Table I. *Baseline characteristics of all patients.*

Baseline characteristics		No. of patients
Sex	Male / Female	20 / 1
Age (years)	Median (Range)	66 (48-75)
ECOG PS	0/1/2	5 /12 /4
Disease extent	LD/ ED	4 / 17
Previous treatment	Chemotherapy only	4
	Chemotherapy + radiotherapy	14
	Chemotherapy + others	3
Previous chemotherapy	Platinum + etopoisde +/- others	18
	Including irinotecan HCl	10
	Others	1
No. of previous chemotherapy regimens	1 / 2 / 3	16 / 4 / 1
Response to prior chemotherapy '	CR / PR / NC / PD / NE	2 / 13 / 5 / 0 / 1

No.: number
PS: performance status, LD: limited disease, ED: extensive disease.

Table II. *Toxicity of treatment for all cycles.*

Toxicity	No. of patients with event by grade				
	G0	G1	G2	G3	G4
Nausea	12	7	2	0	0
Vomiting	19	1	1	0	0
Diarrhea	17	3	1	0	0
Constipation	10	5	6	0	0
Mucositis	21	0	0	0	0
Gastric ulcer	20	0	1	0	0
Fever	16	3	2	0	0
Fatigue	13	0	8	0	0
Skin rash	20	0	0	1	0
Infection	18	0	0	3	0
Neuropathy	9	9	1	2	0
Myalgia	16	4	1	0	0
Dyspnea	17	0	1	2	1
Hemoglobin	1	9	9	1	1
WBC count	2	1	8	8	2
Neutrophil count	0	5	2	8	6
Platelet count	16	5	0	0	0
GOT	12	7	2	0	0
GPT	16	4	1	0	0
Total bilirubin	19	1	1	0	0

Other grade 3 and 4 toxicities included infection, skin rash, neuropathy and pulmonary toxicity. Grade 1 or 2 neuropathy was seen in 10 patients, and greater than grade 2 was observed in 2 individuals. No hypersensitivity reactions were encountered. Grade 3 or 4 pulmonary toxicity was reported in 3 patients and was characterized by dyspnea. Life-threatening complications of grade 4 infection and grade 4 dyspnea were encountered in 1 patient, who experienced febrile neutropenia and respiratory failure secondary to pneumonia after the third weekly dose. He was treated with antibiotics and supportive measures, but the respiratory distress worsened and he died on day 41. One of 2 grade 3 pulmonary toxicities was pneumonitis, probably induced by paclitaxel, but was resolved by steroid therapy.

Response to treatment and survival. The responses to therapy are shown in Table III according to whether the patient had primary refractory disease or primary sensitive cancer that subsequently relapsed. Although 1 out of the 21 patients was not assessable for response, having died during the first cycle, a ≥50% decrease in the sum of the products of the 2 largest perpendicular diameters of the tumor was achieved in this patient. Five of the 22 patients had a PR, but no CRs were observed and the overall response rate

Table III. *Response data.*

		No. of patients					Response rate (%)
		CR	PR	NC	PD	NE	
Total	21	0	5	4	11	1	23.8
Sensitive	11	0	3	3	5	0	27.3
Refractory	10	0	2	1	6	1	20.0

CI = confidence interval; CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; NC = no change.

was 23.8% (95% confidence interval, 5.59 to 42.03). When only evaluable patients were included in the analysis, however, the response rate improved to 25% (95% confidence interval, 6.02 to 43.98). Two PRs (20%) occurred in refractory cases and 3 PRs (27%) were achieved in sensitive cases. Four patients showed no change, and 1 exhibited disease progression. The survival analysis was performed in January 2003, by which point 10 patients had died and 2 were still alive. The median survival time (MST) was 5.8 months and the 1-year survival rate was 13.4% (Figure 1).
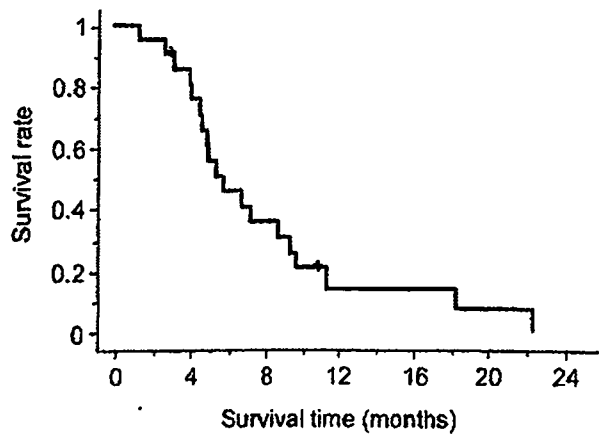
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Figure 1. *Overall survival.*

Discussion

Since the outlook for SCLC patients who receive second-line therapy is poor, several new drugs, such as paclitaxel, docetaxel, gemcitabine, vinorelbine, topotecan and irinotecan, are currently under investigation. The new chemotherapy agents that have been most extensively evaluated in SCLC are the topoisomerase I inhibitors, including topotecan and irinotecan. Von Pawel *et al.* conducted a phase III study comparing single-agent topotecan with cyclophosphamide, doxorubicin and vincristine (CAV) in patients with progression at least 60 days after initial therapy and reported response rates of 24.3% for topotecan and 18.3% for CAV with a median survival time (MST) of 25.0 and 24.7 weeks, respectively, and found that topotecan was at least as effective as CAV in the treatment of patients with recurrent SCLC (10). Two studies of irinotecan in patients with refractory SCLC have been reported in Japan and the response rates in both studies were high, *i.e.*, 50% in 16 patients, and 47% in 15 patients, respectively (11, 12). We therefore consider that topoisomerase I inhibitors, such as topotecan and irinotecan, are key drugs in the second-line treatment of SCLC. However, the number of SCLC patients treated with an irinotecan-containing regimen as first-line chemotherapy has increased in Japan since, in a randomized phase III trial in Japan (13), a combination of irinotecan and cisplatin was shown to yield better survival than the standard etoposide and cisplatin regimen in patients with untreated extensive SCLC. Therefore, the search for effective drugs, other than topoisomerase I inhibitors, for previously treated SCLC, especially refractory SCLC, must be continued.

Single-agent paclitaxel, at a dose of 175 mg/m^2 as a 3-h infusion every 3 weeks in patients with previously treated SCLC, produced a response rate of 29% and an MST of 100

days (4). The results of our phase II study demonstrated that weekly paclitaxel at a dose of 80 mg/m^2 yielded a similar response rate of 23.8% and a much better MST of 5.8 months than that of paclitaxel given every 3 weeks. Because the antiproliferative activity of paclitaxel is cell-specific, prolonging patient exposure to a low dose of the drug beyond a threshold concentration is ultimately more efficacious than a short-term exposure to higher drug concentrations, a hypothesis . supported by *in vitro* experiments with a variety of cell lines and suggested by the results of clinical studies. As clinical experience with paclitaxel treatment of various types of tumors has progressed, so has the use of weekly regimens at lower doses administered as 1-h infusions, as opposed to standard higher doses delivered once every 3 weeks as 3-h infusions.

A response rate of more than 10% is considered evidence of drug efficacy in previously-treated SCLC patients (14). Before newer drugs, such as topoisomerase I inhibitors, taxane, gemcitabine and vinorelbine were introduced, salvage chemotherapy did not usually prolong survival in SCLC and MSTs after relapse were 2.5 - 3.9 months (1). Single-agent phase II trials of gemcitabine, docetaxel and vinorelbine in patients with relapsed or refractory SCLC have been reported. Smyth *et al.* (15), using a 100 mg/m^2 dose of docetaxel, obtained a response rate of 25% in 28 assessable patients who had received prior chemotherapy. A trial of gemcitabine in 46 previously-treated patients yielded an 11.9% response rate (16) and vinorelbine provided response rates of 12% and 16% in second-line patients with sensitive disease (17,18). Thus, the MST of 5.8 months and response rate of 23.8% in this study compare favorably with those of published single-agent trials in relapsed or refractory SCLC.

The toxicity profile noted in this trial was predictable based on the toxicity profile previously described in weekly paclitaxel trials, neutropenia being the major toxic effect. All side-effects, except fatal neutropenic pneumonia in 1 case, were manageble. Grade 3 or 4 neutropenia occurred in 14 of the patients in our study but was immediately alleviated by treatment with G-CSF. Grade 3 or 4 anemia occurred in 1 patient, but there was no grade 3 or 4 thrombocytopenia in our study. The incidence of grade 3/4 myelosuppression was considered tolerable. There were 3 cases of grade 3 or 4 pulmonary toxicity, 2 of which occurred due to bacterial infection. This regimen required a dose of 20 mg of dexamethasone weekly as premedication. We believe that this occurrence of bacterial pneumonia might be related to the use of steroids.

Testing new drugs in previously-treated patients has the clear advantages of determining the degree of non-cross resistance with other drugs. Its greatest disadvantage is the risk of a considerable dose reduction (especially of myelotoxic drugs) to avoid extensive hematological side-

effects, perhaps resulting in doses that are too low to fairly evaluate the drug. Since a weekly administration of paclitaxel causes only mild myelosuppression and as there may be no cross resistance with platinum, etoposide, irinotecan, or topotecan, which are usually used to treat SCLC, we find this regimen suitable for previously-treated SCLC.

In summary, the weekly paclitaxel regimen is moderately effective in SCLC patients who have received prior chemotherapy. Based on the statistical design of this study, the 5 PR observed suggest that weekly paclitaxel warrants further evaluation in this patient population. Additional investigations will serve to clarify the role of this agent, either alone or in combination with other agents. Combining paclitaxel with other agents with proven non-cross resistance such as irinotecan, topotecan, or gemcitabine or new target-based agents is the next step needed to evaluate second-line situations, especially in patients with resistant disease.

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O R I G I N A L   R E P O R T

Phase III Study of Docetaxel Compared With Vinorelbine in Elderly Patients With Advanced Non–Small-Cell Lung Cancer: Results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904)

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A B S T R A C T

Purpose

Docetaxel has shown activity in elderly patients with advanced non–small-cell lung cancer (NSCLC). This randomized phase III trial evaluated the efficacy and safety of docetaxel versus vinorelbine (the current standard treatment) in elderly patients.

