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Interstitial Lung Disease Associated with Gefitinib in Japanese Patients with *EGFR*-mutated Non-small-cell Lung Cancer: Combined Analysis of Two Phase III Trials (NEJ 002 and WJTOG 3405)

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Objective: Interstitial lung disease associated with gefitinib is a critical adverse reaction. When geftinib was administered to *EGFR*-unknown patients, the interstitial lung disease incidence rate was approximately 3–4% in Japan, and usually occurs during the first 4 weeks of treatment. However, it has not been fully investigated in *EGFR*-mutated patients.

Methods: We collected clinical records of participants of two Phase III trials (WJTOG 3405 and NEJ 002), which compared gefitinib with platinum doublet chemotherapy. All patients were *EGFR* mutated, chemo-naïve and had good performance status.

Results: A total of 402 patients were enrolled in this study. In the gefitinib arm, 10 (5.0%) of 201 patients developed interstitial lung disease, of whom five (2.5%) were Grade 3 or greater, with two deaths (1.0%). In contrast, only one patient developed interstitial lung disease (Grade 1) in the chemotherapy arm. With regard to gefitinib, smoking history was significantly associated with developing interstitial lung disease (odds ratio 0.18; 95% confidence interval: 0.05–0.74; $P = 0.01$). The cumulative incidence rate of interstitial lung disease was similar in the 0–4, 5–8 and 9–12 week time periods. However, between smokers and never-smokers, cumulative incidence rates in the first 4 weeks were significantly different (4.7% versus 0%, $P = 0.03$). Three of 10 patients developed interstitial lung disease after 8 weeks of gefitinib administration (days 135, 171 and 190, respectively).

Conclusions: Among *EGFR*-mutated patients, the incidence of interstitial lung disease associated with gefitinib was not different from that in previous reports. Smoking history was associated with developing interstitial lung disease, and smokers had a higher incidence rate of interstitial lung disease in the first 4 weeks.

Key words: epidermal growth factor receptor mutation – gefitinib – epidermal growth factor receptor-tyrosine kinase inhibitor – interstitial lung disease – Japanese

INTRODUCTION

The recent introduction of targeted agents has dramatically changed the treatment of non-small-cell lung cancer (NSCLC). Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) is a prototype of such therapy which targets NSCLC harboring the *EGFR* mutation (1,2). EGFR-TKIs have demonstrated a higher response rate and longer progression-free survival than platinum doublet chemotherapy (3–6). Common adverse events associated with EGFR-TKIs include skin rash, diarrhea and hepatotoxicity. Interstitial lung disease (ILD) is a rare but potentially fatal adverse event (7). The incidence of ILD has been reported to be higher in Japanese than in Caucasians. Two large, multi-institutional studies in Japan (8–10) reported that its incidence is 3.5–4.0%, compared with just 0.3% in the USA (11). They also suggested that male gender, history of smoking, poor performance status, pre-existing lung disorder and prior history of chemotherapy were predictive risk factors (8–10).

Today, clinical guidelines recommend that administration of EGFR-TKIs should be limited to *EGFR*-mutated patients, reflecting the high efficacy of this drug in this patient population (12). Since it is known that *EGFR* mutation is relatively rare in males or smokers, which are known risk factors of ILD, ILD incidence might be lower in patients with *EGFR* mutation. However, a detailed investigation of ILD associated with EGFR-TKIs among *EGFR*-mutated patients has not been done. Therefore, we conducted a combined analysis of two Phase III trials that compared gefitinib with platinum doublet chemotherapy in Japanese NSCLC patients with *EGFR* mutation.

PATIENTS AND METHODS

Patient Selection and Treatment Methods

We collected the clinical records of participants of two Phase III trials (WJTOG 3405 (3) and NEJ 002 (4)). These trials compared gefitinib with platinum doublet chemotherapy in Japanese NSCLC patients with *EGFR* mutation. *EGFR* mutation was screened by PCR-based methods as previously described (13,14). All of the participants were required to be chemo-naïve, with Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1 and aged between 20 and 75 years, with adequate organ function. Patients with active infectious disease or severe heart disease were excluded. All patients were confirmed not to have pulmonary fibrosis by chest computed tomography (CT) within 1 month prior to registration. Both studies were approved by the institutional review board at each participating site.

