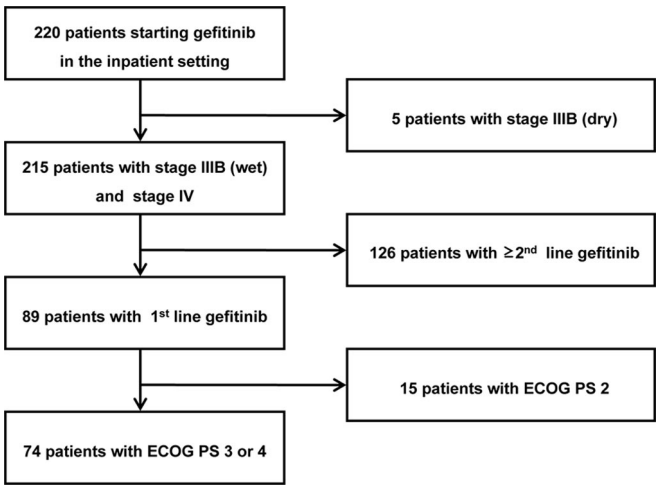

FIGURE 1. Patient collection.

Statistical Analyses

An analysis of drug efficacy and safety was performed in all patients who received at least one dose of gefitinib. However, the response of some patients was not assessable because of early death before formal radiographic evaluation.

TABLE 1. Patient Baseline Characteristics

Characteristics	*n* (%)
Total	74
Age, yr, median (range)	64 (35–86)
Gender	
Female	38 (51.4)
Male	36 (48.6)
Smoking	
Never	40 (54.1)
Ever	34 (45.9)
Histology	
Adenocarcinoma	58 (78.4)
Squamous cell carcinoma	7 (9.5)
Large cell carcinoma	1 (1.4)
Others	8 (10.8)
Stage[a]	
IIIB	7 (9.5)
IV	67 (90.5)
ECOG	
3	48 (64.9)
4	26 (35.1)
Major comorbidity	
Any disease	61 (82.4)
Cerebrovascular disease	15 (20.3)
Cardiovascular disease	16 (21.6)
Respiratory disease	20 (27.0)
Diabetes	4 (5.4)
Liver disease	2 (2.7)
Renal disease	4 (5.4)
None	13 (17.6)
Pneumonia requiring antibiotics	
Yes	14 (18.9)
No	60 (81.0)
Major cancer-related complications	
Respiratory distress	27 (36.5)
Uncontrolled pain	19 (25.7)
Symptomatic CNS metastasis	17 (23.0)
Symptomatic vertebral metastasis	6 (8.1)
SVC syndrome	2 (2.7)
Pericardial tamponade	1 (1.4)
Massive thromboembolism	1 (1.4)
Massive hepatic metastasis	1 (1.4)

[a] Staging according to the revised International System for Staging Lung Cancer.
ECOG, Eastern Cooperative Group; CNS, central nervous system; SVC, superior vena cava.