Patients and Methods

Chemotherapy-naïve patients age 70 years or older with stage IIIB/IV NSCLC and performance status 2 or lower were eligible. Patients randomly received docetaxel 60 mg/m² (day 1) or vinorelbine 25 mg/m² (days 1 and 8) every 21 days for four cycles. The primary end point was overall survival. Overall disease-related symptom improvement was assessed using an eight-item questionnaire.

Results

In total, 182 patients were enrolled. Median age was 76 years (range, 70 years to 86 years). There was no statistical difference in median overall survival with docetaxel versus vinorelbine (14.3 months v 9.9 months; hazard ratio, 0.780; 95% CI, 0.561 to 1.085; P = .138). There was a significant difference in median progression-free survival (5.5 months v 3.1 months; P < .001). Response rates were also significantly improved with docetaxel versus vinorelbine (22.7% v 9.9%; P = .019). The most common grade 3 to 4 toxicities were neutropenia (82.9% for docetaxel; 69.2% for vinorelbine; P = .031) and leukopenia (58.0% for docetaxel; 51.7% for vinorelbine). Other toxicities were mild and generally well tolerated. Docetaxel improved overall disease-related symptoms over vinorelbine (odds ratio, 1.86; 95% CI, 1.09 to 3.20).

Conclusion

Docetaxel improved progression-free survival, response rate, and disease-related symptoms versus vinorelbine. Overall survival was not statistically significantly improved at this time. Docetaxel monotherapy may be considered as an option in the standard treatment of elderly patients with advanced NSCLC.

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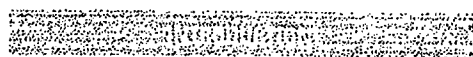
Due to a general increase in life expectancy in developed countries worldwide, the proportion of the general population in these countries that is elderly is increasing. For example, in 1970 in Japan, 7.9% of the general population was 65 years or older, which increased to 17.3% by 2000, and is estimated to reach 29.6% by 2030.[1] As non–small-cell lung cancer (NSCLC) is a common disease in the elderly population, the question of how best to treat elderly NSCLC patients will become increasingly important.[2]

Chemotherapy in patients with advanced NSCLC improves survival, reduces disease-related symptoms, and improves quality of life (QOL) compared with best supportive care.[3] Although platinum-based doublets involving newer agents, such as docetaxel, paclitaxel, gemcitabine, vinorelbine, and irinotecan, are standard first-line chemotherapy for most patients with advanced NSCLC,[4,5] the use of these regimens in elderly patients remains a topic of debate.[2] The main reasons given for withholding standard platinum-based doublet regimens from elderly patients are age-related impairment of organ function, presence of potentially complicating

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comorbid conditions, and a lower ability to tolerate the potential toxicity of combination chemotherapy than younger patients.

Three prospective randomized trials have investigated the optimal chemotherapy for elderly (70 years or older) NSCLC patients.[6-8] The Elderly Lung Cancer Vinorelbine Italian Study Group reported significantly superior survival and QOL with single-agent vinorelbine over best supportive care (median survival time, 6.4 months and 4.8 months, respectively; n = 161).[6] Two other studies have attempted to determine whether doublet regimens are optimal over single-agent therapy in elderly patients.[7,8] The conclusive results were reported in the Multicenter Italian Lung Cancer in the Elderly Study (MILES), which enrolled more than 700 patients and reported no significant survival difference between single-agent vinorelbine, single-agent gemcitabine, or a regimen with both agents combined.[8]

Docetaxel has demonstrated activity and acceptable toxicity in the treatment of advanced NSCLC, including elderly patients.[9-12] However, to date, no prospective randomized trials of docetaxel in elderly patients have been published. Two phase II trials of tri-weekly docetaxel 60 mg/m² (the recommended dose and schedule in Japan) have been performed in adult patients with NSCLC.[13,14] We conducted an exploratory, combined-subset analysis of the cohorts of patients age 70 years or older from these two trials: in 53 patients with a median age of 74 years (range, 70 years to 80 years), the median survival time was 10.3 months and the response rate was 24.5% (unpublished data). This encouraging retrospective result led us to design a prospective phase III trial to evaluate the efficacy of docetaxel versus vinorelbine in elderly patients with previously untreated advanced NSCLC, the results of which are reported herein.

Eligibility Criteria

Chemotherapy- and radiotherapy-naïve patients with histologically or cytologically proven stage IIIB/IV NSCLC were enrolled. Other inclusion criteria included: age 70 years or older with a life expectancy of 3 months or longer; measurable and assessable disease; Eastern Cooperative Oncology Group performance status 2 or lower; adequate function of the bone marrow (leukocyte count, 4,000/μL or higher; absolute neutrophil count, 2,000/μL or higher; hemoglobin concentration, 9.5 g/dL or higher; platelet count, 100,000/μL or higher), kidney (serum creatinine, 1.2 mg/dL or lower), and liver (total bilirubin, 1.5× the institutional upper limits of normal or lower; AST and ALT 2.5× the institutional upper limits of normal or lower). Exclusion criteria included: presence of symptomatic brain metastasis or apparent dementia; active concomitant malignancy; massive pleural effusion or ascites; active infection; severe heart disease or grade 2 or higher ECG abnormality; uncontrolled diabetes mellitus, ileus, pulmonary fibrosis, diarrhea; bleeding tendency. All patients gave written informed consent and the protocol was approved by the institutional review board at each participating center.

Before treatment, all patients underwent a complete medical history and physical examination, chest radiography, fiberoptic bronchoscopy, chest and abdominal computed tomography (CT) scan, a brain CT or magnetic resonance imaging scan, an ECG, pulmonary function tests, and arterial blood gas analysis. A radionuclide bone scan was also performed to document the extent of the disease. Laboratory tests included a CBC with WBC differential, liver function tests, serum electrolytes, serum creatinine, blood urea nitrogen, and urinalysis.

The physical examination and laboratory tests were performed weekly. Chest radiography and/or CT were repeated every cycle to evaluate tumor response.

Treatment Plan

Patients were randomly assigned to receive a minimum of four cycles of tri-weekly docetaxel 60 mg/m² (1-hour intravenous infusion, day 1) or tri-weekly vinorelbine 25 mg/m² (intravenous infusion, days 1 and 8; weekly vinorelbine 25 mg/m² is the recommended dose in Japan[15]). Random assignment was centralized at the West Japan Thoracic Oncology Group (WJTOG) data center in Osaka, Japan; patients were stratified according to institution, disease stage (IIIB v IV), and performance status (0 to 1 v 2).

Vinorelbine was delayed on day 8 if leukocyte and platelet counts were lower than 2,000/μL and lower than 50,000/μL, respectively, and was withheld until the counts had recovered to 4,000/μL or higher and 100,000/μL or higher, respectively; patients were withdrawn from the study if longer than 5 weeks had elapsed from the time of the last treatment until these criteria were satisfied. The presence of grade 4 leukopenia and/or neutropenia led to reductions in the doses of docetaxel and vinorelbine by 10 mg/m² and 5 mg/m², respectively, in the subsequent cycle. Patients were withdrawn from the study in the event of progressive disease, consent withdrawal or grade 3 or higher nonhematologic toxicity without myelosuppression, nausea, vomiting, or alopecia. Second-line treatment was given at the physician's discretion.

Patients were evaluated for objective response before every cycle using WHO criteria.[16] A minimum duration of 4 weeks was required to document a response and the best response was recorded for each patient. Drug-induced toxicity was assessed before every cycle and was classified in accordance with National Cancer Institute Common Toxicity Criteria, version 2.0.[17] The worst data for each patient across all chemotherapy cycles were used in the toxicity analysis.

QOL Assessment

QOL was assessed using a self-administered questionnaire, which included a visual face scale for global QOL[18] (primary QOL analysis) and eight separate measures for assessing disease-related symptoms (secondary QOL analysis; Fig 1). The eight disease-related symptom items were derived from two sources: the disease-specific symptoms score for the first four items of the Lung Cancer Working Party, Medical Research Council[19] and the treatment-related symptoms for the last four items of the Functional Living Index, Cancer.[20] Patients completed the questionnaires at enrollment and at 3 weeks, 9 weeks, and 12 weeks. QOL was considered to have improved if the difference in score between any survey point and baseline was positive and to have worsened if the difference was negative.

Statistical Analysis

The primary objective was to determine whether docetaxel improved survival compared with vinorelbine. The study was designed with an 80% power using a two-sided log-rank test at a level of .05 to detect a 60% improvement in median survival time from 6.4 months with vinorelbine to 10.3 months with docetaxel; this required 90 patients per treatment arm. An interim analysis was performed after 120 patients were accrued; after the data had been reviewed, a decision was made to continue the study.

Survival analyses were conducted on the intent-to-treat population using follow-up data available at March 28, 2005. Overall survival was calculated from the start of therapy to the date of death from any cause or last follow-up. Progression-free survival was calculated from the start of therapy to the date of disease progression, recurrence, or death from any cause. Survival curves were estimated using the Kaplan-Meier method. A Cox proportional hazards regression model adjusted by the stratification factors (performance status, stage) was applied.

The χ^2 test was used in the response rate comparison and the toxicity analysis. For the QOL analyses, the comparison between the arms was conducted using generalized estimating equation regression models by GENMOD procedure in SAS (SAS Institute, Cary, NC).[21] An odds ratio of higher than 1 indicated that QOL was better with docetaxel than vinorelbine, achieving statistical significance if the 95% CI excluded 1.
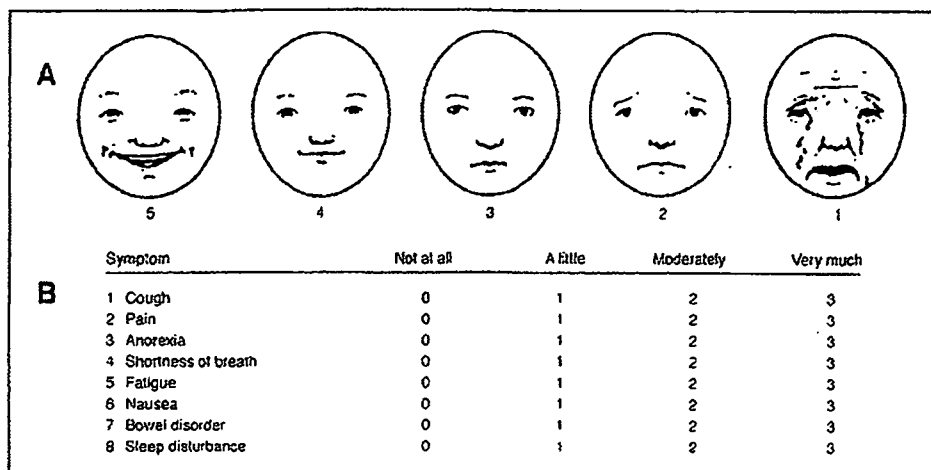
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A

| 5 | 4 | 3 | 2 | 1 |

Symptom	Not at all	A little	Moderately	Very much
B				
1 Cough	0	1	2	3
2 Pain	0	1	2	3
3 Anorexia	0	1	2	3
4 Shortness of breath	0	1	2	3
5 Fatigue	0	1	2	3
6 Nausea	0	1	2	3
7 Bowel disorder	0	1	2	3
8 Sleep disturbance	0	1	2	3

Fig 1. (A) An illustration of the visual face scale for global quality of life and (B) the disease-related symptoms questionnaire.

