which inhibits DNA synthesis, and has shown potent cytocidal activity against solid tumors (4–8).

Docetaxel, an antineoplastic agent that acts on microtubules to promote formation of abnormal microtubule bundles, has also shown cytotoxicity (9–11). Gemcitabine and docetaxel have different mechanisms of action, but by combining them, there is the potential of synergistic antitumor activity (12).

Several studies have been conducted to evaluate the therapeutic benefits of gemcitabine and docetaxel (13–15). The efficacy of gemcitabine–docetaxel is similar to platinum-based regimens, but due to each drug's non-overlapping toxicities, their combination produces toxicities more tolerable than platinum-based regimens. Georgoulias et al. (16) compared gemcitabine 1100 mg/m^2 on days 1 and 8 plus docetaxel 100 mg/m^2 on day 8 with cisplatin 80 mg/m^2 on day 2 plus docetaxel 100 mg/m^2 on day 1 in 441 patients with NSCLC. They reported that the two regimens were equivalent in efficacy, but toxicities were more severe for the combination of docetaxel and cisplatin.

There has been no published report considering both administering dose and schedule for the combination of gemcitabine and docetaxel. Therefore, we conducted a phase I/II study to compare two schedules of gemcitabine–docetaxel in patients with NSCLC and determine the recommended regimen in phase II. We assessed the efficacy and safety in all 59 patients: the efficacy and detailed safety profile were also evaluated in 40 patients who were given the recommended regimen.

SUBJECTS AND METHODS

Eligibility Criteria

Japanese patients with histologically or cytologically confirmed unresectable TNM stage IIIB or IV NSCLC who met the following criteria were eligible for the study: suitable for first-line chemotherapy with no prior chemotherapy; measurable lesions that can be accurately measured in at least one dimension; aged 20–74 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; a life expectancy of at least 3 months; and adequate organ functions as indicated by white blood cell count $\geq 4.0 \times 10^9$/l, absolute neutrophil count $\geq 2.0 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, hemoglobin ≥ 9.5 g/dl, aspartate aminotransferase/alanine aminotransferase ≤ 2.5 times the upper limit of normal, total bilirubin ≤ 1.5 times the upper limit of normal, serum creatinine $\leq$ the upper limit of normal, PaO_2 in arterial blood ≥ 60 torr. If a patient had received radiotherapy during the 3 weeks before enrollment, the measurable disease had to be outside of the radiation port.

Patients were excluded from the study if they had radiologically and clinically apparent interstitial pneumonia or pulmonary fibrosis, intracavitary fluid retention requiring treatment, or grade 2–4 peripheral neuropathy or edema. Additional exclusion criteria included: superior vena cava syndrome; symptomatic brain metastasis; pregnancy or breast-feeding; active concurrent malignancy; any serious concurrent illness (e.g. uncontrolled diabetes mellitus, hepatopathy, angina pectoris, myocardial infarction within 3 months after onset, severe infection, or fever suggestive of severe infection); history of serious drug allergy; or any condition that, in the opinion of the investigator, disqualified the patient based on safety.

This study was conducted in accordance with the Declaration of Helsinki, Japanese Guidelines for Clinical Evaluation of Antineoplastic Agents (promulgated in February 1991) and good clinical practice. All patients who entered into this study were required to give written informed consent.

Study Design And Treatment

This was a multicenter, open-label, phase I/II study of gemcitabine and docetaxel in Japanese patients with advanced NSCLC.

In the phase I portion of this study, patients were randomized into two arms, each with a different treatment schedule. In both arms (Arm 1 and Arm 2), gemcitabine was administered in a 30-min infusion on days 1 and 8, every 21 days. In Arm 1, docetaxel was administered intravenously over at least 1 h on day 1; in Arm 2, docetaxel was given on day 8. The administration of docetaxel followed an intravenous infusion of dexamethasone 4 mg, and gemcitabine was given immediately after the docetaxel infusion.

Patients were discontinued from the study due to progressive disease; inability to initiate a treatment cycle even at 6 weeks after the start of the previous cycle; recurrence of a dose-limiting toxicity (DLT) after resumption of the study treatment at a reduced dose; occurrence of a serious adverse event or aggravation of a concomitant illness (e.g. interstitial pneumonia, pulmonary fibrosis, or severe infection) which caused rapid aggravation of disease and precluded continuation of the study treatment; patient's request to withdraw from the study; or any event that required discontinuation in the opinion of the investigator.

During study enrollment, the current approved maximum dosage of gemcitabine and docetaxel as single agents in Japan was 1000 mg/m^2 and 60 mg/m^2, respectively. In phase I, the sample size was determined to be six per cohort based on the conventional design of phase I clinical studies of antineoplastic agents. In this study, both arms were randomized according to a predetermined schedule, enrolled patients in cohorts of six, and were initially treated at dose level 1 (gemcitabine 1000 mg/m^2 and docetaxel 50 mg/m^2). For the first cycle of treatment, patients were treated on an inpatient basis; if their condition permitted, patients were treated on an outpatient basis thereafter. If fewer than 50% of the patients in dose level 1 experienced DLTs, patients were enrolled at dose level 2 (gemcitabine 1000 mg/m^2 and docetaxel 60 mg/m^2). If 50% or more of the patients in dose level 1 experienced DLTs, patients were enrolled at dose level 0 (gemcitabine 800 mg/m^2 and docetaxel 50 mg/m^2) (Fig. 1). The maximum tolerated dose (MTD) was defined as the dose level that produced any of the following DLTs (per the National Cancer Institute–Common

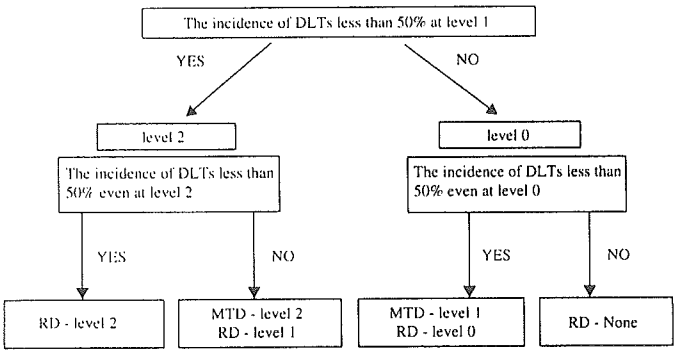

Figure 1. Recommended dosages in each arm. DLT, dose-limiting toxicity; RD, recommended dosage; MTD, maximum tolerated dose.

Toxicity Criteria scale) in 50% or more of patients during the first treatment cycle: grade 4 leukopenia or neutropenia persisting for at least 4 days; grade 3/4 neutropenia associated with a fever ≥38.0°C or infection; thrombocytopenia (<20 × 10^9/l) or need of a platelet transfusion; or grade 3/4 non-hematological toxicities (excluding nausea/vomiting, anorexia, fatigue and hypersensitivity). G-CSFs were administrated for the treatment of grade 4 neutropenia or grade 3 neutropenic fever. A DLT was also reported if any day-8 doses were omitted and dosing requirements were not satisfied until after day 15, or if the second cycle was delayed until after day 29 because the dosing requirements were not satisfied.

The recommended dose for phase II had to be determined from the arm that reached the highest dose level. If at dose level 2 the incidence of DLTs was less than 50%, the recommended dose was defined as dose level 2. The arm that reached the higher dose level reflected the recommended regimen for phase II. If the recommended dose level for the two arms was identical, the recommended regimen would be decided according to the following steps: (i) if frequency of DLTs was 0% in one arm and 33.3% or more in the other arm, the former was selected. If this did not occur, then (ii) if the dose intensity for evaluable patients in one arm was higher by 10% or more than the other arm, the arm with the higher dose intensity was selected. If this did not occur, then (iii) the arm with the fewer day-8 dose omissions in first and second cycles was selected. If the recommended dosage regimen still could not be decided, the sponsor (Aventis Pharma Japan and Eli Lilly Japan K.K.) and the coordinating investigator determined the recommended phase II regimen. If the MTD was dose level 0 in both arms, the study was terminated (Fig. 1).

The sample size for the recommended regimen was determined as follows. The response rate of this regimen and gemcitabine single agent was assumed to be 35 and 20%, respectively, in view of the response rates previously achieved (9,10,17,18). If the sample size of the recommended regimen was set as 40 patients, the probability for the one-sided 90% lower limit of response rate to exceed 20% was 82%. Thus, the target sample size in the recommended regimen including six patients in phase I was set at 40 patients.

The phase II study was conducted with 34 patients. Forty patients who were given the recommended regimen were evaluated for the efficacy and detailed safety profile: these patients consisted of six and 34 patients who entered into the study at phase I and II, respectively.

In this phase I/II study, patients received a minimum of two cycles of gemcitabine–docetaxel and up to four additional cycles.