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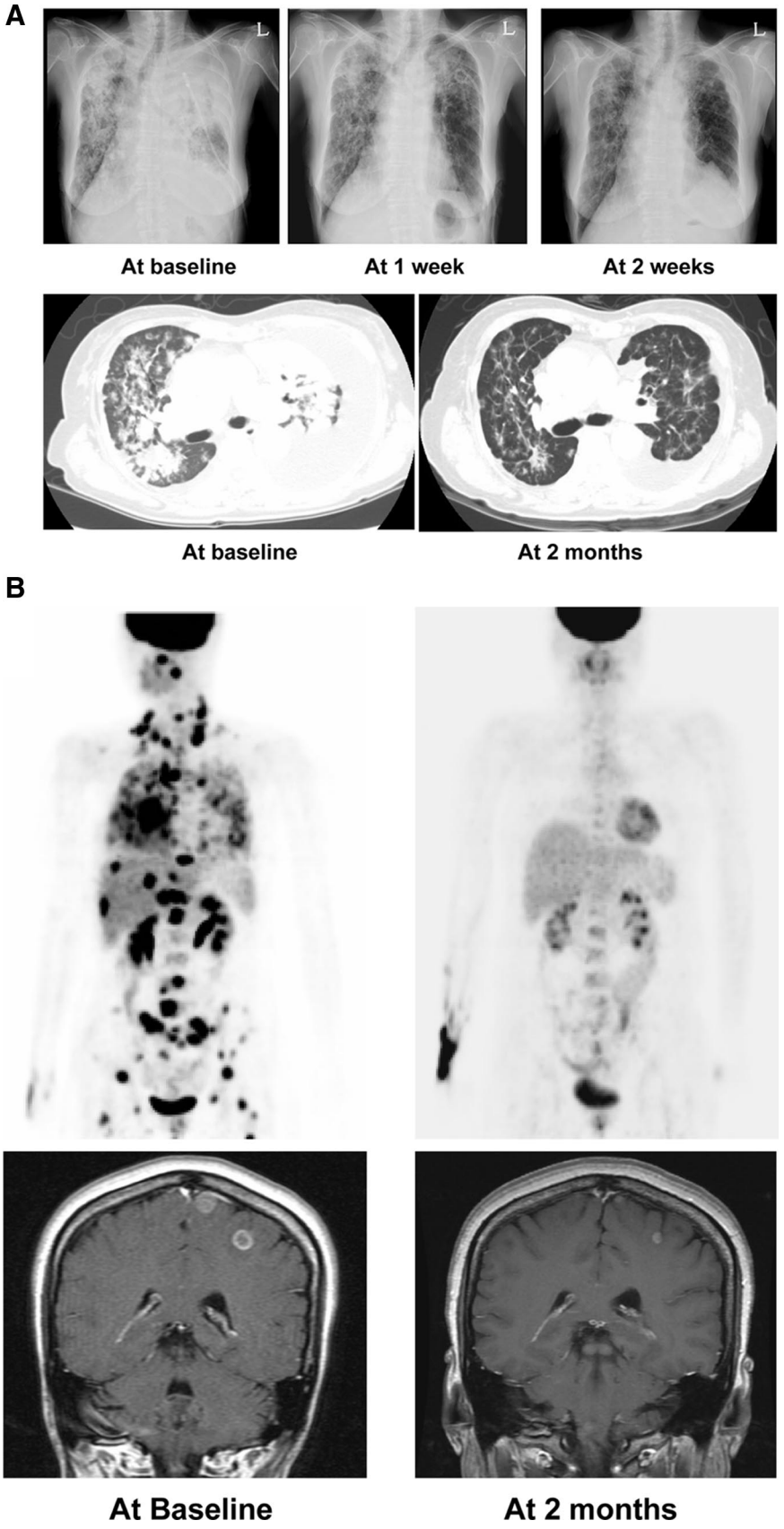

FIGURE 2. Radiologic response to gefitinib in patients with advanced non-small cell lung cancer (NSCLC) with a poor performance status (PS) of Eastern Cooperative Oncology Group (ECOG) 3 or 4. *A*, Case 1: chest x-ray scans (top) and computed tomography scans of the chest (bottom). *B*, Case 2: positron emission tomography scans (top) and magnetic resonance images of brain (bottom), before and after gefitinib treatment.

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In this study, an early death was considered as progressive disease (PD). Response rate represents the percentage of patients whose best tumor response was complete response or partial response (PR). Disease control rate is the frequency of patients whose best tumor response was complete response, PR, or stable disease at 8 weeks. Pearson's χ^2 test or Fisher's exact test was used to determine the relationship between tumor response and categorical variables, where appropriate. PFS was assessed from the first day of treatment until the first documentation of disease progression or death. OS was calculated from the first day of treatment until death or the most recent follow-up. Survival time was estimated using the Kaplan-Meier method, and survival difference between groups was assessed using the log-rank test. The Cox proportional hazards model was used to perform a multivariate analysis of survival. Two-sided p values less than 0.05 were considered significant.