Eligible patients were randomly assigned to receive either gefitinib (250 mg daily) or standard chemotherapy. The latter consisted of paclitaxel 200 mg/m^2 plus carboplatin (area under the curve of six) in NEJ 002 or docetaxel 60 mg/m^2 plus cisplatin 80 mg/m^2 in WJOG 3405, every 3 weeks. All participants who had received at least one dose of a study drug were included in the safety analysis.

Baseline data were collected for each patient, including information on sex, age, history of smoking, ECOG PS, tumor histology, clinical stage and type of *EGFR* mutation.

Evaluation of ILD and Statistical Analysis

All patients were assessed by chest CT for their response to treatment every 2 months. The diagnosis of ILD was based on clinical manifestations (worsening dry cough or dyspnea within days to weeks), accompanied by interstitial pulmonary infiltrates on a chest X-ray and a chest CT (15). Close investigation, such as blood and bacterial examination, was required in the protocols to exclude other ILDs. Bronchoalveolar lavage was also recommended, if possible. ILD was assessed according to the National Cancer Institute

Table 1. Baseline characteristics of the patients in the gefitinib arm

	Total ($n = 201$)	Non-ILD ($n = 191$)	ILD ($n = 10$)	P value
Age (years)				
Mean	64	64	63	0.67
Range	34–75	34–75	56–75	
Sex (no.)				
Male	71	65	6	0.17
Female	130	126	4	
Smoking status (no.)				
Never	137	134	3	0.01
Previous/current	64	57	7	
ECOG performance status (no.)				0.35
0	111	107	4	(PS 0 versus 1)
1	89	83	6	
2	1	1	0	
Histology (no.)				
Ad	187	180	7	1.0
Other	14	14	0	
Clinical stage (no.)				
IIIB	25	25	0	0.52
IV	129	122	7	
Post-operative relapse	47	44	3	
Type of *EGFR* mutation				
Exon 19 del	108	104	4	0.42
L858R	85	80	5	
Other	8	7	1	

ILD, interstitial lung disease; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor.

Common Terminology Criteria (NCI-CTC, version 3.0). All events were assessed by investigators at first; then severe cases were confirmed by independent committees based on medical, pathological and radiological findings.

Differences between covariates in patients with or without ILD were analyzed using Fisher's exact tests or Pearson's tests. The Kaplan–Meier method was used to estimate the cumulative incidence rate of ILD, and differences according to the smoking status were analyzed by the log-rank test. All the analyses were performed using JMP version 7 (SAS Institute Inc., USA).

RESULTS

In WJOG 3405, 177 patients were randomized and 175 were included in the safety analysis. In NEJ 002, 230 patients were randomized and 227 were included in the safety analysis. In our study a total of 402 patients were enrolled, half of them in the gefitinib arm.

Baseline characteristics of the patients were well balanced between the treatment groups. As previously reported (3,4), about two-thirds of patients were female, the median age was 64 years, 65% were never-smokers, 55% had an ECOG PS of 0 and 95% had adenocarcinoma.

At the time of data cut-off, the median duration of gefitinib treatment was 165 days (WJTOG 3405) and 308 days (NEJ 002); the median number of chemotherapy cycles was four. In the gefitinib arm, 10 (5.0%) of 201 patients developed ILD, of whom five (2.5%) were Grade 3 or greater, with two deaths (1.0%). In contrast, only one patient developed ILD (Grade 1) in the chemotherapy arm.

The background and clinical course of the patients in the gefitinib arm are summarized in Tables 1 and 2. The clinical background of patients who developed ILD and those who did not showed no difference other than smoking status. Univariate analysis showed that smoking history was significantly associated with developing ILD (odds ratio 0.18; 95% confidence interval (CI): 0.05–0.74; $P = 0.01$). This accounted for 10.9% (95% CI: 5.4–20.9%) of the incidence rate of ILD among smokers, versus 2.2% (95% CI: 0.8–6.3%) among never-smokers.

Figure 1 shows a Kaplan–Meier curve of the cumulative incidence rate of ILD. Among the overall population, the cumulative incidence rate in the first 4 weeks, 5th–8th weeks and 9th–12th weeks was 1.5% (95% CI: 0.5–4.3%), 1.5% (95% CI: 0.5–4.4%) and 0.5% (95% CI: 0.1–2.9%), respectively. Smoking status was associated with the timing of the onset of ILD . Between smokers and never-smokers, the cumulative incidence rate of ILD in the first 4 weeks was significantly different (4.7 versus 0%, $P = 0.03$), whereas that in the other periods (5th–8th weeks and 9th–12th weeks) was similar (Fig. 1). Three of 10 patients developed ILD after 8 weeks of gefitinib administration (days 135, 171 and 190, respectively).