Dose Modifications

During a cycle, dose modifications were not allowed. If not all of the following requirements were satisfied on either the day of treatment or the previous day, administrations of gemcitabine and docetaxel were delayed until the patient completely recovered. For gemcitabine and docetaxel doses administered on day 1 of Arm 1 or gemcitabine on day 1 of Arm 2, delays occurred for patients with an absolute neutrophil count <1.5 × 10^9/l, a platelet count <70 × 10^9/l, any grade 3/4 non-hematologic toxicities (except PaO_2), or PaO_2 <60 torr. When gemcitabine was given on day 8 of Arm 1, exceptions included leukopenia <2.0 × 10^9/l and an absolute neutrophil count <1.0 × 10^9/l, a platelet count <70 × 10^9/l, any grade 3/4 non-hematological toxicities. When gemcitabine was given on day 8 of Arm 2, exceptions included an absolute neutrophil count <1.5 × 10^9/l, a platelet count <70 × 10^9/l, any grade 3/4 non-hematological toxicities. If a patient developed a DLT, the subsequent doses were cancelled, and in the next cycle the patient could resume the study treatment at the next lower dose level. If a patient developed a DLT at dose level 0, gemcitabine 800 mg/m^2 and docetaxel 40 mg/m^2 were administered in the next cycle.

Baseline and Treatment Assessment

Assessments at baseline included tumor measurements by X-ray and computed tomography (CT) scan within 4 weeks before the day of starting the study treatment. Equally, grading performance status and physical examination were performed within a week; hematology, blood chemistries, urinalysis, arterial blood gas analysis and electrocardiogram were observed within 2 weeks.

After the start of treatment, tumor measurements were obtained every 2 weeks via X-ray and 4 weeks via CT scan. Tumor response was assessed with the World Health Organization (WHO) criteria. Safety assessments, including performance status, hematology, blood chemistries and urinalysis, were obtained weekly. Physical examination, arterial blood gas analysis and electrocardiogram were performed at any time. Adverse events were estimated according to National Cancer Institute–Common Toxicity Criteria version 2.0. All patients were assessed for efficacy and safety. An additional response rate was recorded for patients who received the recommended regimen in phase I and all phase II patients.

RESULTS

Patient Characteristics

Between July 2000 and July 2002, 59 chemonaive patients (43 male, 16 female) with NSCLC were enrolled in phase I and II portions from the five hospitals after approval by the IRB. Twenty-five patients were enrolled in the phase I portion of the study, and 34 patients were enrolled in phase II. Baseline patient characteristics for all patients and patients who received the recommended regimen are summarized in Table 1.

Phase I

Twenty-five patients were enrolled into the phase I portion of the study. The number of patients treated and the DLTs observed in the first cycle at each dose level of gemcitabine and docetaxel are shown in Table 2.

In Arm 1, 50% of patients had DLTs at dose level 1 and dose level 0, therefore Arm 1 could not be the recommended regimen: there were 2/6 and 3/6 patients who achieved partial response (PR) at dose level 1 and 0 in Arm 1, respectively.

Table 1. Baseline characteristics

Patient characteristics	All patients (n = 59), n (%)	Patients who received the recommended regimen (n = 40), n (%)
Gender		
Male	43 (72.9%)	26 (65.0%)
Female	16 (27.1%)	14 (35.0%)
Age		
Median	62	64
Range	38–74	38–74
ECOG performance status		
0	5 (8.5%)	2 (5.0%)
1	54 (91.5%)	38 (95.0%)
Stage		
IIIB	14 (23.7%)	8 (20.0%)
IV	33 (55.9%)	23 (57.5%)
Postsurgical recurrence	12 (20.3%)	9 (22.5%)
Histological type		
Adenocarcinoma	34 (57.6%)	25 (62.5%)
Squamous cell carcinoma	19 (32.2%)	14 (35.0%)
Large cell carcinoma	5 (8.5%)	1 (2.5%)
Other	1 (1.7%)	0 (0%)
Prior therapy		
None	45 (76.3%)	29 (72.5%)
Surgery	13 (22.0%)	11 (27.5%)
Radiotherapy	0 (0%)	0 (0%)
Radiotherapy and surgery	1 (1.7%)	0 (0%)

ECOG, Eastern Cooperative Oncology Group.

In Arm 2, no DLT was observed at dose level 1: 3/6 patients achieved PR. At dose level 2, one patient discontinued due to progressive disease; therefore, one patient was added. However, another patient discontinued due to grade 3 hypersensitivity (not a DLT). In this regimen, two DLTs had already been observed in five other patients, but the sponsors (Aventis Pharma Japan and Eli Lilly Japan K.K.) and investigators decided not to add one more patient to dose level 2 in Arm 2 in consideration of patients' safety. PRs were observed in 2/7 patients at dose level 2 of Arm 2.

Therefore, the recommended regimen was determined as gemcitabine 1000 mg/m^2 on days 1 and 8 plus docetaxel 50 mg/m^2 on day 8 due to the incidence of DLT.

Dose Administration

In Arm 1, a total of 49 cycles were accomplished. One case delayed the date of administration on day 1 (defined as more than 8 days) as a matter of convenience; seven and four cases delayed their dates of administration on day 8 (defined as more than 1 day) because of adverse events and non-medical reasons, respectively; and four cases could not be treated on day 8 because of adverse events. In Arm 2, including phase I and II portions, a total of 145 cycles were accomplished. Four and five cases delayed their dates of administration on day 1 because of adverse events and non-medical reasons, respectively; 21 and nine cases delayed their dates of administration on day 8 because of adverse events and non-medical reasons, respectively; and two cases could not be treated on day 8 because of

Table 2. Phase I dose-limiting toxicities

Dose level	GEM/DOC (mg/m^2)	Arm 1	Arm 2
0	800/50	3/6 patients: • G3 ALT increased • G1 fever, G3 neutropenia • G2 infection, G3 neutropenia	N/A
1	1000/50	3/6 patients: • G3 infection, G3 neutropenia • G4 neutropenia, G1 fever, G3 infection • G3 neutropenia, G2 infection, G3 arrhythmia, G3 diarrhea	0/6 patients
2	1000/60	N/A	2/5 patients: • G3 ALT increased • G2 fever, G3 neutropenia

GEM, gemcitabine; DOC, docetaxel; G, grade; ALT, alanine aminotransferase; N/A, not applicable.

adverse events. The most common adverse event for a dose delay was neutropenia.

EFFICACY

All 59 patients were involved in the analysis for efficacy, and 19 of 59 patients achieved PR for an overall response rate of 32.2% [95% confidence interval (CI) 20.6–45.6%]. Of the 40 patients who received the recommended regimen in either phase I or phase II, 12 patients achieved PRs for a response rate of 30.0% (95% CI 16.6–46.5%).

The median time to progressive disease in all 59 patients was 111 days (95% CI 71–154 days). Median survival time was 11.9 months (95% CI 7.0–15.0 months), with 1-year survival rate at 47.1% (95% CI 34.0–60.2%).

SAFETY

All 59 patients were evaluable for safety. Grade 3 and 4 drug-related toxicities observed in all 59 patients are shown in Table 3. Grade 3 and 4 drug-related toxicities observed in 40 patients who received the recommended regimen are also shown in Table 4.

In all 59 patients, grade 3 and 4 neutropenia were observed in 19 (32.2%) and 20 (33.9%) patients, respectively. Grade 3 and 4 leukopenia were observed in 24 (40.7%) and four (6.8%) patients, respectively. Grade 3 non-hematological toxicities included infection in four patients (6.8%), anorexia in four patients (6.8%), and nausea, diarrhea, rash and constipation in three patients (5.1%) each. After starting docetaxel administration, grade 3 interstitial pneumonia was reported in three patients (5.1%), all of whom recovered shortly after steroid treatment; grade 4 anaphylaxis was reported in two patients (3.4%). There were no toxic deaths.

Table 3. NCI-CTC grade 3/4 toxicities (n = 59)

Toxicities	Grade 3		Grade 4	
	n	%	n	%
Hematological toxicities				
Leukopenia	24	40.7	4	6.8
Neutropenia	19	32.2	20	33.9
Lymphopenia	10	16.9	0	0.0
Hemoglobin decreased	4	6.8	0	0.0
Thrombocytopenia	1	1.7	0	0.0
Thrombocytosis	1	1.7	0	0.0
Non-hematological toxicities				
ALT increased	5	8.5	0	0.0
Infection	4	6.8	0	0.0
Anorexia	4	6.8	0	0.0
Nausea	4	6.8	0	0.0
Diarrhea	3	5.1	0	0.0
Interstitial pneumonia	3	5.1	0	0.0
Rash	3	5.1	0	0.0
Constipation	3	5.1	0	0.0
AST increased	2	3.4	0	0.0
Fatigue	2	3.4	0	0.0
Vomiting	2	3.4	0	0.0
Hyperglycemia	1	1.7	0	0.0
Hyponatremia	1	1.7	0	0.0
Allergic reaction	1	1.7	0	0.0
Vasovagal reaction	1	1.7	0	0.0
Body temperature decrease	1	1.7	0	0.0
Weight increase	1	1.7	0	0.0
Hypotension	1	1.7	0	0.0
Pneumonia	1	1.7	0	0.0
Arrhythmia	1	1.7	0	0.0
Edema	1	1.7	0	0.0
Neuropathy peripheral	1	1.7	0	0.0
Anaphylaxis	0	0.0	2	3.4

NCI-CTC, National Cancer Institute-Common Toxicity Criteria version 2.0; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

DISCUSSION

In this phase I/II study, we examined the activity and tolerability of gemcitabine and docetaxel. In phase I, the recommended regimen was determined as gemcitabine 1000 mg/m^2 on days 1 and 8 plus docetaxel 50 mg/m^2 on day 8. The response rate of all 59 patients was 32.2% (95% CI 20.6–45.6%). When re-evaluated in the 40 patients who received the recommended regimen, the response rate was 30.0% (95% CI 16.6–46.5%). Although the number of patients was limited, Arm 1 (docetaxel on day 1) had a numerically better response: for the 12 patients in Arm 1, five PRs were recorded for a response rate of 42%. However, Arm 1 had more toxicities than the docetaxel on day-8 schedule.