RESULTS

Patient and Treatment Characteristics

The baseline characteristics of the assessed patients are shown in Table 1. The median age was 64 years (range, 35–86 years). The proportions of females, never smokers, and adenocarcinoma were 51.4%, 54.1%, and 78.4%, respectively. From 2003–2006 to 2007–2009, these percentages increased from 48.1 to 60.0% (females), 46.7 to 59.1% (never smokers), and 74.1 to 90.0% (adenocarcinoma). Thirty-eight patients (51.3%) had serious comorbid illness and 14 (18.9%) had pneumonia requiring antibiotics. Most patients suffered from major cancer-related complications, such as respiratory distress, neurologic dysfunction, or uncontrolled pain.

The median drug cycle administrated per patient was 1.5 cycles (range, 1–19 cycles). The proportion of patients receiving gefitinib treatment of less than 3 cycles, 3 to 6 cycles, and more than 6 cycles were 86.6%, 18.9%, and 13.5%, respectively. The median treatment duration was 32.5 days (range, 1–539 days). Nine patients (12.2%) had treatment breaks of 1 week or more. Treatment was discontinued in 70 patients because of PD ($n = 47$), early death ($n = 8$), treatment-related toxicity ($n = 7$), and other causes ($n = 8$). After starting gefitinib treatment, 42 patients (56.8%) visited the outpatient clinic after discharge from inpatient care, whereas 32 patients died during the initial hospitalization, either at the National Cancer Center ($n = 12$) or after transfer to another hospital ($n = 20$).

Tumor Response

Among the 74 patients, the tumor response was PR in 20 patients (27.0%), stable disease in 15 patients (20.3%), PD in 31 patients (41.9%), and nonevaluable in 8 patients (10.8%), which yielded a response rate of 27.0% (95% confidence interval [CI], 16.7–37.3%) and a disease control rate of 47.3% (95% CI, 35.7–58.9%). Among the 35 patients who achieved the disease control, 19 (54.2%) received subsequent chemotherapy after gefitinib failure; platinum-based doublets ($n = 8$), nonplatinum-based doublets ($n = 5$), docetaxel ($n = 3$), and pemetrexed ($n = 3$). However, there was no further chemotherapy in the 39 patients who did not reach the disease control. Tumor response was prompt and dramatic in gefitinib-responsive patients (Figure 2). The first case was a 76-year-old female patient with adenocarcinoma who needed oxygen supply because of severe respiratory difficulty secondary to hematogenous lung metastasis and malignant pleural effusion. This patient exhibited a marked improvement of lung metastasis and pleural effusion at 2 months after gefitinib treatment (Figure 2*A*). The second case was a 45-year-old female patient with adenocarcinoma who initially presented with severe bone pain, generalized weakness, and respiratory difficulty caused by disseminated tumor burden. This patient achieved a remarkable tumor response at 2 months after gefitinib treatment (Figure 2*B*).

The response rate was significantly higher in female patients than in male patients (42.1% versus 11.1%, respectively; $p = 0.003$), in never smokers than in ever smokers (42.5% versus 8.8%, respectively; $p = 0.001$), and in patients with adenocarcinoma than in patients with other histologic types (39.6% versus 18.8%, respectively; $p = 0.03$) (Table 2). Similar differences were observed for the disease control rate.

Survival Outcome

Survival data were followed up until the end of May 2009, and the median follow-up duration was 52 days (range, 1–704 days). At the time of analysis, 67 patients (90.5%) had died and 7 (9.5%) had survived; 4 of the survivors were on gefitinib treatment, 2 had second-line chemotherapy, and 1 was on supportive care. The median PFS and OS were 32 days (95% CI, 22–48 days) and 61 days (95% CI, 7–115 days), respectively (Table 3).