Patient Characteristics

A total of 182 patients were enrolled and randomly assigned (90 to docetaxel, 92 to vinorelbine) between May 2000 and September 2003 from 32 institutions in WJTOG (Fig 2). Two patients were subsequently considered ineligible due to being entered twice in the study (n = 1, vinorelbine arm) and consent withdrawal immediately after random assignment (n = 1, docetaxel arm). Therefore, the intent-to-treat population comprised 180 patients: 89 assigned to docetaxel and 91 assigned to vinorelbine. One patient assigned to docetaxel developed disease progression before starting chemotherapy and was therefore not treated. Thus, toxicity and response were evaluated in 88 docetaxel patients and 91 vinorelbine patients.

Patients' baseline characteristics were well balanced between the treatment arms (Table 1). Although more patients receiving vinorelbine than docetaxel had a performance status of 2, the difference was not significant ($P = .057$).

The median number of treatment cycles was four in the docetaxel arm and three in the vinorelbine arm, which was significantly different ($P = .050$). Overall, 45 (51.1%) of 88 docetaxel patients and 37 (40.7%) of 91 vinorelbine patients completed four cycles of chemotherapy. The major reasons for treatment withdrawal in the docetaxel versus vinorelbine arms were disease progression (19.3% v 35.2%), adverse events (12.5% v 9.9%), physician's decision to withdraw patient (6.8% v 5.5%), protocol violation (3.4% v 3.3%), and consent withdrawal (2.3% v 3.3%). The relative dose intensities were 90.7% and 83.1% for docetaxel
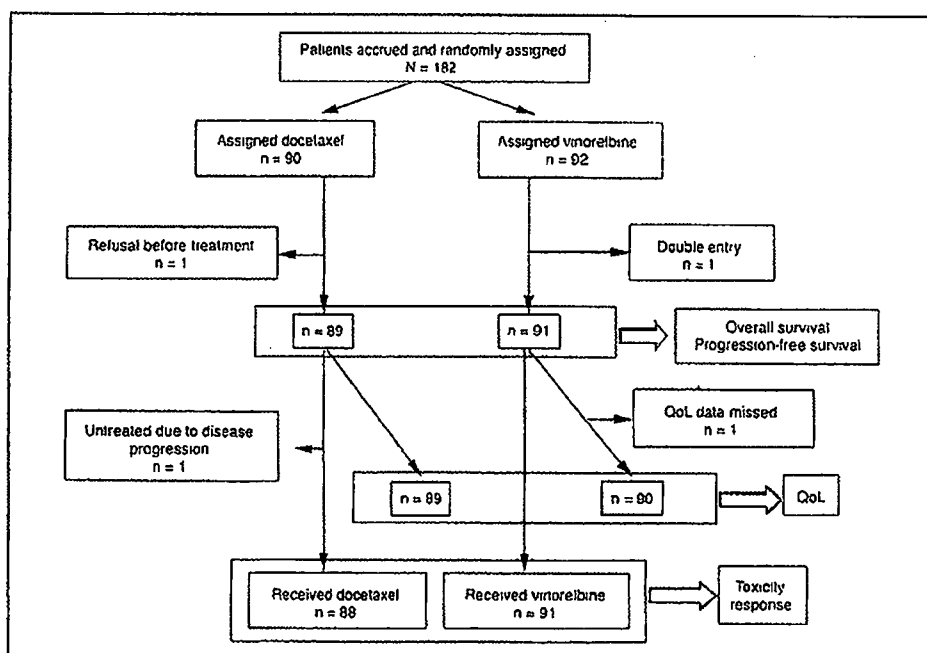

Fig 2. Flow diagram for the study. QoL, quality of life.

Table 1. Patient Characteristics				
	Docetaxel (n = 89)		Vinorelbine (n = 91)	
Characteristic	No. of Patients	%	No. of Patients	%
Age, years				
Median	76		76	
Range	70-86		70-84	
Sex				
Male	69	77.5	68	74.7
Female	20	22.5	23	25.3
Performance status				
0-1	88	98.9	85	93.4
2	1	1.1	6	6.6
Stage				
IIIB	33	37.1	33	36.3
IV	56	62.9	58	63.7
Histology				
Adenocarcinoma	57	64.0	51	56.0
Squamous cell carcinoma	26	29.2	31	34.1
Other	6	6.7	9	9.9
Weight loss*				
> 10%	12	13.5	12	13.1
≤ 10%	77	86.5	78	85.7
Comorbid illness	38	42.6	36	39.6
None	51	57.3	55	60.4
Smoker	18	20.2	23	25.2
Never	71	79.8	68	74.7

*A data was not obtained from one vinorelbine patient.

and vinorelbine, respectively; most patients received the projected dose of chemotherapy in both treatment arms.

Second-line chemotherapy was administered to 85 patients (47.5%; 45 docetaxel patients and 40 vinorelbine patients). Among patients initially treated with docetaxel, five patients received second-line vinorelbine, while nine patients enrolled in the vinorelbine arm received crossover treatment with docetaxel. Fifty-two patients (29.0%) received second-line gefitinib: 33 patients (37.5%) in the docetaxel arm and 19 patients (20.9%) in the vinorelbine arm.

Response and Survival

Overall response rates significantly favored docetaxel over vinorelbine (22.7% v 9.9%; P = .019; Table 2). Progressive disease during treatment occurred in 37.4% of vinorelbine-treated patients

Table 2. Response to Treatment				
	Docetaxel (n = 88)		Vinorelbine (n = 91)	
Response	No. of Patients	%	No. of Patients	%
Complete response	0		0	
Partial response	20	22.7	9	9.9
Stable disease	47	53.4	45	49.5
Progressive disease	18	20.5	34	37.4
Not assessable	3	3.4	3	3.3
Overall response rate	22.7		9.9	
95% CI	13.9 to 31.5		3.8 to 16.0	

NOTE. P = .019.

and in 20.5% of docetaxel-treated patients; the difference between arms was significant (P = .012).

By March 28, 2005, 143 (79.4%) of 180 patients had died (docetaxel, 68; vinorelbine, 75). Median follow-up for survivors was 11.6 months. The median progression-free survival time with docetaxel was significantly longer than with vinorelbine (5.5 months v 3.1 months; hazard ratio, 0.606; 95% CI, 0.450 to 0.816; P < .001; Fig 3). Median survival time was 14.3 months and 9.9 months with docetaxel and vinorelbine, respectively. Although docetaxel prolonged median survival time by 4.4 months, the overall survival distributions were not statistically significant (hazard ratio, 0.780; 95% CI, 0.561 to 1.085; log-rank P = .138 and generalized Wilcoxon test P = .065; Fig 4). One-year survival rates were 58.6% and 36.7% for docetaxel and vinorelbine, respectively.

Toxicity

Overall, 179 patients were assessable for toxicity. Table 3 summarizes the major toxicities. Grade 3 to 4 neutropenia occurred in more patients in the docetaxel arm than in the vinorelbine arm (P = .031). However, there were no significant differences between the docetaxel and vinorelbine arms in the occurrence of grade 3 to 4 febrile neutropenia and infection. The incidence of grade 3 to 4 anemia was relatively low and there was no grade 2 or higher thrombocytopenia in either arm (Table 3). Alopecia (any grade) occurred significantly more frequently in the docetaxel arm than the vinorelbine arm (P < .0001). Overall toxicity in both treatment arms was generally mild and well tolerated in elderly patients with NSCLC.

One patient (age 76 years with stage IV disease and a performance status of 1) developed treatment-related interstitial pneumonia after three cycles of docetaxel; despite steroid pulse treatment, the patient died from this toxicity on day 65 after the start of the third treatment cycle.

QOL

Baseline QOL data were available for all patients except one vinorelbine patient (for whom data were not collected due to human error; Fig 2). Thus, 179 patients completed baseline questionnaires; questionnaire completion rates were 92.2% at 3 weeks, 83.2% at 9 weeks, and 69.8% at 12 weeks. Compliance rates were not significantly different between the arms (P = .311). QOL data were missing in 28 surveys due to death or severe impairment of the patient's general condition; this accounted for 3.9% of the total number of surveys scheduled. The proportions of data missing at baseline and at 3 weeks, 9 weeks, and 12 weeks were 0%, 1.1%, 2.3%, and 6.7% in the docetaxel
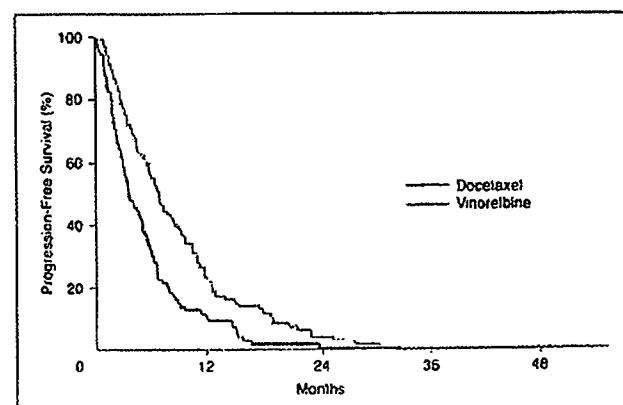