Overall, the toxicity associated with the gemcitabine–docetaxel regimen was manageable. In Arm 1, five patients (42%) had grade 3/4 neutropenia supervened with infection or fever, while only one patient (9%) had grade 3 neutropenia with infection or fever in Arm 2. This indicated that docetaxel was better tolerated on day 8 than on day 1 in a 21-day cycle. It is speculated that the influence of time to nadir of neutropenia is different in each agent: 14–20 days with gemcitabine and 9 days with docetaxel. The time to recover from nadir is 7–8 days with gemcitabine and 8 days with docetaxel. This could explain why docetaxel on day 8 was better tolerated.

Meta-analysis studies have reported that cisplatin-based regimens produce a significant survival benefit in NSCLC (20–23), improve median survival time by 6–8 weeks and 1-year survival rate from 15% to 25% when compared with the best supportive care (24). But studies with platinum-based combinations have also reported severe toxicities, so the deterioration of patients' quality of life is a major problem to be solved (3).

New effective non-platinum-based therapies have been used in various combinations in recent years, and the combination of gemcitabine and docetaxel has been established as one of the

Table 4. NCI–CTC grade 3/4 toxicities (n = 40, recommended regimen)

Toxicities	Grade 3		Grade 4	
	n	%	*n*	%
Hematological toxicities				
Leukopenia	13	32.5	2	5.0
Neutropenia	12	30.0	11	27.5
Lymphopenia	5	12.5	0	0.0
Hemoglobin decreased	2	5.0	0	0.0
Thrombocytopenia	1	2.5	0	0.0
Thrombocytosis	1	2.5	0	0.0
Non-hematological toxicities				
ALT increased	2	5.0	0	0.0
Diarrhea	2	5.0	0	0.0
Infection	2	5.0	0	0.0
Interstitial pneumonia	2	5.0	0	0.0
Rash	2	5.0	0	0.0
Fatigue	2	5.0	0	0.0
Nausea	2	5.0	0	0.0
Vomiting	2	5.0	0	0.0
Hyperglycemia	1	2.5	0	0.0
Hyponatremia	1	2.5	0	0.0
AST increased	1	2.5	0	0.0
Allergic reaction	1	2.5	0	0.0
Vasovagal reaction	1	2.5	0	0.0
Anorexia	1	2.5	0	0.0
Body temperature decrease	1	2.5	0	0.0
Weight increase	1	2.5	0	0.0
Hypotension	1	2.5	0	0.0
Pneumonia	1	2.5	0	0.0
Edema	1	2.5	0	0.0
Constipation	1	2.5	0	0.0
Peripheral neuropathy	1	2.5	0	0.0
Anaphylaxis	0	0.0	2	5.0

NCI–CTC, National Cancer Institute–Common Toxicity Criteria version 2.0; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

well-examined regimens. In recent studies using gemcitabine–docetaxel in NSCLC, response rates of 25–50% (19,25–29) and time-to-progression of disease of 106–132 days (31,32) have been reported. Georgoulias et al. (16) reported that the gemcitabine–docetaxel and docetaxel–cisplatin regimens they compared were equivalent in efficacy, but toxicity was severe in the latter. While docetaxel–cisplatin regimens showed severe toxicities of grade 3 anemia (5%), grade 3/4 neutropenia (13%/21%), grade 3 nausea/vomiting (10%) and grade 3 diarrhea (8%), gemcitabine–docetaxel regimens had grade 3/4 anemia (1%/1%), grade 3/4 neutropenia (11%/11%), grade 3 nausea/vomiting (2%) and grade 3/4 diarrhea (2%/1%) in 441 patients. However, the difference of efficacy and safety by the administration schedule and dosage of gemcitabine and docetaxel has not been well documented.

There are some studies that have examined the efficacy and safety of the same schedule as the recommended regimen in our study, namely gemcitabine on days 1 and 8 plus docetaxel on day 1. In these studies dosages were various: gemcitabine was 800–1100 mg/m^2 and docetaxel was 60–100 mg/m^2 (18,19,27–30). Response rates in these studies also varied from 16 to 38%, which indicates that the response rate of the recommended regimen in our study (30.0%) was clinically meaningful because the dosage of docetaxel (50 mg/m^2) in our study is less than that in any other studies. This might have contributed to the relatively mild toxicities of our recommended regimen.

In another study (26), a high response rate (50.0%) was achieved in patients with another administering schedule: gemcitabine 1000 mg/m^2 on days 1 and 10 plus docetaxel 80 mg/m^2 on day 1, administered every 21 days. The most common treatment-related toxicity was myelosuppression. Grade 3/4 leukopoenia and neutropenia occurred in only six (18%) and eight (24%) patients, respectively.

The median survival was 11.9 months in our study, being slightly better than the result from the median survival of the phase III study with gemcitabine and cisplatin, which was 8.7–9.1 months (33,34). This result suggests that the regimen we selected in the phase II portion of this study is comparable in survival with the cisplatin-based regimen.

In conclusion, the combination of gemcitabine 1000 mg/m^2 on days 1 and 8 plus docetaxel 50 mg/m^2 on day 8 is suggested to be better tolerated and has equivalent efficacy to cisplatin-based therapy. These results should be verified by a phase III study in Japanese patients.

CONCLUSION

In this phase I/II study, we studied the activity and tolerability of gemcitabine and docetaxel in Japanese patients. The combination of gemcitabine 1000 mg/m^2 on days 1 and 8 plus docetaxel 50 mg/m^2 on day 8 is suggested to be well tolerated and has equivalent efficacy to cisplatin-based therapy.

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References

1. Luedke DW, Einhorn L, Omura GA, Sarma PR, Bartolucci AA, Birch R, et al. Randomized comparison of two combination regimens versus minimal chemotherapy in non-small-cell lung cancer: a Southern Cancer Study Group trial. *J Clin Oncol* 1990;8:886–91.
2. Gridelli C, Perrone F, Palmeri S, D'Aprile M, Cognetti F, Rossi A, et al. Mitomycin plus vindesine plus etopoide (MEV) versus mitomycin plus