Most of the patients who developed severe ILD (Gr $\geq$ 3) were given steroid therapy. One patient was treated with an immunosuppressive agent (cyclosporine). Non-invasive positive pressure ventilation was used in one patient (No. 10) but unfortunately this patient died.

DISCUSSION

Three large studies of ILD associated with EGFR-TKI have been conducted in Japan (Table 3). Ando et al. (8) performed a retrospective study including 1976 NSCLC patients treated with gefitinib and found an incidence rate of 3.5% and mortality rate of 1.6%. In a prospective cohort and nested-case control study by Kudoh et al. (9), cumulative incidence rates during 12 weeks of treatment were 4.0%. They also mentioned that the risk of developing ILD was higher

Table 2. Clinical characteristics of 10 patients who developed ILD in the gefitinib arm

No.	Age	Sex	Smoking index (BI)	PS	Stage	Site of *EGFR* mutation	Onset day from EGFR-TKI	ILD (CTCAE grade)	Outcome
1	69	M	800	0	r	Exon 19	48	1	Improved
2	57	F	0	1	4	Exon 19	70	1	Improved
3	60	M	860	1	4	Exon 21	15	1	Improved
4	56	F	370	1	4	Exon 19	14	1	Improved
5	71	F	0	1	4	Exon 21	171	2	Improved
6	57	M	740	0	r	Exon 19	25	3	Improved
7	68	M	1075	0	4	Exon 21	190	3	Improved
8	75	M	525	1	4	Exon 21	53	3	Improved
9	65	M	1320	0	r	Exon 19	135	5	Died
10	60	F	0	1	4	Exon 21	32	5	Died

BI, Brinkman Index; PS, Eastern Cooperative Oncology Group performance status; EGFR-TKI, EGFR-tyrosine kinase inhibitor; CTCAE, Common Terminology Criteria for Adverse Events; M, male; F, female.

with gefitinib than with chemotherapy (the odds ratio was 3.2). With regard to erlotinib, Nakagawa et al. (10) conducted a post-marketing survey in Japan and reported that 158 of 3488 patients were confirmed to have ILD (any grade, 4.5%), with a mortality rate of 1.6%. These studies suggested that male gender, smoking history, poor PS, pre-existing lung disorder and prior history of chemotherapy were risk factors of ILD. However, none of the three studies mentioned *EGFR* mutation status.

To our knowledge, ours is the first study to describe the clinical characteristics of ILD associated with gefitinib limited to *EGFR*-mutated patients. Similar to Kudoh's report, ILD was relatively more common in the gefitinib arm than in the chemotherapy arm. The incidence rate of ILD associated with gefitinib was as high as 5% with a mortality rate of 2.5%, even though our analysis contained a high proportion of patients from low-risk groups (female, non-smokers with good PS).

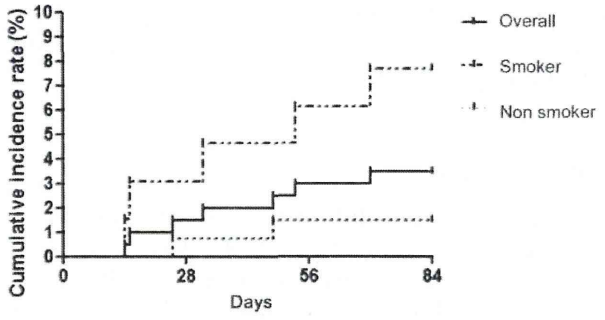

Figure 1. Cumulative incidence rate of interstitial lung disease associated with gefitinib. Kaplan–Meier-estimated cumulative incidence rate of interstitial lung disease in patients who were allocated to the gefitinib arm in WJTOG 3405 and NEJ 002 trial (overall population ($n = 201$), bold line; smoker ($n = 64$), dashed line; non-smoker ($n = 137$), dotted line).