Fig 3. Progression-free survival curves for patients treated with docetaxel (n = 89) or vinorelbine (n = 91).
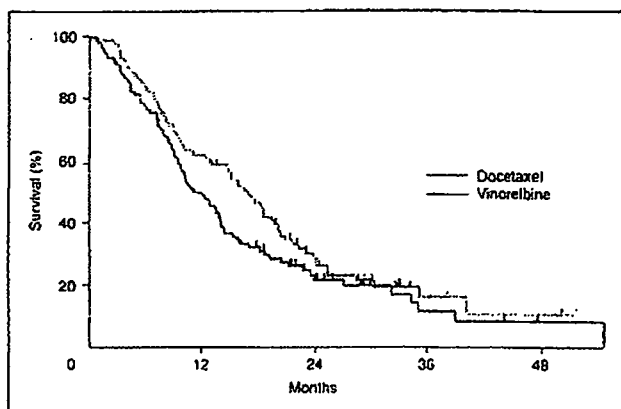
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Fig 4. Overall survival curves for patients treated with docetaxel (n = 89) or vinorelbine (n = 91).
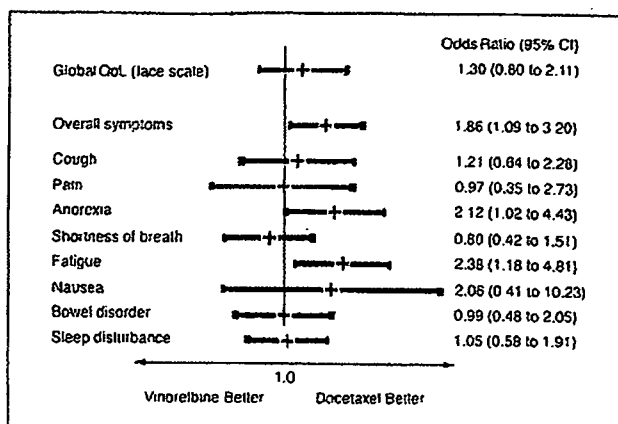

Fig 5. Forest plot of odds ratio for global quality of life (Qol) and disease-related symptoms analyses.

arm compared with 0%, 1.1%, 6.6%, and 13.2% in the vinorelbine arm. The distribution of the missing data was not significantly different between the treatment arms ($P = .150$). In terms of global QOL, no significant difference was observed between the two arms (odds ratio, 1.30; 95% CI, 0.80 to 2.11; Fig 5). Docetaxel was associated with significantly better improvement in the overall symptom score than vinorelbine (odds ratio, 1.86; 95% CI, 1.09 to 3.20; Fig 5). When the eight-symptom scores were analyzed separately, the docetaxel arm showed significantly better improvement in anorexia and fatigue than the vinorelbine arm. These results did not change when the QOL data were reanalyzed with the missing information from the 28 surveys assigned as unimproved.

This phase III trial showed that docetaxel provided significantly longer progression-free survival (5.5 months v 3.1 months; $P < .001$), a significantly higher overall response rate (22.7% v 9.9%; $P = .019$), a more favorable 1-year survival rate (58.6% v 36.7%) and significantly better disease-related symptom improvement than vinorelbine in elderly patients with advanced NSCLC. However, although docetaxel-treated patients also experienced a longer median survival time (14.3 months v 9.9 months) than vinorelbine-treated patients, the primary end point of improved overall survival with docetaxel was not achieved. Possible reasons for failing to detect a significant difference between the docetaxel and vinorelbine survival curves may include an

Table 3. Toxicities								
	Docetaxel (n = 88)				Vinorelbine (n = 91)			
	Grade (%)				Grade (%)			
Toxicity	1	2	3	4	1	2	3	4
Leukopenia	10.2	27.3	52.3	5.7	6.6	30.8	35.2	16.5
Neutropenia	0	6.8	26.1*	56.8*	2.2	9.9	30.8*	38.5*
Anemia (Hb)	59.1	36.4	2.3	1.1	41.8	42.9	8.8	1.1
Thrombocytopenia	13.6	0	0	0	26.4	0	0	0
AST	22.7	2.3	1.1	0	24.2	4.4	3.3	0
ALT	27.3	3.4	1.1	0	19.8	5.5	2.2	0
Creatinine	11.4	0	0	1.1	9.9	0	0	3.3
Nausea	25.0	17.0	10.2	0	20.9	14.3	8.8	0
Vomiting†	9.1	3.4	0	0	0	1.1	1.1	0
Febrile neutropenia	—	—	12.5	0	—	—	11.0	0
Infection	4.5	15.9	11.4	0	5.5	7.7	13.2	0
Constipation	26.1	14.8	2.3	0	18.7	20.9	5.5	1.1
Diarrhea	15.9	5.7	4.5	0	14.3	3.3	1.1	0
Mucositis‡	10.2	5.7	0	0	3.3	0	0	0
Alopecia§	45.5	28.4	—	—	30.8	0	—	—
Peripheral neuropathy	12.5	1.1	0	0	7.7	0	0	0

NOTE. P values ware obtained by χ^2 test.
Abbreviation: Hb, hemoglobin.
*Indicates grade 3 to 4 neutropenia; $P = .031$.
†Indicates grade 1 to 4 vomiting; $P = .007$.
‡Indicates grade 1 to 4 mucositis; $P = .004$.
§Indicates grade 1 to 2 alopecia; $P < .001$.

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insufficient occurrence of documented events as a result of the study population comprising patients with relatively good prognosis, in addition to a high proportion of patients (47.5%) subsequently receiving second-line therapy. Another reason may have been the small sample size and the prespecified aim of detecting an improvement in survival from 6.4 months to 10.3 months. The selection of a median survival in the reference arm of 6.4 months for the sample size calculation was based on the results of the Elderly Lung Cancer Vinorelbine Italian Study Group study.[6] However, more recent survival data from the MILES study[8] reporting a median survival of 8.3 months with vinorelbine may have been more appropriate. Had this value been used in the sample size calculation a larger study population would have been required which would likely have allowed the present analysis to detect statistically significant differences between the treatment arms.

The survival findings with vinorelbine in this study were similar to or slightly better than those reported in other studies; vinorelbine monotherapy in elderly NSCLC patients has previously shown median survival times of 4.5 months to 8.3 months and 1-year survival rates of 13% to 38%.[6-8] One reason for a slightly longer median survival time in our study may be the relatively better prognosis of the enrolled patients. Interestingly, the median survival time of 14.3 months with docetaxel in this study appears to be similar to that reported for platinum-doublet chemotherapies assessed in a recent Japanese randomized trial in chemotherapy-naïve NSCLC patients, which reported median survival times of 11.4 months to 14.8 months.[5] The improved overall survival time in the docetaxel arm may be attributed to gefitinib treatment as a second-line treatment. Japanese patients are sensitive to gefitinib, and 37% of patients who were treated with docetaxel also received gefitinib, compared with 20.9% of vinorelbine treated patients although this difference may be attributable to the numerically greater number of patients alive after initial docetaxel treatment. Crossover to second-line chemotherapy was permitted in this protocol and could have also influenced outcomes. However, as only a small number of patients in either treatment arm were treated with alternative chemotherapy as salvage (five patients from the docetaxel arm and nine patients from the vinorelbine arm), outcomes for these patients were not felt to significantly alter the overall results of the study.

Age should still be taken into consideration when selecting appropriate chemotherapy in the clinical setting given the likelihood of metabolic changes with advancing age, the increased likelihood of comorbidities, and general lack of clinical trial data specifically in older patients.

The toxicity profiles for both treatment arms were generally mild and tolerable in this study. Although severe neutropenia occurred significantly more often with docetaxel, there were no differences in the incidence of febrile neutropenia or other hematologic toxicities between the two arms. The incidence of grade 3 to 4 neutropenia (69.3%) with vinorelbine treatment in our study was somewhat higher than that reported in the MILES (25%).[8] The reason for these differences is unclear. In our study, patients treated with docetaxel experienced a relatively higher incidence of severe neutropenia compared with patients treated with vinorelbine, although the incidence with docetaxel was similar to that seen in Japanese phase II studies of docetaxel in patients with advanced NSCLC (87%, grade 3-4 neutropenia).[13] However, the incidences of grade 3 febrile neutropenia and grade 3 infection were relatively low and similar between the treatment arms in our study. Importantly, there was no difference in global QOL between the treatment arms. Furthermore, docetaxel significantly improved QOL in terms of disease-related symptoms compared with vinorelbine.

The WJTOG 9904 study is the first prospective, randomized, phase III trial of taxane monotherapy for elderly patients with advanced NSCLC, and has shown encouraging efficacy with single-agent docetaxel. To further improve outcomes, we would suggest that the next step for treating elderly patients might be to prospectively investigate platinum-doublet regimens, particularly docetaxel with carboplatin, in phase III trials. Retrospective analyses suggest that platinum doublets are effective and tolerable in fit, elderly patients.[2,22-24] For further future studies in elderly patients, it would be of interest to investigate regimens involving docetaxel combined with a molecular-targeted agent (such as gefitinib, erlotinib,[25] or bevacizumab), as molecular-targeted agents are associated with relatively mild toxicity profiles compared with cytotoxic agents.

In conclusion, docetaxel improved response rate, progression-free survival, and overall disease-related symptoms compared with vinorelbine in elderly patients with advanced NSCLC; overall survival was not significantly improved. Based on these results, docetaxel monotherapy may be considered as an option in the standard treatment of elderly patients with advanced NSCLC.
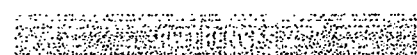
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Acknowledgment

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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ORIGINAL ARTICLE

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Yasuhiko Kano · Tetsuro Kodama

Pilot phase II study of weekly chemotherapy with paclitaxel and carboplatin for refractory or relapsed small-cell lung cancer

Abstract *Purpose*: The safety and efficacy of weekly chemotherapy with paclitaxel and carboplatin for the treatment of patients with refractory or relapsed small-cell lung cancer (SCLC) were evaluated. *Patients and methods*: Paclitaxel (100 mg/m^2) and carboplatin (with a target area under the concentration versus time curve of 2 mg min/ml using the Calvert formula) were administered to patients with previously- treated SCLC on days 1 and 8 at every 3–4 weeks. *Results*: A total of 29 patients (pts) [male/female, 26/3 pts; median age 62.7 years (43–74); performance status 0/1/2, 9/10/10 pts] were enrolled between March 2000 and June 2002. The mean number of cycles administered per pt was 3 (1–7). The overall response rate was 69% (95% confidence interval 52–86%), and 83% (15/18) in sensitive pts and 45% (5/11) in refractory pts ($P < 0.01$). The overall median survival time was 29.6 weeks with a 1-year survival rate of 37% [34.1 weeks in sensitive pts and 23.1 weeks in refractory pts ($P = 0.085$), 46.9 weeks in PS 0–1 and 16.3 weeks in PS 2 ($P < 0.001$)]. The median time to progressive disease was 16.4 weeks [21.7 weeks in sensitive pts and 15.3 weeks in refractory pts ($P = 0.32$)]. Hematologic toxicities observed included grade ≥ 3 neutropenia in 55%, grade ≥ 3 anemia in 36%, and grade ≥ 3 thrombocytopenia in 3%. Non-hematologic toxicities were mild except for grade 3 diarrhea in three pts and grade 3 pneumonitis in one pt. *Conclusion*: Weekly chemotherapy with paclitaxel and carboplatin was well-tolerated and gave a high-response rate in pts with refractory or relapsed small-cell lung cancer.