Univariate analysis revealed that smoking history and histology type were significant predictors of PFS, whereas

TABLE 2. Tumor Response According to Clinicopathologic Factors

	Response Rate		Disease Control Rate	
Variables	*n*/Total (%)	p^a	*n*/Total (%)	p^a
Total	20/74 (27.0)		35/74 (47.3)	
Age (yr)		0.44		0.23
<65	12/39 (30.8)		21/39 (53.8)	
≥65	8/35 (22.9)		14/35 (40.0)	
Gender		0.01		0.005
Female	15/38 (39.5)		24/38 (63.2)	
Male	5/36 (13.9)		11/36 (30.6)	
Smoking		0.001		0.001
Never	17/40 (42.5)		26/40 (65.0)	
Ever	3/34 (8.8)		9/34 (26.5)	
Stage		0.66		0.42
IIIB	1/7 (14.3)		2/7 (28.6)	
IV	19/67 (28.4)		33/67 (49.3)	
Histology		0.04		0.01
ADC	19/58 (32.8)		32/58 (55.2)	
Non-ADC	1/16 (6.3)		3/16 (18.8)	

[a] Tested by χ^2 test.
ADC, adenocarcinoma.

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TABLE 3. Survival in Univariate Analysis

	PFS			OS		
Variables	**Median, d (95% CI)**	**HR (95% CI)**	***p*[a]**	**Median, d (95% CI)**	**HR (95% CI)**	***p*[a]**
Total	32 (22–48)			61 (7–115)		
Age (yr)			0.15			0.10
<65	56 (20–92)	0.70 (0.43–1.14)		197 (95–299)	0.67 (0.41–1.09)	
≥65	29 (13–49)	1.0		49 (43–55)	1.0	
Gender			0.11			0.02
Female	57 (7–107)	0.68 (0.41–1.10)		186 (60–312)	0.65 (0.40–0.99)	
Male	22 (11–33)	1.0		29 (6–52)	1.0	
Smoking			0.01			0.005
Never	61 (17–105)	0.55 (0.34–0.89)		159 (20–298)	0.58 (0.35–0.94)	
Ever	22 (11–33)	1.0		37 (19–55)	1.0	
ECOG			0.52			0.35
3	45 (22–68)	0.85 (0.51–1.40)		83 (0–202)	0.69 (0.42–1.14)	
4	22 (15–29)	1.0		48 (13–83)	1.0	
Stage			0.07			0.50
IIIB	21 (3–39)	2.00 (0.90–4.47)		23 (20–26)	1.27 (0.57–2.81)	
IV	38 (23–53)	1.0		68 (0–145)	1.0	
Histology			0.007			0.32
ADC	45 (24–66)	0.46 (0.25–0.83)		68 (0–135)	0.73 (0.41–1.30)	
Non-ADC	23 (11–35)	1.0		53 (12–82)	1.0	

[a] Tested by the log rank test.

PFS, progression free survival; OS, overall survival; CI, confidential interval; HR, hazard ratio; ECOG, Eastern Cooperative Group; ADC, adenocarcinoma.

TABLE 4. Survival in Multivariate Analysis

	PFS		OS	
Variables	**HR (95% CI)**	***p*[a]**	**HR (95% CI)**	***p*[a]**
Age (<65 yr vs. ≥65 yr)	0.73 (0.44–1.21)	0.22	0.67 (0.40–1.11)	0.12
Gender (female vs. male)	0.77 (0.34–1.69)	0.53	0.88 (0.41–1.86)	0.73
Smoking history (never vs. ever)	0.46 (0.21–0.97)	0.04	0.64 (0.30–1.33)	0.23
Histology (ADC vs. non-ADC)	0.50 (0.26–0.94)	0.03	0.91 (0.48–1.73)	0.78

[a] Tested in Cox regression model with age, gender, smoking history, and histology.

PFS, progression free survival; OS, overall survival; HR, hazard ratio; CI, confidential interval.