Similarly to the previous studies, our analysis showed that smoking history was highly associated with developing ILD associated with gefitinib (odds ratio 0.18). Smoking induces airway epithelial damage, and lung injury could be prolonged and worsened by gefitinib in a preclinical model (16). Most of the other risk factors were excluded at the time of registration, because enrolled patients were required to be chemo-naïve, with a PS of 0–1, and confirmed not to have pulmonary fibrosis. Therefore, we should pay more attention to smoking status even if the patient has *EGFR* mutation. In terms of the timing of the onset of ILD, smoking history seemed to be an important factor. Between smokers and never-smokers, the cumulative incidence rate of ILD in the first 4 weeks was significantly different (4.7 versus 0%, $P = 0.03$). Previous studies stated that ILD occurred most commonly in the first 4 weeks (median: 23–31 days) and 60% of participants were smokers. So, despite the small subset analysis in the present study, the higher incidence rate observed in the first 4 weeks among smokers is noteworthy.

Another point is that three of 10 patients developed ILD after several months of gefitinib treatment. With erlotinib, it was reported that ILD occurred at the rate of 0.11 per 100 patient-weeks after 8 weeks of treatment. It is not clear whether the mechanism of ILD varies over time from its onset; further investigation on late-onset ILD is needed.

Our analysis has several limitations. First, this was an investigator-dependent analysis. Most of the ILD cases were diagnosed by clinical manifestations and a chest CT. Bronchoalveolar lavage was recommended in the protocols, but actually done in only one case. As acute exacerbation of ILD after bronchoscopy has been reported (15), this may be acceptable. In our analysis, all patients were assessed by chest CT every 2 months, and severe cases were confirmed by independent, multidisciplinary committees. Secondly, this analysis was done with a small sample size due to the population and rarity of incidence.

Table 3. ILD associated with EGFR-TKI in Japanese patients: pivotal studies and ours

	Ando et al. (8)	Kudoh et al. (9)	Nakagawa et al. (10)	Present data
Study design	Retrospective	Prospective	Retrospective	Retrospective
No. of patients	1976	1482	3488	201
Type of EGFR-TKI	Gefitinib	Gefitinib	Erlotinib	Gefitinib
Patient selection by *EGFR* mutation status	No	No	No	Yes
ILD (any Grade; %)	70 (3.5)	59 (4.0)	158 (4.5)	10 (5.0)
ILD (Grade 5; %)	31 (1.6)	25 (1.7)	55 (1.6)	2 (1.0)
Risk factors of ILD	Smoking Pre-existing lung disorder Male	Smoking Pre-existing lung disorder Poor PS Elderly Cardiac disease	Smoking Pre-existing lung disorder Poor PS Lung infection	Smoking

In conclusion, the incidence of ILD associated with gefitinib among *EGFR*-mutated patients was not different from that in previous reports. Smoking history was highly associated with developing ILD. In addition, a substantial number of patients developed ILD after several months of gefitinib treatment.

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Conflict of interest statement

A.I., K.N. and N.Y. have received honoraria from Astra Zeneca. T.M. has received honoraria from Astra Zeneca and Chugai. T.N. has received honoraria from Chugai. Y.N. has received honoraria and research grants from Chugai. All other authors declare no conflicts of interest.

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Histology and Smoking Status Predict Survival of Patients with Advanced Non–Small-Cell Lung Cancer

Results of West Japan Oncology Group (WJOG) Study 3906L

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Introduction: Smoking status is one of the prognostic factors in advanced non–small-cell lung cancer (NSCLC). Currently, adenocarcinoma (Ad) histology is considered a predictive factor in advanced NSCLC. We investigated the correlation between histology or smoking status and survival of NSCLC patients receiving chemotherapy.

Methods: We retrospectively reviewed clinical data from stage IIIB or IV NSCLC patients who started first-line chemotherapy at affiliated institutions of West Japan Oncology Group from 2004 to 2005. We also collected information on pack-years of cigarette smoking and years since cessation. Overall survival was compared using log-rank test, and Cox regression analysis was used to identify independent prognostic factors.

Results: In total, 2542 consecutive patients were enrolled at 40 institutions. Of those, 71 were excluded because of unknown smoking history. The median overall survival of nonsmoking Ad patients (593 days) was longer than that of smoking Ad, nonsmoking non-Ad, and smoking non-Ad patients (384, 374, and 319 days, respectively; $p < 0.001$). In Cox regression with sex, age, stage, performance, and treatment as covariates, we found significant interaction ($p = 0.039$) between histology (Ad/non-Ad) and smoking status (smoker/nonsmoker); smoking conferred a hazard ratio of 1.34 (95% confidence interval, 1.15–1.55) in Ad, but only 0.99 (0.75–1.31) in non-Ad. Higher pack-years and shorter period since cessation were significantly associated with poorer survival in Ad ($p < 0.001$), but not in non-Ad ($p \geq 0.434$).