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Introduction

Small-cell lung cancer (SCLC) accounts for 15–20% of the total number of lung cancer patients. It grows more rapidly and shows a higher incidence of remote metastasis than non-small-cell lung cancer (NSCLC). It is apparently more sensitive to chemotherapy and radiotherapy than NSCLC, but is cured only in a small number of patients and recurs in a great majority of them. Recurrent SCLC is less responsive to chemotherapy, and the median survival time from recurrence to death is 2–3 months [3]. Chemotherapy has been reported to contribute to the improvement of symptoms and prolongation of the survival time in patients with recurrent SCLC [2, 6]. In general, first-line chemotherapy is conducted for sensitive disease (relapse ≥ 90 days after completion of first-line chemotherapy). For refractory disease (relapse during first-line chemotherapy or less than 90 days after completion of initial chemotherapy), however, salvage chemotherapy is undertaken due to the lack of a standard chemotherapy regimen. However, no standard chemotherapy has been established for recurrent SCLC [17].

In recent years, a number of institutions have undertaken weekly chemotherapy for lung cancer and reported the outcome [11, 14]. Weekly chemotherapy is being reported to be useful for recurrent SCLC as well [1, 4, 7, 10]. It is considered to be more suitable than the standard chemotherapy conducted every 3–4 weeks for recurrent cases with impaired bone marrow due to initial chemotherapy because it uses smaller doses of anti-cancer drugs in each administration cycle and it is possible to titrate their doses after starting the treatment depending on hemotoxicity and the patients' physical condition.

When used alone, paclitaxel was reported to produce good therapeutic results in patients with refractory SCLC with a response rate of 29% and a median survival time of 100 days [15]. When coadministered with carboplatin, paclitaxel showed even better results with a response rate of 73.5% and a median survival time of 31 weeks [5]. This report prompted us to conduct the present study to evaluate the efficacy and safety of weekly chemotherapy using carboplatin and paclitaxel in recurrent SCLC patients.

Patients and methods

Patient selection

All patients with histologically or cytologically confirmed SCLC with documented progression after chemotherapy were eligible for this phase II trial. Patients with either limited- or extensive-stage disease were allowed. The trial was initiated after a rest period of at least 4 weeks following previous chemotherapy (2 weeks in the case of radiotherapy). Patients were required to have recovered completely from prior therapy, with no ongoing toxicity greater than grade 1.

Other eligibility criteria included expected survival of 12 weeks, age ≤ 75 years, Eastern cooperative oncology group performance score of 0–2, measurable lesions, and adequate hematological function. Primary refractory disease was defined as relapse during first-line chemotherapy or less than 90 days after completing initial chemotherapy, and sensitive disease was defined as relapse ≥90 days after completion of first-line chemotherapy.

The ethical committee of the Tochigi cancer center approved the protocols. Written informed consent stating that the patient was aware of the investigational nature of this treatment regimen was obtained in every case.

Treatment

Paclitaxel was administered at a dose of 100 mg/m^2 intravenously during a 1-h infusion on days 1and 8 of the treatment cycle. Carboplatin was given at a dose designed to give an area under the curve (AUC) of 2 on days 1 and 8 with the use of the Calvert formula: 2 × (creatinine clearance + 25). Prior to each treatment, patients were given 50 mg diphenhydramine orally, and an H2 blocker intravenously along with 16 mg dexamethasone . Intrvenously administered antiemetics, 3 mg graniston, were used. The length of each chemotherapy cycle was 21 days. Patients who experienced grade 4 leukopenia or neutropenia that lasted for three days or more , or who experienced grade 4 thrombocytopenia, reversible grade 2 neurotoxicity, or liver dysfunction, received reduced doses of both paclitaxel and carboplatin (paclitaxel 80 mg/m^2, carboplatin AUC1.5)

for the next cycle. If non-hematologic toxicities of grade 3 or more occurred, treatment was stopped. Subsequent courses of chemotherapy were started after 3–4 weeks when the leukocyte count was 3,000/mm^3 or more, the neutrophil count 1,500/mm^3 or more, the platelet count 75,000/mm^3 or more, serum creatinine less than 1.5 mg/dl, GOT and GPT less than twice the upper limit of the normal range, and neurotoxicity was grade 1 or less. If these variables did not return to adequate levels by the first day of the next course of chemotherapy, treatment was withheld until full recovery. If more than 6 weeks passed from the time of the last treatment before these criteria were satisfied, or if more than dose reduction were indicated, the patient was taken off the study at that time, but still included in the analysis.

Evaluation of response and toxicity

Pretreatment evaluation included medical history, physical examination, complete blood count, bone marrow examination, serum biochemical analyses, chest roentgenogram, electrocardiogram, and urinalysis. All patients underwent radionuclide bone scan, bone marrow aspiration or biopsy, magnetic resonance or computerized tomography (CT) of the brain, and CT of thorax and abdomen. Complete blood count, biochemical tests, serum electrolytes, urinalysis, and chest roentgenograms were obtained weekly during this phase II trial.

Response and toxicity were evaluated on the basis of tumor images obtained by CT and other techniques, laboratory data and subjective/objective symptoms before, during, and after administration of the study drugs and during the period from completion of treatment to final analysis. Measurable disease parameters were determined every 4 weeks by various means such as CT. Evaluation was made in compliance with response evaluation criteria in solid tumors (RECIST) guidelines [16] for anti-tumor activity, and with NCI common toxicity criteria Version 2 for safety. Patients were withdrawn from the study if evidence of tumor progression was observed. The Institutional Ethical Review Committee approved the study.

Statistical analyses

Time to progression was measured as a period from the start of this treatment to the identifiable time for progression. Survival time was measured from the start of the present treatment until death or last follow-up. The Kaplan–Meier method was used to calculate survival curves. Survival differences between subgroups were compared using the log-rank test. The chi-square test was used to compare the percentage of patients in each group.

Primary endpoints were response rate and toxicity; secondary endpoints were survival and time to pro-

gression. We chose a 50% response rate as a desirable target level and a 25% response rate as an undesirable target. Our design had a power in excess of 95% and less than 20% type 1 error, requiring 26 patients. Considering the percentage of probable dropout cases, 29 patients were required.

Results

Patient characteristics

Twenty-nine patients were enrolled in this study from March 2000 to June 2002. All patients were assessed for toxicity, response and survival. Characteristics of the 29 patients are listed in Table 1. There were 11 refractory cases and 18 sensitive cases against the first-line chemotherapy.

Efficacy of treatment

The mean number of cycles administered per patient was three, and ranged from one to seven. There were no cycles of dose reduction. One patient achieved a complete response (CR) and 19 patients showed partial response (PR). Overall response rate was 69% (20/29) [95% confidence interval (CI) 52–86%]. The response rate was 83% (15/18, 95% CI: 66–100%) in sensitive cases and 45% (5/11, 95% CI: 16–75%) in refractory cases, with significant differences between the two groups $(P < 0.01)$. The median time to progressive disease was 16.4 weeks [21.7 weeks in sensitive pts and 15.3 weeks in refractory pts $(P = 0.32)$]. The overall median survival time was 29.6 weeks (Fig. 1) with no significant differences between sensitive cases (34.1 weeks) and refractory cases (23.1 weeks) $(P = 0.085)$. The median survival time differed significantly between PS 0 or 1 patients (46.9 weeks) and PS 2 patients (16.3 weeks) $(P < 0.001)$. The 1-year survival rate was 38% (11/29).

Toxicities

Table 2 lists the toxicities observed during this study. Hematological and blood biochemical reactions included a high incidence of leukopenia and neutropenia, leukopenia, and neutropenia of grade 3 or higher occurred in 55 and 55%, respectively. All neutropenia patients recovered upon treatment with G-CSF. Anemia and thrombocytopenia of grade 3 or higher occurred in 27 and 3%, respectively. Subjective and objective symptoms observed included grade 3 diarrhea in three patients who all showed improvement after administration of anti-cholinergic drugs, and grade 3 pneumonitis in one, who showed rapid recovery following administration of steroids. Other subjective and objective symptoms observed were of grade 2 or less and included

nausea in 34%, vomiting in 10%, alopecia in 59%, neuropathy in 28%, and flushing in 17%. All of these toxicities disappeared or improved by symptomatic treatment. There were no toxic deaths.

Discussion

No standard chemotherapy for recurrent SCLC has been established since only two Phase III clinical studies have been reported to date on chemotherapy for this disease [13, 17]. In contrast, many studies have been undertaken on salvage chemotherapy for recurrent SCLC, with monotherapy with new third-generation anti-cancer agents and platinum-based multi-drug chemotherapy being the mainstay in recent years [1, 4, 5, 8–10, 14, 15]. Some institutions administer anti-cancer drugs on a weekly basis (weekly chemotherapy) [1, 4, 7, 10]. This treatment regimen makes it possible to titrate the dose of anti-cancer drugs depending on adverse reactions and the patients' physical condition after starting the treatment by dividing the dose into some installments.

The results reported with weekly chemotherapy are summarized in Table 3 [1, 4, 7, 10]. While the study by Goto et al. [4] included only sensitive cases, all other studies included 35–64% of refractory cases. The overall response rate ranged between 31% and 88%: 37–91% in sensitive cases and 23–83% in refractory cases. No study, apart from ours, reported any significant difference between sensitive and refractory cases. The overall median survival time was 6.1–11.8 months with no significant differences between sensitive and refractory cases [10]. In our study, the median survival time was 46.9 weeks in PS 0 or 1 patients and 16.3 weeks in PS 2 patients $(P < 0.001)$. Naka et al. [10] reported significant differences between PS 0 or 1 patients (6.9 months) and PS 2 patients (3.8 months) [10]. Hemotoxicity was the main adverse reaction in all studies. Thrombocytopenia was milder in our study than in other studies. Diarrhea also showed a high incidence in regimens including CPT-11.