TABLE 5. Treatment-Related Adverse Effects

	Grade,[a] *n* (%)				
Variables	**0**	**1**	**2**	**3**	**4**
Anorexia	58 (78.3)	7 (9.5)	7 (9.5)	2 (2.7)	0 (0.0)
Nausea/vomiting	55 (74.3)	15 (20.3)	3 (4.1)	1 (1.4)	0 (0.0)
Diarrhea	37 (50.0)	33 (44.6)	4 (5.4)	0 (0.0)	0 (0.0)
Skin rash	47 (63.5)	18 (24.3)	9 (12.1)	0 (0.0)	0 (0.0)
Pruritis	63 (85.1)	4 (5.4)	7 (9.5)	0 (0.0)	0 (0.0)
Pneumonitis	60 (81.1)	7 (9.5)	3 (4.1)	2 (2.7)	2 (2.7)
AST/ALT	63 (85.1)	9 (12.1)	1 (1.4)	1 (1.4)	0 (0.0)

[a] Assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

age, gender, ECOG PS, and tumor stage were not. These two predictor variables remained significant even in the multivariate analysis of PFS using covariates of age, gender, smoking history, and histology type (Table 4). The risk of progression was significantly lower in never smokers (hazard ratio [HR], 0.46; 95% CI, 0.21–0.97; $p = 0.04$) and in patients with adenocarcinoma (HR, 0.50; 95% CI, 0.26–0.94; $p = 0.03$) compared with ever smokers and patients with nonadenocarcinoma, respectively.

The median OS was significantly longer in female patients than in male patients (186 days; 95% CI, 60–312 days versus 29 days; 95% CI, 8.5–15.8 days; $p = 0.02$) and longer in never smokers than in ever smokers (159 days; 95% CI, 20–298 days versus 37 days; 95% CI, 19–55 days; $p = 0.005$). However, gender and smoking history were not independent predictors of OS, as assessed by multivariate analysis.

Safety and Tolerability

Treatment-related adverse effects were evaluated in 74 patients (Table 5). Serious treatment-related adverse effects with grade 3 or more were observed in seven patients, including pneumonitis ($n = 4$), anorexia ($n = 2$), nausea/vomiting ($n = 1$), and elevated liver enzymes ($n = 1$). Treatment-related death occurred in two patients because of interstitial pneumonitis. The first patient was a 66-year-old male patient who had previously suffered from interstitial pulmonary fibrosis. The patient developed pneumonitis after

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TABLE 6. Response Rates According to Three Favorable Clinical Predictors

	Never Smoker			Ever Smoker		
	Female	Male	Total	Female	Male	Total
ADC	14/28 (50.0%)	2/5 (40.0%)	16/33 (48.5%)	0/4 (0.0%)	3/21 (14.3%)	3/25 (12.0%)
Non-ADC	1/5 (20.0%)	0/2 (0.0%)	1/7 (14.3%)	0/1 (0.0%)	0/8 (0.0%)	0/9 (0.0%)
Total	15/33 (45.5%)	2/7 (28.6%)	17/40 (42.5%)	0/5 (0.0%)	3/29 (10.3%)	3/34 (8.8%)

ADC, adenocarcinoma.