vindesine plus cisplatin (MVP) in stage IV non-small-cell lung cancer: a phase III multicenter randomized trial. *Ann Oncol* 1996;7:821–6.
3. Georgoulias V, Scagliotti G, Miller V, Eckardt J, Douillard JY, Manegold C. Challenging the platinum combinations: docetaxel (Taxotere) combined with gemcitabine or vinorelbine in non-small cell lung cancer. *Semin Oncol* 2001;28:15–21.
4. Fujita M, Fujita F, Inaba S, Taguchi T. Antitumor activity of LY188011, a new deoxycytidine analog, against human cancers xenografted into nude mice. *Gan To Kagaku Ryoho* 1994;21:517–23 (in Japanese).
5. Fukuoka M, Negoro S, Kudo S, Furuse K, Nishikawa H, Takada Y, et al. Late phase II study of LY188011 (gemcitabine hydrochloride) in patients with non-small-cell lung cancer. Gemcitabine Late Phase II Cooperative Study Group A. *Gan To Kagaku Ryoho* 1996;23:1825–32 (in Japanese).
6. Heinemann V, Hertel LW, Grindey GB, Plunkett W. Comparison of the cellular pharmacokinetics and toxicity of 2′,2′-difluorodeoxycytidine and 1-beta-D-arabinofuranosylcytosine. *Cancer Res* 1988;48:4024–31.
7. Hertel LW, Boder GB, Kroin JS, Rinzel SM, Poore GA, Todd GC, et al. Evaluation of the antitumor activity of gemcitabine (2′,2′-difluoro-2′-deoxycytidine). *Cancer Res* 1990;50:4417–22.
8. Yokoyama A, Nakai H, Yoneda S, Kurita Y, Niitani H, Taguchi T. A late phase II study of LY188011 (gemcitabine hydrochloride) in patients with non-small-cell lung cancer. Gemcitabine Cooperative Study Group B for Late Phase II. *Gan To Kagaku Ryoho* 1996;23:1681–8 (in Japanese).
9. Kudo S, Hino M, Fujita A, Igarashi T, Arita K, Niitani H, et al. Late phase II study of RP56976 (docetaxel) in patients with non-small cell lung cancer. *Gan To Kagaku Ryoho* 1994;21:2617–23 (in Japanese).
10. Onoshi T, Watanabe K, Furuse K, Kurita Y, Sugiura T, Sato K, et al. Late phase II study of RP56976 (docetaxel) in patients with non-small-cell lung cancer. *Gan To Kagaku Ryoho* 1995;22:59–65 (in Japanese).
11. Ringel I, Horwitz SB. Studies with RP56976 (taxotere): a semisynthetic analogue of taxol. *J Natl Cancer Inst* 1991;83:288–91.
12. Zoli W, Ricotti L, Dal Susino M, Barzanti F, Frassineti GL, Folli S, et al. Docetaxel and gemictabine activity in NSCLC cell lines and in primary cultures from human lung cancer. *Br J Cancer* 1999;81:609–15.
13. Rebattu P, Quantin X, Ardiet C, Morere JF, Azarian MR, Schuller-Lebeau MP, et al. Dose-finding, pharmacokinetic and phase II study of docetaxel in combination with gemcitabine in patients with inoperable non-small cell lung cancer. *Lung Cancer* 2001;33:227–87.
14. Rigas JR. Non-platinum based combination chemotherapy: phase I and II trials of docetaxel plus gemcitabine, vinorelbine, or irinotecan. *Semin Oncol* 2001;28:15–20.
15. Spiridonidis CH, Laufman LR, Carman L, Moore T, Blair S, Jones J, et al. Second-line chemotherapy for non-small cell lung cancer with monthly docetaxel and weekly gemcitabine: a phase II trial. *Ann Oncol* 2001;12:89–94.
16. Georgoulias V, Papadakis E, Alexopoulos A, Tsiafaki X, Rapti A, Veslemes M, et al. Greek Oncology Cooperative Group (GOCG) for Lung Cancer. Platinum-based and non-platinum-based chemotherapy in advanced non-small cell lung cancer: a randomised multicentre trial. *Lancet* 2001;357:1478–84.
17. Georgoulias V, Papadakis E, Alexopoulos A, et al. Docetaxel plus cisplatin versus docetaxel plus gemcitabine chemotherapy in advanced non-small cell lung cancer: a preliminary analysis of a multicenter randomized phase II trial. *Proc Am Soc Clin Oncol* 1999;18:461a (Abstr).
18. Kakolyris S, Papadakis E, Tsiafaki X, Kalofonos C, Rapti A, Toubis M, et al. Doxetaxel in combination with gemcitabine plus rhG-CSF support as second-line treatment in non-small cell lung cancer. A multicenter phase II study. *Lung Cancer* 2001;32:179–87.
19. Georgoulias V, Kouroussis C, Androulakis N, et al. Front-line treatment of advanced non-small cell lung cancer with docetaxel and gemcitabine: a multicenter phase II trial. *J Clin Oncol* 1999;17:914–20.
20. Grilli R, Oxman AD, Julian JA. Chemotherapy for advanced non-small-cell lung cancer: how much benefit is enough? *J Clin Oncol* 1993;11:1866–72.
21. Marino P, Pampallona S, Preatoni A, Cantoni A, Invernizzi F. Chemotherapy vs supportive care in advanced non-small cell lung cancer. Results of a meta-analysis of the literature. *Chest* 1994;106:861–5.
22. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *Br Med J* 1995;311:899–909.
23. Souquet PJ, Chauvin F, Boissel JP, et al. Polychemotherapy in advanced non-small cell lung cancer: a meta-analysis. *Lancet* 1993;342:19–21.
24. ASCO Special Article. Clinical practice guidelines for the treatment of unresectable non-small-cell lung cancer. *J Clin Oncol* 1997;15:2996–3018.
25. Lizon J, Feliu J, Morales S, Dorta J, Belon J. A phase II study of gemcitabine plus docetaxel as first line treatment in non-small-cell lung cancer (NSCLC). An Oncopaz and Associated Hospitals study. *Proc Am Soc Clin Oncol* 2001;20:270b.
26. Hejna M, Kornek GV, Raderer M, Ulrich-Pur H, Fiebiger WC, Marosi L, et al. Treatment of patients with advanced non small cell lung carcinoma using docetaxel and gemcitabine plus granulocyte-colony stimulating factor. *Cancer* 2000;89:516–22.
27. Kosmas C, Tsavaris N, Vadiaka M, Stavroyianni N, Koutras A, Malamos N, et al. Gemcitabine and docetaxel as second-line chemotherapy for patients with non-small cell lung carcinoma who fail prior paclitaxel plus platinum-based regimens. *Cancer* 2001;92:2902–10.
28. Georgoulias V, Papadakis E, Alexopoulos A, Tsiafaki X, Rapti A, Veslemes M, et al. Platinum-based and non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a randomised multicentre trial. *Lancet* 2001;357:1478–84.
29. Rebattu P, Quantin X, Ardiet C, Morere JF, Azarian MR, Schuller-Lebeau MP, et al. Dose-finding, pharmacokinetic and phase II study of docetaxel in combination with gemcitabine in patients with inoperable non-small cell lung cancer. *Lung Cancer* 2001;33:277–87.
30. Niho S, Kubota K, Goto K, Ohmatsu H, Matsumoto T, Kakinuma R, et al. Combination second-line chemotherapy with gemcitabine and docetaxel for recurrent non-small-cell lung cancer after platinum-containing chemotherapy: a phase I/II trial. *Cancer Chemother Pharmacol* 2003;52:19–24.
31. Garcia C, Milla A, Fellu J, Lorenzo A, Madronal C, Gilli F, et al. Phase II study of gemcitabine (G) in combination with docetaxel (D) in advanced non-small-cell lung cancer (NSCLC) patients (Oncopaz and Hospitals Associated). *Ann Oncol* 2000;11 (Suppl 4):113 (516P).
32. Amenedo M, Mel J, Huidobro G, Rodriguez M, Anton M, Constenla M, et al. Phase II multicenter clinical trial of gemcitabine (G) and docetaxel (D) in advanced non-small-cell lung cancer (NSCLC): final results. *Proc Am Soc Clin Oncol* 2001;20:265b.
33. Cardenal F, Lopez-Cabrerizo MP, Anton A, Alberola V, Massuti B, Carrato A, et al. Randomized phase III study of gemcitabine–cisplatin versus etoposide–cisplatin in the treatment of locally advanced or metastatic non-small cell lung cancer. *J Clin Oncol* 1999;17:12–8.
34. Sandler AB, Nemunaitis J, Denham C, von Pawel J, Cormier Y, Gatzemeier U, et al. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2000;18:122–30.

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ORIGINAL REPORT

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose
To evaluate the relationship between mutations of the epidermal growth factor receptor (*EGFR*) gene and the effectiveness of gefitinib treatment in patients with recurrent lung cancer after pulmonary resection.

Patients and Methods
We sequenced exons 18-21 of the *EGFR* gene using total RNA extracted from 59 patients with lung cancer who were treated with gefitinib for recurrent lung cancer. Gefitinib effectiveness was evaluated by both imaging studies and change in serum carcinoembryonic antigen (CEA) levels.

Results
EGFR mutations were found in 33 patients (56%). Of these mutations, 17 were deletions around codons 746-750 and 15 were point mutations (12 at codon 858, three at other codons), and one was an insertion. *EGFR* mutations were significantly more prevalent in females, adenocarcinoma, and never-smokers. Gefitinib treatment resulted in tumor shrinkage and/or CEA decrease to less than half of the baseline level in 26 patients, tumor growth and/or CEA elevation in 24 patients, and gefitinib effect was not assessable in nine patients. Female, never-smoking patients with adenocarcinoma tended to respond better to gefitinib treatment. Gefitinib was effective in 24 of 29 patients with *EGFR* mutations, compared with two of 21 patients without mutations ($P < .0001$). Of note, del746-750 might be superior to L858R mutations for prediction of gefitinib response. Patients with *EGFR* mutations survived for a longer period than those without the mutations after initiation of gefitinib treatment ($P = .0053$).

Conclusion
EGFR mutations were a good predictor of clinical benefit of gefitinib in this setting.