Conclusion: Ad histology is associated with better prognosis, and only smoking status had a prognostic impact in Ad.

Key Words: Non–small-cell lung cancer, Histology, Adenocarcinoma, Smoking status.

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This study is registered with University Hospital Medical Information Network-Clinical Trial Registry (UMIN-CTR) (http://www.umin.ac.jp/ctr/index.htm umin.ac.jp/ctr; identification number UMIN000001263).

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Lung cancer is the leading cause of cancer-related mortality in Japan, and the rest of the world, with more than one million people dying from it each year. Non–small-cell lung cancer (NSCLC), which accounts for nearly 80% of all lung cancers, comprises several histological types, including adenocarcinoma (Ad), squamous cell carcinoma (Sq), and large-cell carcinoma (La). NSCLC had been treated as a single disease because of similar therapeutic effects of conventional chemotherapeutic agents. In the last few decades, however, treatment with new drugs, such as epidermal

growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), bevacizumab, and pemetrexed revealed that tumor histology has profound impact on the benefits of a variety of chemotherapy or targeted-therapy regimens for advanced NSCLC.[1–4] Thus, histology came to be considered a predictive factor for the effectiveness of specific chemotherapy in patients with advanced NSCLC. However, there is no previous report on histology as a prognostic factor, that is, a variable determining survival irrespective of the chemotherapy regimen administered.

Previous studies showed that cigarette smoking is an independent prognostic factor in patients with NSCLC,[2,5–7] but a dose–response relationship between the quantity of smoking and survival has not been established. Although Yelena et al.[6] noted that patients who had smoked up to 15 pack-years had a longer survival than those with more than a 15 pack-year history, other cutoff points for the amount of cigarette smoking have not been considered. In addition, the relationship between smoking and survival was not investigated with respect to differences in NSCLC histological subtypes, and the studies that did evaluate survival in Sq versus non-Sq patients did not reach a firm conclusion.[7,8] However, Kawaguchi et al.[8] showed that Ad had better prognosis than Sq in never-smokers, but not in ever-smokers, suggesting that the prognostic impact of cigarette smoking may differ among histologic subtypes in NSCLC.

We hypothesized that Ad histology and lower smoking status would result in better overall survival (OS) in advanced NSCLC. To test this hypothesis, we investigated the impact and possible interaction of histology and smoking status on survival of advanced NSCLC patients receiving chemotherapy in the clinic.

PATIENTS AND METHODS

Study Patients

We sent case report forms to 40 affiliated institutions of West Japan Oncology Group, and requested them to provide demographic and clinical data from medical records for all patients with stage IIIB or IV NSCLC, who started first-line systemic chemotherapy between January 1, 2004 and December 31, 2005. Patients who had a relapse after surgery or radiotherapy were excluded. The case report forms were submitted by the participating institutions during the period from September 2008 to January 2009. This study was approved by the institutional review board of each participating institution.

Demographic and Clinical Variables

We obtained the following baseline demographic and clinical information from the case report forms: age, sex, histology, disease stage, Eastern Cooperative Oncology Group performance status (PS), smoking status, type of first-line chemotherapy, number of treatment regimens, and the year in which first-line chemotherapy was started. Disease stage was determined according to the tumor, node, metastasis system.[9] Staging classification was performed by physical examination, chest–abdominal computed tomography, brain magnetic resonance imaging, bone scan, and positron emission tomography if necessary. Patients were categorized into nonsmokers and smokers according to smoking status. Nonsmokers were defined as those who had smoked less than 100 cigarettes. Among smokers, exsmokers were defined as those who had quit smoking 1 year or more before diagnosis, and current smokers as those who continued their smoking habit at diagnosis. Pack-years of smoking were calculated by multiplying the number of packs (20 cigarettes in one pack) smoked per day by the number of years smoked, and categorized as less than 10, 10 to 19, 20 to 29, 30 to 39, 40 to 49, 50 to 59, and 60 or more. Years of smoking cessation were categorized as 1 to 4, 5 to 9, 10 to 14, 15 to 19, and 20 or more. Type of first-line chemotherapy was categorized into platinum-based combination, nonplatinum combination, and single-agent chemotherapy. Because the only approved EGFR-TKI for the treatment of inoperable or recurrent NSCLC in Japan before October 2007 was gefitinib, we collected information on gefitinib usage during the observation period and noted the starting day of gefitinib treatment. OS was calculated from the start of first-line chemotherapy to the date of death. Patients still alive were censored as of the last known follow-up.