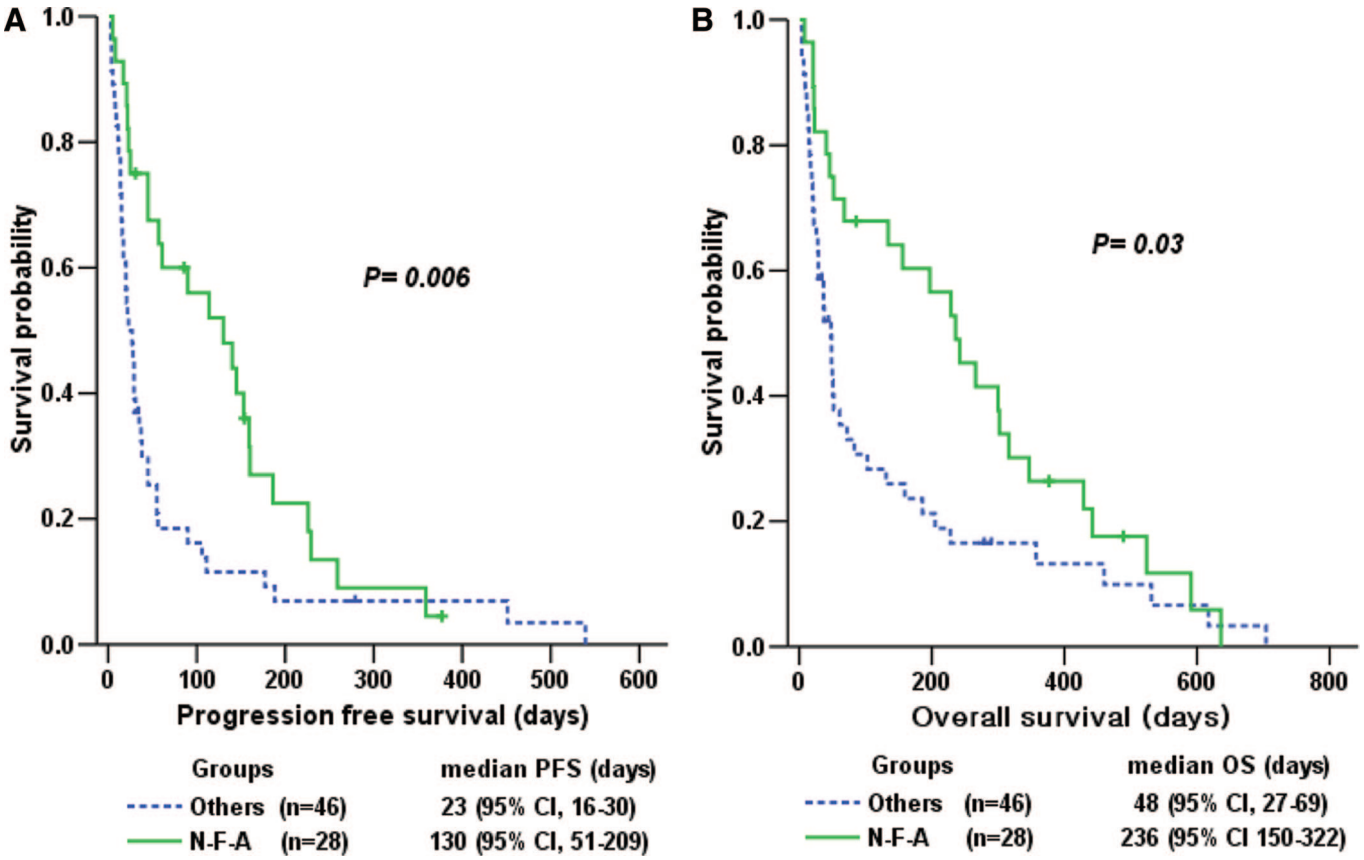

FIGURE 3. Progression-free survival (PFS) curves (*A*) and overall survival (OS) curves (*B*) for the group of never-smoker females with adenocarcinoma (N-F-A) and for the other groups among patients with advanced non-small cell lung cancer (NSCLC) with a poor performance status (PS) who were treated with first-line gefitinib. Survival difference was tested using the log-rank test.

day 35 of gefitinib treatment and died of respiratory failure. The second patient, a 69-year-old male with massive tumor burden on both lung fields, died of pneumonitis after day 15 of gefitinib treatment. All serious adverse events other than elevated liver enzymes developed within the second cycle of gefitinib administration.

Treatment Outcomes According to Favorable Clinical Predictors

Table 6 lists the response rates in the subgroups classified according to the three clinical predictors (smoking history, gender, and histology type). The group of never-smoker females with adenocarcinoma showed response rate of 50.0% (95% CI, 30.0–69.7%), whereas the remaining groups had response rate of 13.0% (95% CI, 2.9–23.1%). There was a significant difference in PFS (130 days [95% CI, 51–209 days] versus 23 days [95% CI, 16–30 days]; $p = 0.006$) and in OS (236 days [95% CI, 150–322 days] versus 48 days [95% CI, 27–69 days]; $p = 0.03$) between never-smoker females with adenocarcinoma and the other patients (Figure 3).