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INTRODUCTION

Lung cancer has long been the leading cause of cancer death in North America. In 1998, it became the leading cause of cancer death in Japan, and now claims more than 55,000 lives annually.[1] Lung cancer is divided into two morphologic types: small-cell lung cancer and non–small-cell lung cancer (NSCLC). NSCLCs are further subdivided into adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma. Adenocarcinoma is the predominant histologic subtype, and is increasing among patients with lung cancer who are candidates for surgical treatment in Japan. In our institution, adenocarcinoma accounted for 76% of 407 patients who were operated on from 2001 through 2003. Adenocarcinomas are characterized by a high degree of morphologic heterogeneity. Analyses of various cancer-associated genes, including *K-ras*,[2] *p53*,[3,4] cyclin D1,[5] $p27^{Kip1}$,[6] and cyclooxygenase-2,[7]

suggests a different molecular pathway for carcinogenesis in lung adenocarcinomas at least partly accounts for this heterogeneity. In addition, the NSCLC frequently overexpresses receptors of the ErbB family, including the epidermal growth factor receptor (EGFR) encoded by ErbB1 (HER-1).[8,9]

EGFR is a 170 kd receptor tyrosine kinases (TK) that dimerizes and phosphorylates several tyrosine residues upon binding of several specific ligands including epidermal growth factor and transforming growth factor alpha.[8] These phosphorylated tyrosines serve as the binding sites for several signal transducers that initiate multiple signaling pathways resulting in cell proliferation, migration and metastasis, evasion from apoptosis, or angiogenesis, all of which are associated with cancer phenotypes.[8] Downstream pathways include ras-raf-MEK-ERK, phosphatidylinositol-3 kinase-Akt, and PAK-JNKK-JNK.[8]

Gefitinib is an orally bioavailable small molecule that specifically inhibits EGFR tyrosine phosphorylation.[10] Clinical trials revealed that there is significant variability in response to gefitinib. Good clinical responses have been observed most frequently in women, in nonsmokers, in patients with adenocarcinomas, and in Japanese patients.[11,12] However, it was not possible to predict gefitinib sensitivity by levels of EGFR overexpression as determined by immunohistochemistry[13] or immunoblotting.[14] The factors that determine gefitinib sensitivity have long been an enigma. Recently, it has been reported that activating mutations of *EGFR* are present in a subset of pulmonary adenocarcinomas and that tumors with *EGFR* mutations are highly sensitive to gefitinib[15-17] or erlotinib, another EGFR TK inhibitor. Furthermore, the incidence of *EGFR* mutations is significantly higher in female, never-smoking, Japanese patients with adenocarcinoma.[15] These features coincide with those of good responders to gefitinib.

In this study, we studied patients who had recurrent disease after pulmonary resection for NSCLC and who were subsequently treated with gefitinib. We searched for mutations of the *EGFR* gene in tumor specimens taken at the time of surgery and we correlated *EGFR* mutations with gefitinib effectiveness, including tumor response and patient survival.

PATIENTS AND METHODS

Patients

Seventy-five patients were treated with gefitinib for their recurrent diseases after they had undergone surgery between 1999 and 2003. We studied 59 patients whose tumors were available for RNA extraction, which was a sole determinant of inclusion into the present study. There were 32 men and 27 women with ages ranging from 48 to 79 years. Fifty patients had adenocarcinomas, five had squamous cell carcinomas, three had large-cell carcinomas, and one had adenosquamous carcinoma. Eight patients had stage IA disease; seven stage IB; three stage IIA; five stage IIB; 24 stage IIIA; eight stage IIIB; and three stage IV at the time of surgery. Lobectomy had been performed in 57, and pneumonectomy and partial resection in one patient each. Four patients received postoperative adjuvant chemotherapy (two with oral uracil/tegafur and two with gemcitabine monotherapy). Forty patients had had chemotherapy before gefitinib treatment (23 patients, platinum doublet; 16 patients, monotherapy with vinorelbine or gemcitabine, one patient, oral uracil/tegafur). Gefitinib treatment with a daily dose of 250 mg was initiated between July 2002 and May 2004, with the median interval between operation and gefitinib treatment being 778 days (range, 107 to 1,931 days). Fifty patients had distant metastatic tumors, eight patients had pleural dissemination and malignant effusion, and one patient had hilar lymph-node metastasis at initiation of gefitinib treatment.

Molecular Analysis of Lung Cancer Specimens

After we obtained appropriate approval from the institution and written informed consent for comprehensive use of molecular and pathologic analysis from the patients, tumor samples were collected during surgery, rapidly frozen in liquid nitrogen and stored at −80°C. A surgical pathologist (Y.Y.) grossly dissected the frozen tumor specimens to enrich the tumor cell population as much as possible. Total RNA was isolated using the RNeasy kit (Qiagen, Valencia, CA).

The first four exons (exons 18-21) of the seven exons (exons 18-24) that code for TK domain of the *EGFR* gene (which includes all the mutations reported so far[15-17]) was amplified with primers F1 (5′-AGCTTGTGGAGCCTCTTACACC-3′) and R1 (5′-TAAAATTGATTCCAATGCCATCC-3′) in a one-step reverse transcription polymerase chain reaction (RT-PCR) using the QIAGEN OneStep RT-PCR Kit (Qiagen). The cDNA sequence of the *EGFR* gene was obtained from GenBank (accession number NM 005228). The RT-PCR conditions were: one cycle of 50°C for 30 minutes, 95°C for 15 minutes, 40 cycles of 94°C for 50 seconds, 62°C for 50 seconds, and 72°C for 60 seconds, followed by one cycle of 72°C for 10 minutes.

RT-PCR products were diluted and cycle-sequenced using the Big Dye Terminator v3.1/1.1 cycle sequencing kit (Applied Biosystems, Foster City, CA) according to the manufacturer's instructions. Sequencing products were electrophoresed on an ABI PRISM 3100 (Applied Biosystems). Both the forward and reverse sequences obtained were analyzed by BLAST (basic local alignment search tool) and chromatograms by manual review. High-quality sequence variations found in both directions were scored as candidate mutations.

Definition of Effectiveness of Gefitinib

Because this study was a retrospective analysis of the daily clinical practice of oncology, the evaluation of tumor response could not be performed strictly according to predefined criteria, such as Response Evaluation Criteria in Solid Tumors (RECIST).[18] RECIST are not necessarily applicable or complete in such a context and the evaluation may instead be based on a subjective medical judgment that results from clinical and laboratory data.[18] Therefore, gefitinib treatment was judged as effective when the tumors showed at least a 30% decrease in tumor diameter in imaging studies. However, because of the nature of the study, confirmation of tumor response no less than 4 weeks apart, as in RECIST,[18] was not necessarily required.

As patients with recurrent lung cancer often do not have measurable disease, we also included change in serum carcinoembryonic antigen (CEA) level (cut off, 5 ng/mL) as an evaluation

criterion to avoid underestimating gefitinib effectiveness. CEA has been reported as a useful clinical therapeutic marker.[19] When the elevated CEA level decreased to a level less than half of the baseline level, gefitinib treatment was judged as effective. On the other hand, gefitinib treatment was judged as ineffective when the tumors showed any growth or a new lesion appeared in the imaging studies, or when the serum CEA level increased. Any patient who did not fit either of these criteria was classified as not assessable. All these evaluations were done before the *EGFR* gene analysis, without knowledge of mutational status of the *EGFR* gene.

Statistical Analysis

For comparisons of proportions, the χ^2 test or Fisher's exact test was used. The Kaplan-Meier method was used to estimate the probability of survival as a function of time, and survival differences were analyzed by the log-rank test. The two-sided significance level was set at $P < .05$. To identify which independent factors had a joint significant influence on gefitinib effectiveness, the logistic regression modeling technique was used, and for multivariate analysis of the overall survival, the Cox proportional hazards modeling technique was applied. All analyses were performed using StatView version 5 (SAS institute Inc, Cary, NC) software on a Macintosh computer.

RESULTS

EGFR *Mutations*

Mutations of the *EGFR* gene were detected in 33 (56%) of 59 patients. Seventeen were deletions, 15 were point mutations, and one was an insertion. Details of these mutations are shown in Figure 1. As previously reported,[15-17] *EGFR* mutations were significantly associated with adenocarcinoma histology, female sex, and never-smoking status (Table 1). However, the mutations were not associated with the age or stage of the patients. Furthermore, median time from the original surgery to