Groen et al. [5] reported therapeutic results similar to ours with carboplatin and paclitaxel therapy: overall response rate of 73.5% and overall median survival time of 31 weeks. They administered carboplatin and paclitaxel at AUC 7 and 175 mg/m^2, respectively at an interval of 3 weeks. These doses were 1.7 and 0.88 times that obtained by us. . The main adverse reaction was hemotoxicity in both studies, but thrombocytopenia was milder in our study. In the study by Groen et al., 22 and 4 of 34 patients received RBC transfusions and platelet transfusions, respectively [5].

In a phase III trial, which compared topotecan versus cyclophosphamide, doxorubicin and vincristine (CAV) in patients with recurrent SCLC [17], the response rate was 24.3 and 18.3%, respectively; time to progression 13.3 and 12.3 weeks; median survival time 25.0 and 24.7 weeks; 1-year survival rate 14.2 and 14.4%. In our study, the response rate was 69%, time to progression 16.4 weeks,

Table 1 Patient characteristics

Eligible patients	29
Gender	
Male	26
Female	3
Age (years)	
Median	63
Range	43–74
Performance status	
0	9
1	10
2	10
Disease extent at relapse	
Limited disease	7
Extensive disease	22
Relapse type	
Refractory case	11
Sensitive relapse case	18
Prior therapy	
Chemotherapy alone	21
Chemotherapy and irradiation	8
Prior chemotherapy regime	
CBDCA + ETOP	3
CDDP + ETOP(PE)	11
CODE + PE	1
CDDP + CPT-11(PI)	9
CDDP + ETOP + CPT-11	3
PE + PI	2
Response to prior chemotherapy	
Complete response	4
Partial response	21
Stable disease	3
Progressive disease	1

CBDCA carboplatin, *ETOP* etoposide, *CDDP* cisplatin, *CODE* cisplatin/vincristine/doxorubicin/etoposide, *CPT-11* irinotecan

median survival time 29.6 weeks, and 1-year survival rate 37%, and our study showed better therapeutic performance in terms of all four parameters although ours was a pilot study and direct comparisons cannot be made.
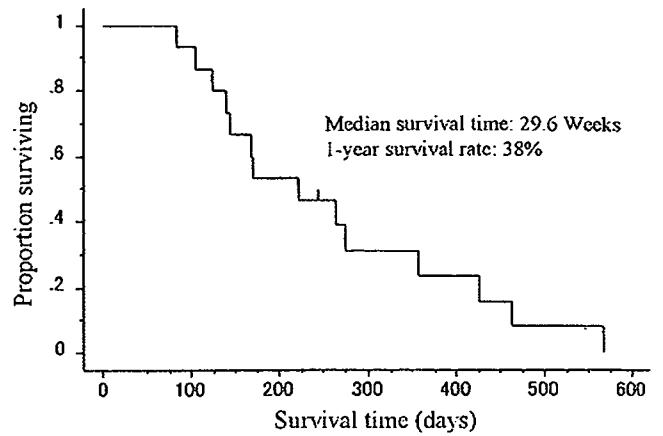

Fig. 1 Kaplan–Meier estimated overall survival curves. Median survival time, 29.6 weeks; 1-year survival rate, 38%

In Japan, cisplatin and irinotecan chemotherapy is the standard therapy for untreated patients in extensive SCLC. Only 8 of 40 patients in the study by Goto et al. [4] and 14 of 29 in our study received irinotecan-based regimens in initial therapy, and no other weekly chemotherapy studies included in Table 3 used such regimens. Carboplatin and paclitaxel combination chemotherapy appears rational in patients with recurrence following initial therapy with cisplatin and irinotecan because the two regimens are not cross resistant.

Conclusion

Weekly chemotherapy with paclitaxel and carboplatin is tolerable and an active regimen for patients with refractory or relapsed SCLC. It is to be recommended as a candidate regimen in planning a phase III clinical study in refractory or relapsed SCLC, and this regimen will ultimately be evaluated in a phase III clinical study.

Table 2 Toxicities (*n* = 29)

	Grade (common toxicity criteria)				Grade ≤ 3 (%)
	1	2	3	4	
Leukopenia	1	7	14	2	16 (55%)
Neutropenia	1	5	9	7	16 (55%)
Anemia	5	8	6	2	8 (27%)
Thrombocytopenia	8	3	1	0	1 (3%)
Diarrhea	7	0	3	0	3 (10%)
Pneumonitis	0	0	1	0	1 (3%)
Nausea	9	1	0	–	
Vomiting	3	0	0	–	
Fatigue	3	3	0	0	
Alopecia	17	0	–	–	
Neuropathy	8	0	0	0	
Flushing	5	–	–	–	
Edema	4	0	0	0	
Arthralgia	3	0	0	0	
Rash	3	0	0	0	
Arrythmia	2	0	0	0	

Table 3 Weekly chemotherapy studies for relapsed small-cell lung cancer

References	Regimen	No. of pts	% of ref pts (%)	RR	RR in sen pts (%)	RR in ref pts (%)	MST (months)
7	CODE	17	35	88	91	83	8.2
10	CPT-11/CBDCA	28	46⁻	31	37	23	6.1
1	CPT-11/CDDP	25	64	80	78	81	7.9
4	CPT-11/CDDP/ETOP	40	0	78	78	–	11.8
Present study	CBDCA/PTX	29	38	69	83	45	7.4

pts patients, *ref* refractory, *sen* sensitive, *RR* response rate, *MST* median survival time, *CODE* cisplatin/vincristine/doxorubicin/etoposide, *CPT-11* irinotecan, *ETOP* etoposide, *CDDP* cisplatin, *PTX* paclitaxel, *CBDCA* carboplatin

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ORIGINAL REPORT

Predictive Factors for Interstitial Lung Disease, Antitumor Response, and Survival in Non–Small-Cell Lung Cancer Patients Treated With Gefitinib

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A B S T R A C T

Purpose
Interstitial lung disease (ILD) is a serious adverse effect of gefitinib, but its prevalence and risk factors remain largely unknown. We examined the prevalence of and risk factors for gefitinib-induced ILD associated with practical use of the drug in Japanese with non–small-cell lung cancer (NSCLC).

Patients and Methods
Clinical information was retrospectively assembled for NSCLC patients who started gefitinib treatment at affiliated institutions of the West Japan Thoracic Oncology Group between August 31 and December 31, 2002. Medical records of patients who developed pulmonary infiltrates were reviewed by a central committee of extramural experts for identification of patients with gefitinib-induced ILD. Multivariate logistic or Cox regression analysis was performed to identify independent predictive factors for ILD, antitumor response, and survival.

Results
Seventy cases of and 31 deaths from gefitinib-induced ILD were identified among 1,976 consecutively treated patients at 84 institutions, corresponding to a prevalence of 3.5% and mortality of 1.6%. Gefitinib-induced ILD was significantly associated with male sex, a history of smoking, and coincidence of interstitial pneumonia (odds ratios = 3.10, 4.79, and 2.89, respectively). Predictive factors for response were female sex, no history of smoking, adenocarcinoma histology, metastatic disease, and good performance status (PS), whereas predictive factors for survival were female sex, no history of smoking, adenocarcinoma histology, nonmetastatic disease, good PS, and previous chest surgery.

Conclusion
ILD is a serious adverse effect of gefitinib in the clinical setting that cannot be ignored. However, patient selection based on sex and smoking history can minimize ILD risk and maximize the clinical benefit of gefitinib.

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The discovery that signaling by the epidermal growth factor receptor (EGFR) plays an important role in tumorigenesis prompted efforts to target this receptor in anticancer therapy, leading to the development of inhibitors of its tyrosine kinase activity.[1-3] Gefitinib, an orally active inhibitor of the EGFR tyrosine kinase, is a leading agent in the field of EGFR-targeted therapy.[4,5] Two large phase II trials involving previously treated patients with advanced non–small-cell lung cancer (NSCLC) revealed that gefitinib monotherapy was well tolerated and manifested clinically meaningful antitumor activity.[6,7] Objective responses that were both rapid and persistent were apparent at a dose of 250

mg/d in 12% to 18% of patients; the median survival time was 7 to 8 months, with a 1-year survival rate of 27% to 35%, and the most common adverse effects were rash and diarrhea, which were generally mild. Similar response and survival rates were apparent at a dose of 500 mg/d but were accompanied by a higher frequency of adverse events. Higher response rates were apparent in women, Japanese patients, patients with no history of smoking, and patients with adenocarcinoma.[6-8]

Gefitinib was licensed in Japan for the treatment of inoperable or recurrent NSCLC in July 2002. Soon after its introduction, however, life-threatening interstitial lung disease (ILD) attributed to the drug became apparent, despite the absence of severe cases of ILD in the preceding phase I and II

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trials, which included a total of 132 Japanese patients.[6,9-11] The publicity associated with this unexpected severe adverse event led to concern among patients and physicians about the risks of taking gefitinib. Although the prevalence of gefitinib-associated ILD in Japan was estimated at approximately 2%, this estimate was based only on case series studies, with no systematic survey allowing direct determination of the prevalence and identification of risk factors for gefitinib-induced ILD having been performed.[12]

In the present study, the West Japan Thoracic Oncology Group (WJTOG) conducted a retrospective survey of 1,976 individuals with NSCLC, representing all the patients who started gefitinib treatment at 84 WJTOG-affiliated institutions between August 31 and December 31, 2002. We examined the prevalence of and risk factors for gefitinib-induced ILD in this Japanese patient population. The therapeutic efficacy of gefitinib was also evaluated to assess risk and benefit in real-life use of gefitinib.
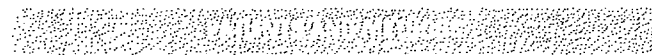
Study Patients

To collect all data of the potential patients with gefitinib-induced ILD, we initially asked 112 affiliated institutions of WJTOG to report the number of NSCLC patients who started gefitinib treatment between August 31 and December 31, 2002 and subsequently developed pulmonary infiltrates. We also asked them to report the total number of patients who started gefitinib treatment during the same period. After confirming the number of potential cases and total patients, we sent case report forms to the respective institutions and asked them to provide demographic and clinical data for the patients. We finally updated the information of all the patients concerning pulmonary infiltrates, antitumor response, and survival status on December 31, 2003, providing an observation period of at least 12 months. This study was approved by the Review Board of the WJTOG.