TABLE 1. Patient Characteristics

Parameter	Ad (n = 1731)	Non-Ad (n = 740)	p
Men/women	1056/675	641/99	<0.001
Smoking status			<0.001
Nonsmoker	659	79	
Exsmoker	300	165	
Current smoker	772	496	
Stage IIIB/IV	444/1287	271/469	<0.001
PS			0.002
0	546	206	
1	873	402	
2	191	96	
3	90	25	
4	31	11	
Histology			—
Sq	—	516	
La	—	71	
Others	—	153	
Chemotherapy			0.181
Single-agent	354	137	
P doublet	1306	571	
Non-P doublet	71	32	
Regimen			<0.001
1	536	285	
2	445	201	
3	322	115	
≥4	428	139	
Gefitinib Y/N	959/772	146/594	<0.001

Ad, adenocarcinoma; PS, performance status; Sq, squamous cell; La, large cell; P, platinum; Y, yes; N, no.

Statistical Analysis

Demographic and clinical variables were compared among groups according to lung cancer histology, using the χ^2 test. The primary endpoint of this study was OS. Survival curves were calculated by the Kaplan–Meier method and compared using the log-rank test. Prognostic importance of histology and smoking status were analyzed using the Cox regression analysis adjusted for sex, age, disease stage, PS, type of first-line chemotherapy, and the year in which first-line chemotherapy was started. For detection of possible interaction between histology and smoking status, the terms of interaction of the two variables were evaluated by the likelihood ratio test. Because gefitinib was the preferred choice in patients with Ad, another Cox regression analysis was performed, in which patients were censored at the start of gefitinib administration, and the results were compared with the original Cox analysis. Significance level was set at a p value of 0.05. Statistical analyses were performed with SAS version 9.2 software (SAS Institute, Cary, NC).

RESULTS

Between January 1, 2004 and December 31, 2005, 2542 consecutively treated patients were enrolled at 40 institutions. Of these, 71 were excluded because of unknown smoking history. The characteristics of the study population, categorized into Ad and non-Ad, are listed in Table 1. There were 1731 Ad and 740 non-Ad patients (29.9% and 70.1%, respectively). Among them, we confirmed 1346 and 599 deaths in Ad and non-Ad patients, respectively. There were significantly more women (39.0% in Ad versus 13.4% in non-Ad) and nonsmokers (38.1% in Ad versus 10.7% in non-Ad) in the Ad group than in the non-Ad group. Patients who received single-agent chemotherapy accounted for approximately 20% of the study population. Compared with combination regimens, single-agent chemotherapy was associated with old age (63.6 years for combination regimens versus 71.1 years for single-agent chemotherapy), high proportions of female patients (29.3% versus 40.0%), nonsmokers (27.8% versus 34.0%), stage IV (69.4% versus 78.3%), and PS 0 to 1 (60.9% versus 87.1%). The proportion of Ad histology was not significantly different between single-agent and combination regimens (72.1% and 69.5%, respectively). The OS was 464 days in Ad compared with 326 days in non-Ad ($p < 0.001$; Fig. 1*A*). Between Ad and non-Ad, which was divided into Sq and La, Ad had significantly better survival than the other two histological groups (Sq, 341 days; La, 254 days; $p < 0.0001$; Fig. 1*B*). With regard