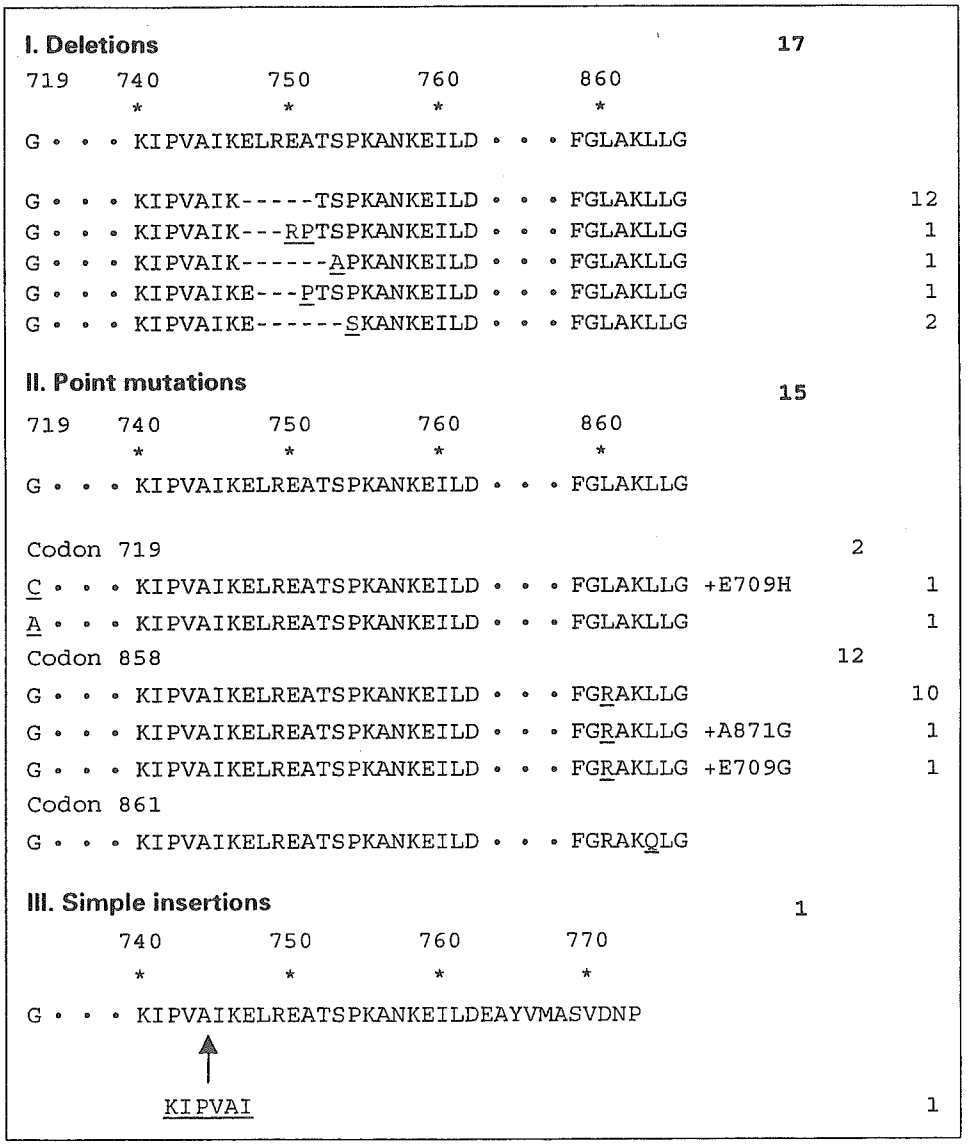

Fig 1. Analysis of 33 epidermal growth factor receptor (EGFR) mutations in tyrosine kinase domain of the *EGFR* gene found in unselected patients with lung cancer.

Table 1. Incidence of EGFR Mutations and Clinical and Pathologic Features

Variable	EGFR Mutation		EGFR Wild-Type	P
	No. of Patients	%		
All cases	33	56	26	
Sex				
Male	14	44	18	.0402
Female	19	70	8	
Age, years				
≤ 64	22	55	18	.8342
> 64	11	58	8	
Histologic type				
Adenocarcinoma	32	64	18	.0033
Nonadenocarcinoma	1	11	8	
Squamous cell carcinoma	0	0	5	
Large-cell carcinoma	0	0	3	
Adenosquamous carcinoma	1	100	0	
Smoking status				
Never smoker	20	71	8	.0227
Former or current smoker	13	42	18	
Stage				
I-II	12	50	12	.4472
III-IV	21	60	14	

Abbreviation: EGFR, epidermal growth factor receptor.

recurrence was almost identical in patients with *EGFR* mutations (362 days) and in those without *EGFR* mutations (363 days; $P = .8265$).

Clinical Improvement After Gefitinib Treatment

Forty-one of 59 patients had measurable disease at recurrence with imaging studies. Of these, 20 showed appreciable tumor shrinkage after gefitinib treatment, whereas 17 tumors increased in size, and there was no change in tumor size in four patients. All of these 20 tumors (pulmonary metastases in 11, pleural disseminated nodules in two, hepatic metastases in two, mediastinal lymph node swelling in two, brain metastases in two, and chest wall tumor in one) showed at least a 30% decrease in diameter. Figure 2 shows representative imaging studies. A computed tomography scan of the chest in patient L703 (73-year-old woman, adenocarcinoma) showed masses in the right-lower lobe and marked improvement 8 weeks after gefitinib initiation. A computed tomography scan of the liver in patient L1492 (52-year-old woman, adenocarcinoma) showed masses in the right lobe of the liver and dramatic improvement 10 days after gefitinib initiation. A large chest-wall mass in the left back of patient L1362 (62-year-old man, adenosquamous carcinoma) before gefitinib treatment almost disappeared 13 weeks after gefitinib initiation. A left-lung tumor in patient L1171 (70-year-old woman, adenocarcinoma) was smaller 6 weeks after gefitinib initiation.

CEA was above the upper normal limit (5 ng/mL) at baseline in 32 patients. Serum CEA level decreased to < 10%, < 50%, and to > 50% of the baseline level in three, 12, and five patients, respectively, whereas CEA level increased in 12 patients. When we combined the results of imaging studies with CEA and judged according to our criteria, gefitinib treatment was effective in 26 (52%), not effective in 24 (48%), and not assessable in nine patients (Table 2). There was a good correlation between these two examinations. The imaging studies and change in CEA levels did not conflict in any patients. In 17 patients with measurable diseases and whose baseline CEA level was elevated, the CEA level decreased in all 11 patients showing tumor shrinkage and increased in all five patients showing tumor growth, except for one patient whose tumors showed no change in size ($P < .001$, Fisher's exact test), supporting the validity of our criteria.

We searched for a relation between gefitinib effectiveness and various clinical and pathologic features (Table 2). Never-smokers and patients with adenocarcinoma had a significantly higher incidence of gefitinib effect. However, we could not detect significant difference in gefitinib sensitivity by sex or presence of prior chemotherapy, probably because of the small sample size, although there was a trend that female and chemotherapy-naïve patients were more responsive.

Relationship Between Clinical Response to Gefitinib Treatment and EGFR Mutations

The incidence of *EGFR* mutations in terms of response to gefitinib treatment as judged by imaging studies and CEA levels is shown in Table 3. Of 20 patients who showed tumor shrinkage, 19 (95%) had mutations of the *EGFR* gene. On the other hand, two (12%) of 17 patients whose tumors grew after gefitinib treatment harbored *EGFR* mutations ($P < .001$, Fisher's exact test). In Figure 2, patient L703, L1492, and L1362 had *EGFR* mutations (delE746-A750, L858R, and E746-S752insA, respectively). Of three, 12, and five patients whose CEA level decreased to less than 10%, less than 50%, and to more than 50% of the baseline level after gefitinib treatment, three (100%), 10 (83%), and four (80%) had *EGFR* mutations, respectively. On the other hand, of 12 patients whose CEA level increased, three (25%) had *EGFR* mutations ($P = .004$, Fisher's exact test).

When we used our criteria combining the results of imaging studies with CEA, gefitinib was effective in 24 (83%) of 29 patients with *EGFR* mutations, whereas it was effective only in two (10%) of 21 patients without *EGFR* mutations ($P < .0001$; Table 2). There were three patients with *EGFR* mutations (two with L858R and one with G719A) whose CEA level increased after gefitinib treatment but did not have measurable diseases. There were also two patients with *EGFR* mutations, one with L858R+E709H and one with I744-K745 ins KIPVAI whose tumor progressed.

Logistic regression analysis (Table 4) showed that *EGFR* mutation was the only significant factor contributing to gefitinib sensitivity.

On the other hand, patient L1171, who showed a decrease in size of multiple pulmonary metastatic nodules