Confirmation of Gefitinib-Induced ILD

For patients who developed pulmonary infiltrates, in addition to the information collected on case report forms, we obtained detailed clinical data, including chest roentgenograms and computed tomograms taken before and after gefitinib administration; results of examination of bronchoalveolar lavage fluid or lung biopsies when performed at the onset of pulmonary infiltration; laboratory data obtained at the onset of pulmonary infiltration; gefitinib treatment duration before the development of pulmonary infiltrates; and details of treatment for the pulmonary injury. All this information was submitted to a central review committee of extramural experts, comprising at least three thoracic radiologists, one pulmonologist, and one oncologist, for determination of whether each patient indeed developed gefitinib-induced ILD. The committee reviewed all available information including findings of bronchoscopy, clinical course after development of pulmonary infiltrates, and radiologic findings. An infectious etiology was excluded on the basis of extensive microbiologic analysis of blood or other cultures, bronchoalveolar lavage examinations, and titers of antimicrobial antibodies. All experts evaluated the data together to reach unanimous final decisions.

Demographic and Clinical Variables

The following pretreatment demographic and clinical information was obtained from case report forms and evaluated for its relationship to gefitinib-induced ILD: age, sex, smoking status, Eastern Cooperative Oncology Group performance status (PS), coincidental complications, histology, disease stage, body-surface area (BSA), and previous anticancer treatments. Smoking status was classified as no history of smoking (smoking a total of < 100 cigarettes) or a positive history. With regard to coincidental complications, we assessed the presence of pulmonary diseases, diabetes mellitus, and sequelae of previous treatment such as radiation pneumonitis. Disease stage was determined according to the TNM system.[13] Previous anticancer treatment was classified as surgery, radiotherapy, or chemotherapy. We obtained additional information

about the field, dose, and modality of radiotherapy and about the regimen, dose, and number of treatment cycles for chemotherapy. We also collected information about antitumor response and survival after the initiation of gefitinib treatment. We asked the participating institutions to report antitumor response according to the Response Evaluation Criteria in Solid Tumors Group criteria,[14] although it was not confirmed extramurally. Overall survival was calculated from the initiation of gefitinib treatment to the date of death. Patients still alive were censored as of the last known follow-up. Survival data were last updated on December 31, 2003.

Statistical Analysis

Variables were examined for association with ILD development or antitumor response by univariate analysis with the χ^2 test or Fisher's exact test. Multivariate logistic regression analysis was performed to identify predictors of ILD development or antitumor response.[15] Survival curves were calculated by the Kaplan-Meier method and compared with the log-rank test. Prognostic importance of factors was analyzed with the Cox regression model.[16] In multivariate analysis, a forward stepwise procedure was used to select factors for inclusion in the final model with a cutoff value of $P = .2$. For detection of possible synergistic effects of clinical factors, interaction terms of variables selected in the final model were sequentially included and evaluated by the likelihood ratio test. All significance levels were set at $P = .05$. Statistical analyses were performed with SAS version 9 software (SAS Institute, Cary, NC).

Prevalence and Mortality of Gefitinib-Induced ILD

A total of 1,976 patients with NSCLC from 84 (75%) of 112 institutions surveyed were reported as having started gefitinib treatment between August 31 and December 31, 2002 (Fig 1). Among these patients, 102 individuals developed pulmonary infiltrates after treatment initiation and were reported as potential cases of gefitinib-induced ILD. The central review committee evaluated the clinical data of these 102 patients and determined that 70 cases of ILD and 31 deaths were attributable to gefitinib, corresponding to a prevalence of 3.5% (95% CI, 2.8% to 4.5%) and a mortality of 1.6% (95% CI, 1.1% to 2.2%) for gefitinib-induced ILD. All ILD patients had been treated with gefitinib monotherapy, with the exception of one patient who received gefitinib concurrently with cisplatin. None of the ILD patients received radiotherapy simultaneously with gefitinib treatment. The median time from the start of gefitinib treatment to the development of ILD was 31 days (interquartile range, 18 to 50 days), and the median duration of gefitinib treatment before ILD development was 29 days (interquartile range, 18 to 49 days). Among the 70 patients with gefitinib-induced ILD, nine patients (13%) underwent bronchoscopic examination, including six lung biopsies and four bronchoalveolar lavages; all the lung biopsy specimens showed interstitial inflammation and fibrosis, and bronchoalveolar lavage revealed no signs (such as neutrophilia) of infection. Cultures of blood or other specimens were performed for 49 patients with ILD (70%), with no infection detected. After the development of gefitinib-induced ILD, 66 patients (94%) received corticosteroids, and additional antibiotic treatment in 17 of these patients did not increase the proportion of individuals whose ILD improved (18% and 61% with and without antibiotics, respectively).

Risk Factors for Gefitinib-Induced ILD

Of the 1,874 patients who did not develop pulmonary infiltrates, 245 individuals (13.1%) were excluded from further analysis because of insufficient clinical information (Fig 1). We also excluded the 11
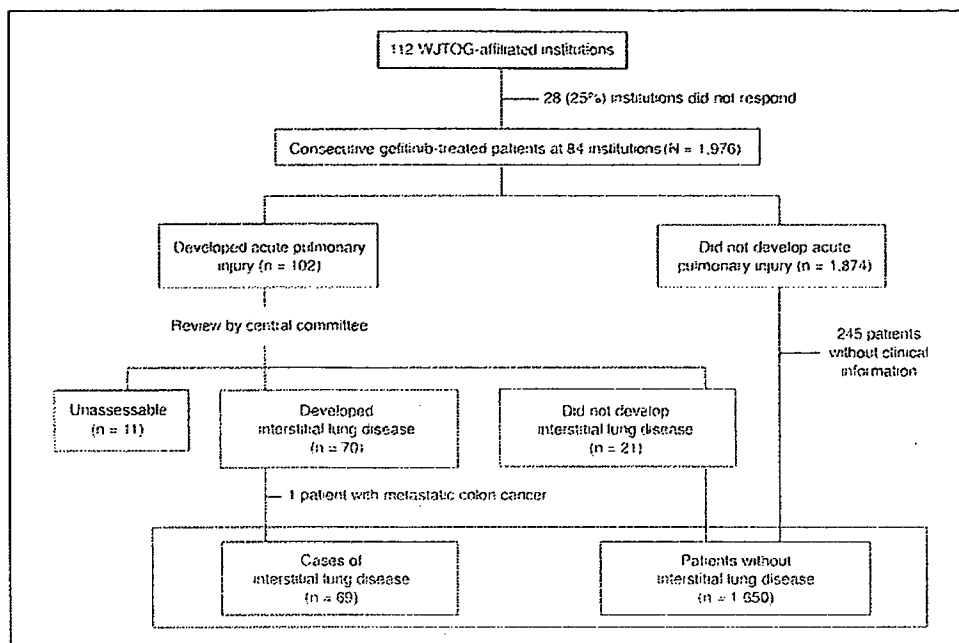
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Fig 1. Outline of patient recruitment and classification. WJTOG, West Japan Thoracic Oncology Group.

unassessable patients with pulmonary infiltrates as well as one confirmed patient with gefitinib-induced ILD whose lung tumor proved to be metastatic colon cancer. Therefore, a total of 1,719 patients (69 patients with gefitinib-induced ILD and 1,650 patients without ILD) were subjected to subsequent analyses to identify predictive factors for the development of ILD, antitumor response, and survival. Among these 1,719 patients, 1,599 individuals (93%) received gefitinib as a monotherapy, whereas 71 and 49 individuals received gefitinib simultaneously with chemotherapy or palliative radiation, respectively. Univariate analysis identified male sex, a history of smoking, and the coincidence of interstitial pneumonia as being associated with the development of ILD (Table 1). Multivariate logistic regression analysis revealed sex, smoking status, and coincidence of interstitial pneumonia as independent risk factors for gefitinib-induced ILD; BSA was also selected in a forward stepwise procedure and included in the multivariate analysis to adjust for its potential confounding effect, although it was not significant in the final model (Table 2). A potential interaction between sex and smoking status was not significant ($P = .399$). The adjusted odds ratio for development of ILD was 20.5 (95% CI, 4.9 to 85.7) for males with a history of smoking compared with females with no history of smoking. Among 1,671 patients with known smoking status, the prevalence of ILD ranged from 0.4% in women with no history of smoking to 6.6% in men with a history of smoking (Table 3).

Predictive Factors for Antitumor Response

An antitumor response was observed in 348 of the total of 1,976 patients (including 256 unassessable patients), corresponding to a response rate of 17.6% (95% CI, 16.0% to 19.4%). Univariate analysis revealed that an age of less than 70 years, female sex, no history of smoking, adenocarcinoma histology, metastatic disease, good PS, a history of chest surgery, no history of chest irradiation, the absence of interstitial pneumonia, and a BSA of less than 1.5 m² were associated with an antitumor response (Table 1). Multivariate logistic regression analysis revealed that sex, smoking status, histology, disease stage, and

PS were independently associated with response rate (Table 4). No synergistic effect on antitumor response was apparent between sex and smoking status, sex and histology, or smoking status and histology ($P = .514, .734,$ and $.573$, respectively). The adjusted odds ratio for an antitumor response was 9.2 (95% CI, 5.5 to 15.3) for women with adenocarcinoma and no history of smoking compared with male smokers with a nonadenocarcinoma histology.

Predictive Factors for Survival

We confirmed 1,076 deaths among the study population as of December 31, 2003. Overall, the median survival time and 1-year survival rate were 312 days (interquartile range, 114 to 579 days) and 44.8% (95% CI, 42.3% to 47.2%), respectively. Univariate analysis identified female sex, no history of smoking, adenocarcinoma histology, nonmetastatic disease, good PS, previous chest surgery, no history of chest irradiation, the absence of interstitial pneumonia or diabetes, and a BSA of less than 1.5 m² as being associated with longer survival (Table 1). Cox regression analysis showed that sex, smoking status, histology, disease stage, PS, and previous chest surgery were independent prognostic factors (Table 5). No synergistic effect on survival was observed between sex and smoking status, sex and histology, or smoking status and histology ($P = .490, .785,$ and $.531$, respectively). Given that previous chemotherapy status is a clinically important factor, we re-examined the survival data separately according to chemotherapy history (Table 6). Survival curves for patients with metastatic disease and a history of chemotherapy (according to independent prognostic factors identified in the Cox regression model) are shown in Figure 2.