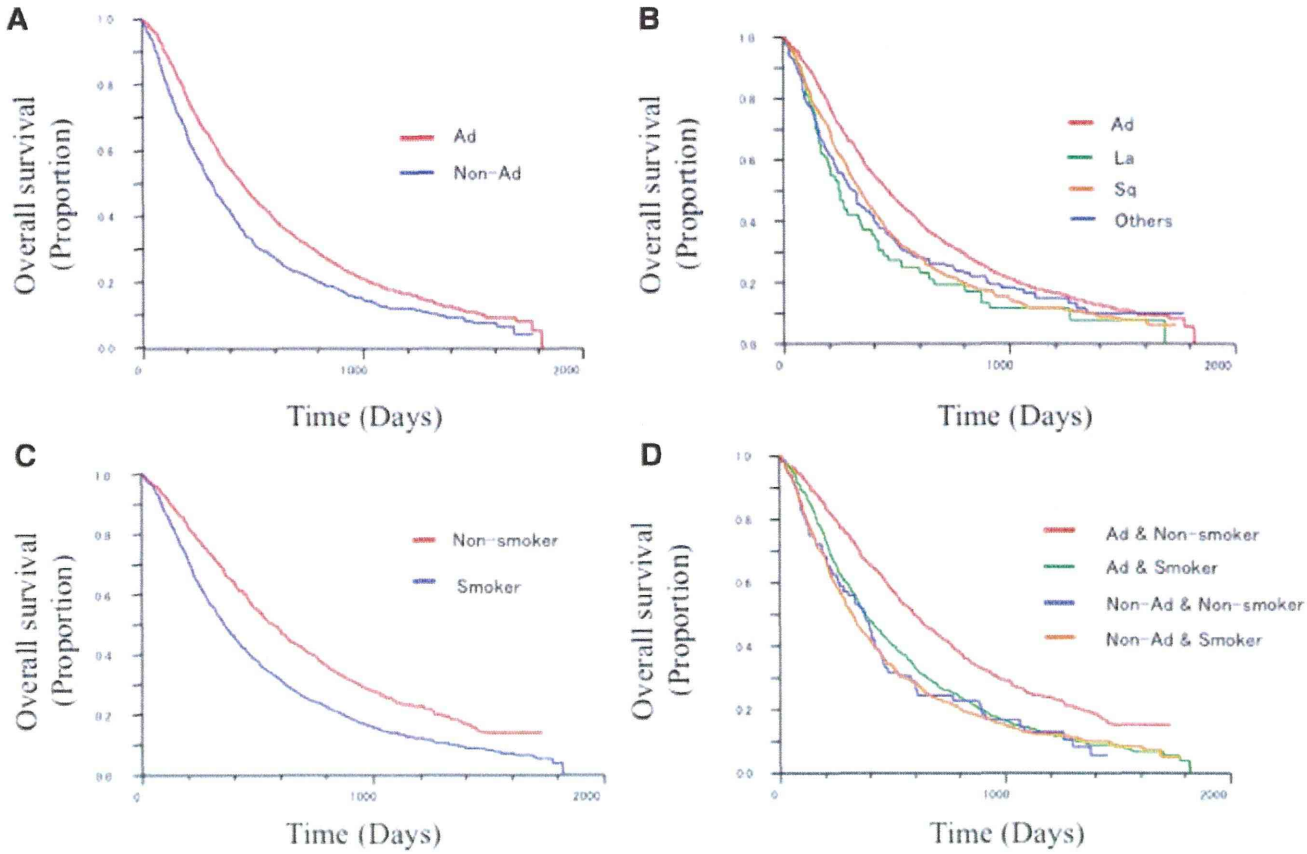

FIGURE 1. Kaplan–Meier plots of overall survival for patients classified according to histology type as (*A*) Ad and Non-Ad; histologic subtype as (*B*) Ad, La, Sq, and others; smoking status as (*C*) smokers and nonsmokers; and combination of smoking status and histology as (*D*) Ad and nonsmoker, Ad and smoker, Non-Ad and nonsmoker, and Non-Ad and smoker. Ad, adenocarcinoma; La, large cell; Sq, squamous cell.

TABLE 2. Survival Analysis by Cox Proportional Hazards Model (n = 2471)

Parameter	HR	95% CI	p
Sex			
Women	1		
Men	1.342	1.168–1.541	<0.001
Age yrs	1.007	1.002–1.012	0.005
Smoking status			
Nonsmoker	1		
Exsmoker	1.178	0.997–1.391	0.054
Current smoker	1.335	1.155–1.543	<0.001
Clinical stage			
Stage IIIB	1		
Stage IV	1.505	1.358–1.669	<0.001
PS			
0	1		
1	1.609	1.446–1.790	<0.001
2	2.229	1.910–2.601	<0.001
3	3.048	2.455–3.785	<0.001
4	5.487	3.864–7.790	<0.001
Histology			
Ad	1		
Sq	1.143	1.015–1.286	0.028
La	1.542	1.182–2.011	0.001
Others	1.397	1.159–1.683	<0.001
Chemotherapy			
Single-agent	1		
Non-P doublet	0.842	0.657–1.080	0.175
P doublet	0.793	0.699–0.899	<0.001