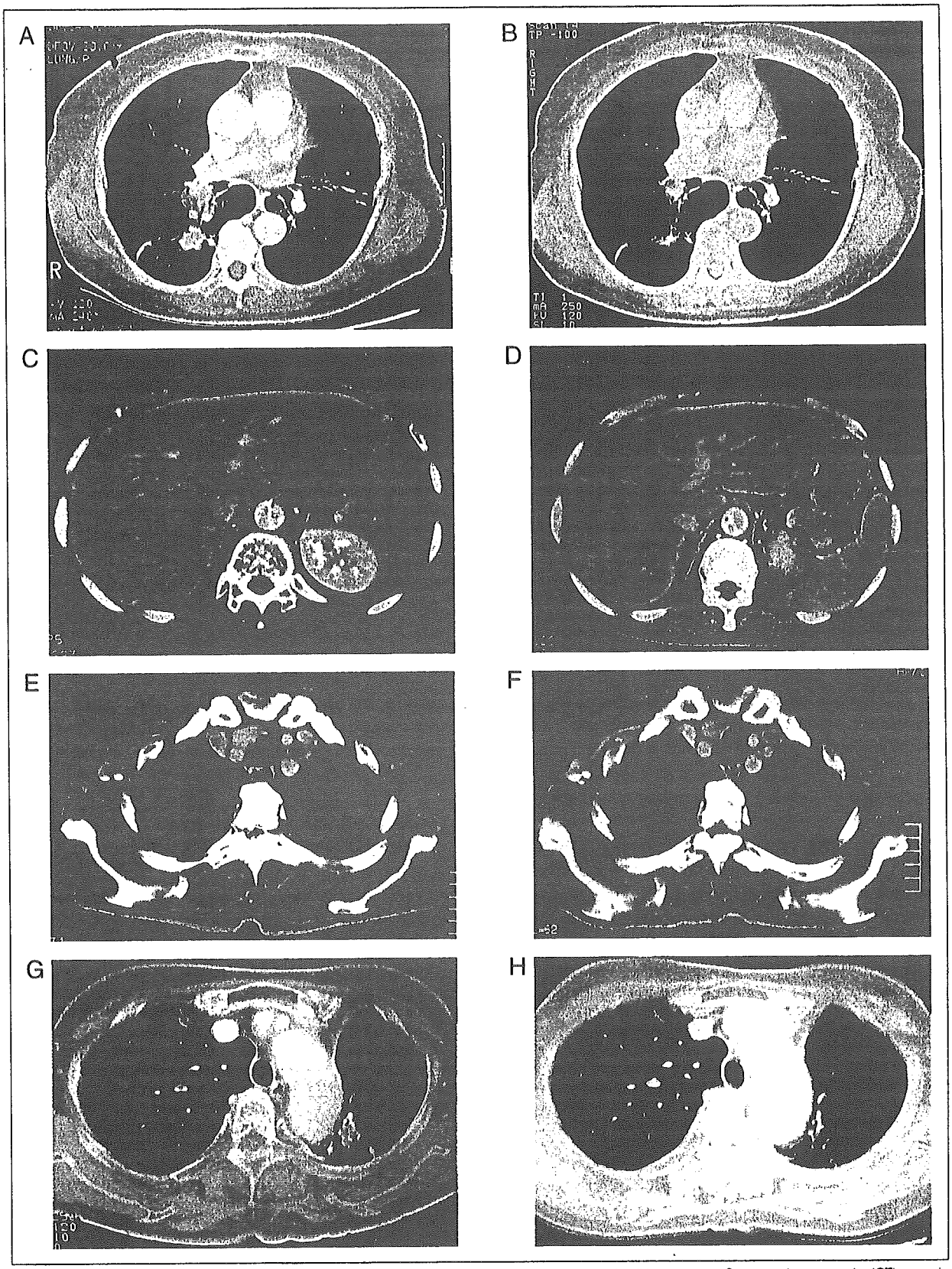

Fig 2. Examples of the response to gefitinib in representative four patients with recurrent non–small-cell lung cancer. Computed tomography (CT) scans before gefitinib treatment (A, C, E, G) and after the gefitinib was initiated (B, D, F, H) are shown. CT scans of patient L703 (A, B), patient L1492 (C, D), patient L1362 (E, F), and patient L1171 (G, H).

Table 2. Relation Between Gefitinib Effectiveness and Various Clinical and Pathologic Features

Variable	Effective: No. of Patients	Effective: %*	Not Effective	Not Assessable	P†
All patients	26	52	24	9	
Sex					
Male	11	41	16	5	.0842
Female	15	65	8	4	
Smoking status					
Never-smoker	17	68	8	3	.0235
Former or current smoker	9	36	16	6	
Histologic type					
Adenocarcinoma	25	58	18	7	.0313
Nonadenocarcinoma	1	14	6	2	
Prior chemotherapy					
Present	17	47	19	4	.2782
Absent	9	64	5	5	
EGFR mutation					
Mutation	24	83	5	4	< .0001
Deletion	16	100	0	1	.0108‡
Insertion	0	0	1	0	
Point mutation	8	67	4	3	
Wild-type	2	10	19	5	

Abbreviation: EGFR, epidermal growth factor receptor.
*Percentages were calculated excluding patients who were not assessable.
†*P* values were calculated excluding patients who were not assessable.
‡*P* value for Fisher's exact test comparing deletion mutants with the other mutants.

(Figs 2G and H) and a decrease in CEA level from 16.8 to 4.3 ng/mL, did not have *EGFR* mutations. In this patient, we extended our search for mutations to exons 22 and 23 of the *EGFR* gene, and still found none. Another patient without *EGFR* mutation in whom gefitinib was effective was a 59-year-old man who showed a decrease in serum CEA level from 10.6 to 1.5 ng/mL after 2 weeks of gefitinib treatment; this low level of CEA was maintained at least for 7 months.

When we further analyzed gefitinib response by classes of *EGFR* mutation, we found that there was a difference of response between patients with deletion mutations and those with the other types of mutations. Gefitinib was effective in all 16 patients with deletions, and effective in eight of 13 with other types of mutation ($P = .0108$).

Effect of EGFR *Mutation on Patient Survival After Gefitinib Treatment*

Patients with *EGFR* mutations survived for a significantly longer time calculated from the day of gefitinib initiation than those without *EGFR* mutations ($P = .0053$, log-rank test; Fig 3). Likewise, 26 gefitinib responders survived for a longer time than 24 nonresponders ($P = .0320$, log-rank test; not shown). Multivariate analysis revealed that *EGFR* mutation was the only factor that significantly and independently affected overall survival (Table 5). *EGFR* mutation class did not affect overall survival (not shown).

DISCUSSION

Recurrence after complete resection of NSCLC often presents as a form of distant metastases.[20] In clinical practice, chemotherapy is given to these patients except for a small number in whom re-resection of the tumor is indicated. Many studies have shown that chemotherapy prolongs survival and improves quality of life in unresectable stage IV tumors.[21] However, patients with unresectable tumors and patients with recurrent diseases may not be the same. There have been no large-scale randomized clinical trials addressing whether chemotherapy improves survival of patients with recurrence. Yoshino et al[22] found that chemotherapy for recurrence only tended to prolong survival in 118 of 468 consecutive patients who had recurrence after pulmonary resections. After introduction of gefitinib to clinical practice in 2002 in Japan, some patients with recurrent disease showed dramatic responses to gefitinib treatment, but many others did not respond. It has been unclear which patients respond to gefitinib and also whether gefitinib treatment prolongs survival in these patients.

Recent studies have showed striking correlation between gefitinib sensitivity and *EGFR* mutations both in vitro and in clinical studies.[15-17] Because this study was a retrospective analysis of response to gefitinib prescribed as routine care, judgment of gefitinib effectiveness tended to be less strict than that in a prospective clinical trial. Yet, changes in serum CEA level never conflicted with imaging studies. We were able to confirm a relation between *EGFR*

Table 3. Response to Gefitinib Treatment in 59 Patients With Recurrent Disease

CEA Level	Imaging Results: Shrinkage	No Change	Not Measurable	Growth	Total
Decreased					
<10% of the baseline	**3 (3)**				3 (3)
<50% of the baseline	**6 (5)**	**1 (1)**	**5 (4)**		12 (10)
>50% of the baseline	**2 (2)**		*3 (2)*		5 (4)
Not assessable	**9 (9)**	*3 (1)*	*3 (1)*	12 (2)	27 (13)
Elevated			7 (3)	5 (0)	12 (3)
Total	20 (19)	4 (2)	18 (10)	17 (2)	59 (33)

NOTE. Numbers in bold indicate that gefitinib treatment resulted in clinical improvement in these patients; numbers with underlines indicate the treatment resulted in progression of the disease; numbers in parentheses show number of patients with EGFR mutations in each category; and italicized numbers indicate that gefitinib treatment could not be assessed.
Abbreviations: EGFR, epidermal growth factor receptor; CEA, carcinoembryonic antigen.

Table 4. Logistic Regression Analysis of Various Factors That Predict EGFR Effectiveness

Variable	Odds Ratio	95% CI	*P*
Sex			
Male/female	1.139	0.130 to 9.953	.9063
Smoking status			
Never/former/current	1.496	0.165 to 13.535	.7202
Histologic type			
Adenocarcinoma/nonadenocarcinoma	1.727	0.091 to 33.33	.7159
Prior chemotherapy			
Yes/no	0.427	0.060 to 3.027	.3948
EGFR mutation			
Mutant/wild-type	40.000	6.024 to 2750	< .0001

Abbreviation: EGFR, epidermal growth factor receptor.

mutations and gefitinib sensitivity in a slightly different clinical setting. We correlated *EGFR* mutations found in specimens taken at the time of surgery with response to gefitinib, often after several courses of cytotoxic chemotherapy for recurrent disease. Multivariate analysis revealed that *EGFR* mutation was the only independent predictor for gefitinib response among several allegedly contributing factors. As in previous studies, *EGFR* mutation was not a perfect predictor of gefitinib effectiveness.[15-17] Two patients without *EGFR* mutations showed response to gefitinib. It is not clear at this time whether *EGFR* mutations are present in other parts of the gene or whether mechanisms other than *EGFR* mutations govern sensitivity in these patients.

We found a significant difference in gefitinib sensitivity according to classes of *EGFR* mutations. All 16 patients with deletion mutants responded to gefitinib, compared with eight of 12 patients with other mutations (P = .0108). It is not clear whether this difference is based on differences in biologic activity of these mutant proteins.

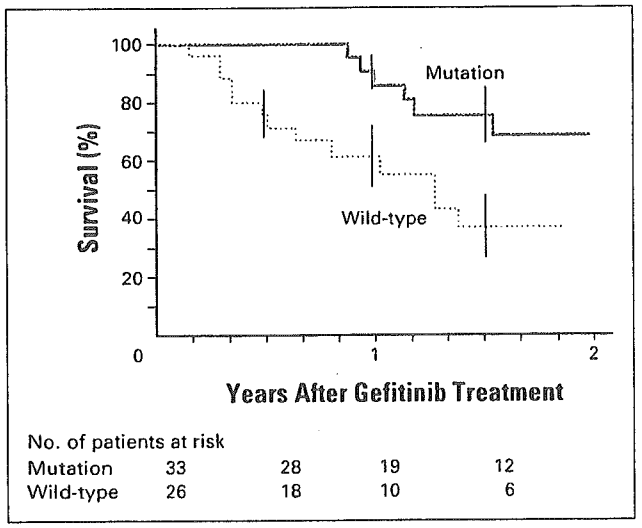

Fig 3. Effect of epidermal growth factor receptor mutations on survival, calculated from the day of initiating gefitinib treatment in patients who had recurrent disease after surgery (P = .0053, log-rank test).