We have evaluated clinical data from 1,976 patients with advanced NSCLC who were treated with gefitinib since its licensure in Japan.

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Table 1. Relationship Between Clinical Variables and ILD, Antitumor Response, and Survival in Non–Small-Cell Lung Cancer Patients Treated With Gefitinib

Variable	ILD Total No. of Patients	Patients With ILD No.	Patients With ILD %	P	Antitumor Response Total No. of Patients	Responders No.	Responders %	P	Survival Total No. of Patients	Median Survival (days)	P
Age, years											
< 70	1,047	39	3.7	.446	1,042	230	22.1	.024	1,044	296	.418
≥ 70	672	30	4.5		671	118	17.6		669	333	
Sex											
Female	631	6	1.0	< .001	627	222	35.4	< .001	631	499	< .001
Male	1,088	63	5.8		1,086	126	11.6		1,082	230	
Smoking status											
No smoking history	658	5	0.8	< .001	653	225	34.5	< .001	658	467	< .001
Positive smoking history	1,013	63	6.2		1,012	116	11.5		1,008	227	
Histology											
Adenocarcinoma	1,294	47	3.6	.130	1,288	311	24.2	< .001	1,291	362	< .001
Others	414	22	5.3		414	34	8.2		411	190	
Disease stage											
Metastatic	1,313	59	4.5	.069	1,310	296	22.6	< .001	1,309	280	< .001
Nonmetastatic	406	10	2.5		403	52	12.9		404	435	
Performance status											
0-1	1,161	44	3.8	.664	1,157	274	23.7	< .001	1,157	441	< .001
2	336	14	4.2		336	47	14.0		335	147	
3-4	216	11	5.1		214	26	12.2		216	67	
Previous chest surgery											
Yes	528	15	2.8	.093	527	128	24.3	.008	527	466	< .001
No	1,181	54	4.6		1,177	220	18.7		1,176	253	
Previous thoracic RT											
Yes	472	18	3.8	.767	471	73	15.5	.002	468	263	.005
No	1,235	51	4.1		1,230	273	22.2		1,233	335	
Previous chemotherapy											
Yes	1,356	57	4.2	.440	1,351	275	20.4	.937	1,353	301	.900
No	363	12	3.3		362	73	20.2		360	345	
Coincidence of IP											
Yes	36	5	13.9	.013*	36	1	2.8	.008	35	103	< .001
No	1,683	64	3.8		1,677	347	20.7		1,678	317	
Coincidence of diabetes											
Yes	85	5	5.9	.386*	85	12	14.1	.145	85	190	.002
No	1,634	64	3.9		1,628	336	20.6		1,628	322	
Coincidence of renal failure											
Yes	10	1	10.0	.333*	10	2	20.0	.99*	10	353	.588
No	1,707	67	3.9		1,701	346	20.3		1,701	312	
Body-surface area, m²											
< 1.5	755	30	4.0	.796	751	197	26.2	< .001	755	355	< .001
≥ 1.5	875	37	4.2		874	135	15.5		872	280	

Abbreviations: ILD, interstitial lung disease; RT, radiotherapy; IP, interstitial pneumonia.
*Calculated using Fisher's exact test.

The present study constitutes the first large-scale survey designed to assess the prevalence of and risk factors for gefitinib-induced ILD during practical use of this drug in the Japanese population. The development of ILD subsequent to treatment with conventional cyto-toxic chemotherapeutic agents has been recognized for many years, with the use of standard drugs for treatment of NSCLC being associated with ILD at a prevalence of up to 5%.[17,18] Drug-induced ILD in lung cancer patients is difficult to diagnose because of the high prevalence of pre-existing lung disease and respiratory tract infections as well as the progressive malignancy in such individuals. Clinical symptoms of ILD, such as escalating dyspnea, cough, and fever, may be indistinguishable from the symptoms of progressive tumor growth or

infection. Computed tomographic features of ILD include pulmonary reticular changes and ground-glass opacity, which are also nonspecific and may not readily indicate a precise etiology.[18] Diagnosis of drug-induced ILD thus relies on rigorous exclusion of all other differential diagnoses, especially those of infection and tumor progression.

In the present study, all suspected cases of ILD were meticulously reviewed at a single study site by extramural experts, including at least three thoracic radiologists, one pulmonologist, and one oncologist, taking into account clinical history, the results of clinical examination, and comparisons of current and previous radiologic findings. Seventy patients with gefitinib-related ILD were thereby confirmed, yielding an overall prevalence of 3.5% and mortality of 1.6%. The prevalence of

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Table 2. Risk Factors for Interstitial Lung Disease Identified by Multivariate Logistic Regression Analysis (n = 1,586*)

Variable	Odds Ratio	95% CI	P
Male	3.10	1.15 to 8.36	.025
Positive smoking history	4.79	1.69 to 13.54	.003
Coincidence of IP	2.89	1.06 to 7.84	.038
BSA of < 1.5 m²	1.67	0.98 to 2.83	.059

Abbreviations: IP, interstitial pneumonia; BSA, body-surface area.
*Including 66 patients with gefitinib-induced interstitial lung disease.

Table 4. Predictive Factors for Antitumor Response Identified by Multivariate Logistic Regression Analysis (n = 1,650*)

Variable	Odds Ratio	95% CI	P
Female	2.14	1.53 to 2.98	< .001
No smoking history	2.13	1.53 to 2.96	< .001
Adenocarcinoma	1.97	1.31 to 2.98	.001
Metastatic disease	1.88	1.32 to 2.67	< .001
Performance status†			
2	0.54	0.38 to 0.77	< .001
3-4	0.47	0.30 to 0.76	.001

*Including 338 responders.
†Performance status of 0 to 1 set as reference category.

ILD in our study was slightly higher than the prevalence (1.1%) among gefitinib-treated patients in recent phase III trials of standard chemotherapy with or without gefitinib conducted in the United States and Europe.[19,20] In addition, the worldwide prevalence of ILD among 92,750 patients treated with gefitinib was approximately 1%, being approximately 0.3% in a US AstraZeneca Expanded Access Program.[21,22] The reason for the difference in the frequency of gefitinib-related ILD between Japan and Western countries remains unclear. It is possible that a greater awareness of the disease in Japan might lead to more careful and critical examination for ILD or that Japanese may have an increased genetic susceptibility to ILD.[22]

The mechanism of gefitinib-induced ILD has not been fully elucidated. EGFR and transforming growth factor alpha, a member of the EGF family of proteins that binds to and activates the EGFR, are both upregulated early in the response to acute lung injury,[23,24] and EGF family members are implicated in the repair of pulmonary damage.[25,26] In a rodent model of bleomycin-induced pulmonary fibrosis, treatment with gefitinib was shown to augment fibrosis.[27] These findings suggest that inhibition of EGFR signaling by gefitinib impairs the repair of and, thereby, exacerbates pulmonary injury, especially in patients with pulmonary comorbidities. In the present study, we have sought to identify clinical features of NSCLC patients that might increase the risk for development of ILD. Multivariate analysis identified male sex, a history of smoking, and coincidence of interstitial pneumonia as significant risk factors. Thus, the prevalence of gefitinib-induced ILD differed markedly according to sex and smoking status, ranging from 0.4% in females with no history of smoking to 6.6% in male smokers.

This is the first study in which predictive factors for ILD, antitumor response, and survival have been evaluated with the same data set. Multivariate analysis showed that sex, smoking status, tumor histology, disease stage, and PS were independently associated with both antitumor response and survival, mostly consistent with results of previous studies.[6-8] Although not confirmed by multivariate analysis, a smaller BSA might also confer greater efficacy on gefitinib, with further investigation of possible dose dependency being warranted. Female sex and the absence of a history of smoking were both associated with a lower risk for ILD, a higher response rate, and longer survival, suggesting that patient selection on the basis of this favorable profile will not only increase the clinical benefit of treatment with gefitinib but also reduce the risk for development of this life-threatening toxicity. Activating mutations of the EGFR have been identified in a subset of NSCLC patients, and tumors with EGFR mutations are highly sensitive to gefitinib.[28,29] However, these genetic factors have not been confirmed to be predictive of true clinical benefit because they have not yet been found to be associated with survival in NSCLC patients treated with gefitinib.[30] These previous studies showed that EGFR mutations were more frequent in females, individuals with no history of smoking, and patients with adenocarcinoma. We have no data on the frequency of EGFR mutations in the present patient cohort, and further studies to explore the relationship of genetic alterations with ILD risk and treatment efficacy are warranted.

The objective response rate in the present study was 17.6%, which is indicative of an acceptable single-agent activity of gefitinib outside clinical trial settings. Our data showed the median survival time and 1-year survival rate to be 10.0 months and 44%, respectively,

Table 3. Prevalence of ILD, Response Rate, and 1-Year Survival According to Sex and Smoking Status (n = 1,671)

Measure	No Smoking History		Positive Smoking History	
	Female	Male	Female	Male
Prevalence of ILD				
%	0.4	1.8	3.3	6.6
95% CI	0.0 to 1.5	0.4 to 5.3	0.9 to 8.2	5.1 to 8.4
Response rate				
%	38.2	22.1	23.1	9.9
95% CI	33.9 to 42.6	16.0 to 29.2	16.0 to 31.7	8.0 to 12.0
1-year survival				
%	64.6	47.1	50.7	32.1
95% CI	60.2 to 69.0	39.2 to 55.0	41.6 to 59.8	28.9 to 35.3

Abbreviation: ILD, interstitial lung disease.

Table 5. Survival Analysis by the Cox Regression Model (n = 1,643*)

Variable	Hazard Ratio	95% CI	P
Female	0.63	0.53 to 0.75	< .001
No smoking history	0.71	0.60 to 0.84	< .001
Adenocarcinoma	0.69	0.60 to 0.80	< .001
Metastatic disease	1.58	1.35 to 1.84	< .001
Performance status†			
2	2.58	2.23 to 2.99	< .001
3-4	3.71	3.12 to 4.41	< .001
Previous chest surgery	0.70	0.60 to 0.81	< .001

*Including 611 patients censored.
†Performance status of 0 to 1 set as reference category.

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