HR, hazard ratio, CI, confidence interval; PS, performance status; Ad, adenocarcinoma; Sq, squamous cell; La, large cell; P, platinum.

to smoking status, nonsmokers (568 days) had significantly longer survival than smokers (358 days; $p < 0.0001$; Fig. 1*C*). In a combined analysis of smoking status and histology, the median OS of Ad in nonsmokers was longer than that of Ad in smokers, non-Ad in nonsmokers, and non-Ad in smokers (593, 384, 374, and 319 days, respectively; $p < 0.001$; Fig. 1*D*). In Cox regression analysis, sex, age, smoking status, disease stage, PS, histology, and chemotherapy showed a statistically significant prognostic impact on survival (Table 2). When the interaction between histology (Ad/non-Ad) and smoking status (smoker/nonsmoker) was included in the Cox model, significant interaction was observed ($p = 0.039$); smoking conferred a hazard ratio (HR) of 1.34 (95% confidence interval [CI], 1.15–1.55) in Ad, in contrast to 0.99 (0.75–1.31) in non-Ad. In detailed analyses that excluded the 104 patients (current smokers, 89; unknown, 15) with unknown amount of cigarette smoking, shorter period since cessation showed a significant trend for poorer survival in the whole population ($p < 0.001$). This trend was also observed in Ad ($p < 0.001$; Table 3), but not in non-Ad ($p \geq 0.434$; Table 3). When non-Ad patients were divided into Sq and La or others, the trend p was 0.534 in Sq and 0.165 in La or others. The prognosis became significantly worse with higher pack-years of cigarette smoking in the whole population and Ad ($p < 0.001$; Table 3), but no significance was not achieved for the non-Ad group ($p = 0.519$; Table 3). When non-Ad patients were divided into Sq and La or others, the trend p was 0.798 in Sq and 0.380 in La or others. The prognostic impact of histology and smoking status remained significant in the Cox regression analysis, in which patients were censored at the start of gefitinib administration; positive smoking history, Sq histology, and La or other histology conferred an HR of 1.51 (95% CI, 1.21–1.88), 1.22 (95% CI, 1.06–1.41), and 1.59 (95% CI, 1.32–1.93), respectively. The negative prognostic impact of shorter period since cessation and pack-years of cigarette smoking was also essentially unchanged ($p < 0.001$ in both).

DISCUSSION

The consensus report of prognostic factors in NSCLC at the 1990 International Association for the Study of Lung Cancer Workshop showed that histology was not a prognostic factor for advanced NSCLC.[10] Our study is the first report to reveal that histology is a significant prognostic factor for advanced NSCLC. Importantly, we showed that Ad patients have the longest survival of all three histological groups (Ad, Sq, and La). Ad is the most common histological subtype of lung cancer in nonsmokers,[11] who have been reported to have a better prognosis than smokers.[12–14]

Smoking has been described as a prognostic factor in lung cancer. Although multiple studies have demonstrated the negative effects of smoking in patients with NSCLC, most included a heterogeneous population comprising patients with all stages and types of lung cancer.[5] In contrast, our study cohort consisted exclusively of patients with advanced NSCLC treated with first-line chemotherapy. We showed that smoking status is an independent prognostic factor for survival in those patients. Similar data have been shown in former studies.[2,5] However, those reports did not show whether smoking conferred any survival impact for advanced NSCLC irrespective of histological subtypes. In our study, only Ad histology had significant interaction with smoking status or smoking index and prognosis. A higher level of smoking was related to shorter survival in Ad patients, whereas smoking level and survival were not associated in non-Ad patients. Although the proportion of non-Ad patients was 29.9% of the total, the observed number of deaths in this study yielded a statistical power of more than 80% for detecting an HR of 1.5 at the 5% significance level in both Ad and non-Ad patients. Others have found that Ad histology is a significant prognostic factor in separate multivariate analysis for never-smokers in advanced NSCLC.[8] Yelena et al.[6] showed that high cigarette smoking, as measured in pack-years, is associated with decreased survival after diagnosis of stage IIIB/IV NSCLC. However, the patients of that study received a wide variety of therapies, raising the possibility that the outcomes might have been the result of distinct therapeutic responses. Although we only assessed the prognostic value of smoking status at diagnosis, assessment of smoking status at a later point, that is, at the time of treatment, would also have been of interest to determine whether cessation at the time of diagnosis leads to improved survival.