DISCUSSION

In this study, patients treated with gefitinib showed overall response rate of 27.0%, median PFS of 44 days, and median OS of 61 days, consistent with the retrospective study of Yang et al.,[19] which showed that gefitinib treatment

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yielded response rate of 28% and median OS of 2.4 months in 76 Taiwan patients who had ECOG PS 3 or 4 without prior chemotherapy. Among the various clinicopathological variables analyzed in this study, female gender, never-smoking history, and adenocarcinoma histology were strong predictors of tumor response or disease control with gefitinib, as described in prior studies.[5,6] A history of never smoking and adenocarcinoma histology remained an independent predictor of longer PFS in the multivariate analysis.

The subgroup of never-smoker females with adenocarcinoma showed a better tumor response and longer survival time compared with the other groups. Although this group had a poor PS of ECOG 3 or 4, its response rate of 50.0% was comparable with that observed in the group with the same characteristics but with a good PS of ECOG 0 to 2 (52.2%), as reported previously by our group.[20] Furthermore, this group clearly showed improved survival (median PFS, 130 days; median OS, 236 days) compared with chemonaïve patients with an ECOG PS of 2 or 3 who were given best supportive care exclusively, as assessed in a randomized prospective study (median PFS, 1.3 months; median OS, 2.7 months).[9] Although we cannot completely exclude the effect of the good prognostic aspect of these three clinical characteristics,[21–23] these survival differences observed for patients with poor PS cannot be explained by intrinsic biologic features only without the gefitinib treatment effect.

The response rate to gefitinib in the clinically selected patients included in this study was numerically lower than that detected in the genetically selected patients assessed in a Japanese phase II study,[10] although it is difficult to perform a direct comparison between the studies. These differences reflect the superiority of this genetic predictor over clinical predictors in the identification of responders to gefitinib. However, the technical feasibility of the genetic test should be considered in clinical applications, together with the predictive accuracy. A mutational study is feasible only in a small portion of patients with poor PS, because they are vulnerable to complications associated with the invasive procedures necessary for tissue sampling and do not have sufficient time to delay treatment. Thus, it seems reasonable to use clinical predictors for the selection of patients with poor PS who would benefit from gefitinib treatment, especially in East Asian patients who are likely to harbor *EGFR* mutations. In addition, it is necessary to identify potential molecular markers in more easily accessible materials for patients with poor PS, such as sputum or blood samples.

One major concern is that patients with poor PS may be more prone to drug toxicity than are patients with good PS, even in the case of targeted agents.[24] A Japanese feasibility study noted that gefitinib should be given with caution to patients with an ECOG PS of 3 because of the high risk-to-benefit ratio of this treatment.[24] In this earlier study, grade 3 and 4 toxicity occurred in 5 (42%) of 12 patients, including 2 cases of pneumonitis. In our study, however, the incidence of grade 3 to 4 treatment-related adverse events was similar to that reported in previous studies involving patients with good PS.[11–14] The overall incidence of adverse events did not seem to be increased in this study, although it is possible that not all adverse events were captured because of the retrospective nature of this study. Furthermore, two other prospective studies of poor PS patients demonstrated that gefitinib can be applied safely in this clinical setting.[9,10] Based on its favorable safety profile and possible efficacy on East Asian descent, the Korean-National Comprehensive Cancer Network guideline (v.2.2008) recommends best supportive care or EGFR tyrosine kinase inhibitors as first-line therapy for patients with advanced NSCLC with ECOG PS 3 or 4.[25]

This study has several limitations. First, the validity of the data presented is to some extent limited by the retrospective nature of the study. Second, there were inherent limitations in collecting systematic toxicity data and also more detailed information on quality of life parameters, which would have been an important outcome measures in patients with poor PS. Third, short-term assessment of tumor responses in clinically unstable patients with poor PS could have adversely affected the PFS. Despite of these limitations, however, there is no doubt that some patients benefited from gefitinib monotherapy.

In conclusion, gefitinib monotherapy provided clinical benefits in a selected group of chemonaïve patients with NSCLC with poor PS of ECOG 3 or 4 who were unfit for standard chemotherapy. In particular, three clinically favorable predictors of response (i.e., never-smoking history, female gender, and adenocarcinoma) may be useful for the identification of subjects eligible for gefitinib treatment among the patient population with poor PS.

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