Table 5. Cox Proportional Hazards Model for Survival Analysis

Variable	Hazard Ratio	95% CI	*P*
Sex			
Female/male	0.359	0.068 to 1.900	.2280
Smoking status			
Never/former/current	0.511	0.092 to 2.854	.4445
Histologic type			
Adenocarcinoma/nonadenocarcinoma	0.335	0.095 to 1.184	.0894
Prior chemotherapy			
Yes/no	0.653	0.222 to 1.923	.4397
Stage			
I-II/III-IV	0.848	0.322 to 2.232	.7380
Age, years			
> 64/≤ 64	0.964	0.342 to 2.717	.9457
EGFR mutation			
Mutant/wild-type	0.342	0.117 to 0.998	.0496

Abbreviation: EGFR, epidermal growth factor receptor.

Gefitinib sensitivity was essentially the same in COS cells transfected with L858R and in cells transfected with del L747-P753insS.[16] A more recent study showed that the tyrosine residue at codon 845 is highly phosphorylated in L858R mutants, but not in deletion mutants after epidermal growth factor binding.[23] This might explain the difference in gefitinib response between tumors with L858R and those with deletions.

Although our criteria for tumor response are soft, these are merely a surrogate marker for the effect on survival. We were able to show, for the first time, that *EGFR* mutation was the only significant and independent predictor for a prolonged survival after gefitinib treatment. In a previous study, we showed that *EGFR* mutation itself is not a predictor for better postoperative survival in 236 unselected patients with adenocarcinoma,[24] and in the present study, median disease-free interval was almost identical in patients with or without *EGFR* mutations. A recent placebo-controlled clinical trial showed that treatment with erlotinib, another oral EGFR TK inhibitor, significantly prolongs survival after first and second chemotherapy for NSCLC,[25] although *EGFR* mutation frequency is reported to be around 10% in Western countries.[15-17] This result is interpreted to mean that a subset of patients without mutations have also benefited from erlotinib therapy. The present study suggests that if patients were selected by presence of *EGFR* mutations, it would be possible to concentrate patients with benefits from gefitinib treatment, avoiding unnecessary adverse reactions such as fatal interstitial lung disease, which is relatively common in Japanese patients.[26] Furthermore, our results provide a basis for postoperative adjuvant gefitinib treatment in NSCLC patients with *EGFR* mutations, as adjuvant treatment is considered the earliest treatment of metastatic disease. These possibilities should be tested in future clinical trials.

It is common for patients to show progressive disease soon after presenting an initial striking response to

gefitinib. However, we could not detect any evidence that differences in classes of *EGFR* mutations are associated with duration of response (data not shown).

In conclusion, tumors with *EGFR* mutations showed good, but not perfect, correlation with clinical response in patients with postoperative recurrence of NSCLC. Furthermore, patients with *EGFR* mutations survived for a significantly longer period than those without *EGFR* mutations. Future clinical trials using gefitinib should examine *EGFR* mutations for effective selection of patients who are most likely to benefit from this molecular-targeted drug.

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Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Honoraria: Tetsuya Mitsudomi, AstraZeneca Japan, Bristol-Myers Squibb Japan, TAIHO Pharmaceutical. For a detailed description of this category, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and Disclosures of Potential Conflicts of Interest found in Information for Contributors in the front of each issue.

REFERENCES

1. Kuroishi T, Hirose K, Tajima K: Cancer mortality in Japan, in Tominaga S, Oshima A (eds): Gann Monograph Cancer Research. Tokyo, Japan Scientific Societies Press, 1999, pp 1-38
2. Mitsudomi T, Viallet J, Linnoila RI, et al: Mutations of ras genes distinguish a subset of non-small cell lung cancer cell lines from small cell lung cancer cell lines. Oncogene 6:1353-1362, 1991
3. Mitsudomi T, Oyama T, Nishida K, et al: p53 nuclear immunostaining and gene mutations in non-small-cell lung cancer and their effects on patient survival. Ann Oncol 6:S9-13, 1995
4. Nishio M, Koshikawa T, Kuroishi T, et al: Prognostic significance of abnormal p53 accumulation in primary, resected non-small-cell lung cancers. J Clin Oncol 14:497-502, 1996
5. Nishio M, Koshikawa T, Yatabe Y, et al: Prognostic significance of cyclin D1 and Rb expression in combination with p53 abnormalities in primary, resected non-small cell lung cancer. Clin Cancer Res 3:1051-1058, 1997
6. Yatabe Y, Masuda A, Koshikawa T, et al: p27kip1 in human lung cancers: Differential changes in small cell and non-small cell carcinomas. Cancer Res 58:1042-1047, 1998
7. Hida T, Yatabe Y, Achiwa H, et al: Increased expression of cyclooxygenase 2 occurs frequently in human lung cancers, specifically in adenocarcinomas. Cancer Res 58:3761-3764, 1998
8. Arteaga CL: Overview of epidermal growth factor receptor biology and its role as a therapeutic target in human neoplasia. Semin Oncol 29:3-9, 2002
9. Bunn PA, Jr., Franklin W: Epidermal growth factor receptor expression, signal pathway, and inhibitors in non-small cell lung cancer. Semin Oncol 29:38-44, 2002
10. Ciardiello F, Tortora G: A novel approach in the treatment of cancer: Targeting the epidermal growth factor receptor. Clin Cancer Res 7:2958-2970, 2001
11. Kris MG, Natale RB, Herbst RS, et al: Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: A randomized trial. JAMA 290:2149-2158, 2003
12. Fukuoka M, Yano S, Giaccone G, et al: Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. J Clin Oncol 21:2237-2246, 2003
13. Cappuzzo F, Gregorc V, Rossi E, et al: Gefitinib in pretreated non-small-cell lung cancer (NSCLC): Analysis of efficacy and correlation with HER2 and epidermal growth factor receptor expression in locally advanced or metastatic NSCLC. J Clin Oncol 21:2658-2663, 2003
14. Suzuki T, Nakagawa T, Endo H, et al: The sensitivity of lung cancer cell lines to the EGFR-selective tyrosine kinase inhibitor ZD1839 ('Iressa') is not related to the expression of EGFR or HER-2 or to K-ras gene status. Lung Cancer 42:35-41, 2003
15. Paez JG, Janne PA, Lee JC, et al: EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. Science 304:1497-1500, 2004
16. Lynch TJ, Bell DW, Sordella R, et al: Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 350:2129-2139, 2004
17. Pao W, Miller V, Zakowski M, et al: EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci U S A 101:13306-13311, 2004
18. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors. European Organisation for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205-216, 2000
19. Salgia R, Harpole D, Herndon JE, 2nd, et al: Role of serum tumor markers CA 125 and CEA in non-small cell lung cancer. Anticancer Res 21:1241-1246, 2001
20. Mitsudomi T, Nishioka K, Maruyama R, et al: Kinetic analysis of recurrence and survival after potentially curative resection of nonsmall cell lung cancer. J Surg Oncol 63:159-165, 1996
21. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized trials. Non-Small Cell Lung Cancer Collaborative Group. BMJ 311:899-909, 1995
22. Yoshino I, Yohena T, Kitajima M, et al: Survival of non-small cell lung cancer patients with postoperative recurrence at distant organs. Ann Thorac Cardiovasc Surg 7:204-209, 2001
23. Sordella R, Bell DW, Haber DA, et al: Gefitinib-sensitizing EGFR mutations in lung cancer activate anti-apoptotic pathways. Science 305:1163-1167, 2004
24. Kosaka T, Yatabe Y, Endoh H, et al: Mutations of the epidermal growth factor receptor gene in lung cancer: Biological and clinical implications. Cancer Res 64:8919-8923, 2004
25. Shepherd FA, Pereira J, Ciuleanu TE, et al: A randomized placebo-controlled trial of erlotinib in patients with advanced non-small cell lung cancer following failure of 1st line or 2nd line chemotherapy. Proc Am Soc Clin Oncol 22:622s, 2004 (abstr 7022)
26. Inoue A, Saijo Y, Maemondo M, et al: Severe acute interstitial pneumonia and gefitinib. Lancet 361:137-139, 2003

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A Phase II Study of Docetaxel and Infusional Cisplatin in Advanced Non-Small-Cell Lung Cancer

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Key Words
Non-small-cell lung cancer · Chemotherapy · Cisplatin · Docetaxel · Infusion, continuous

Abstract
Background: To evaluate the efficacy and safety of combination chemotherapy of cisplatin (5-day continuous infusion) and docetaxel for the treatment of previously untreated patients with advanced non-small-cell lung cancer (NSCLC). ***Materials and Methods:*** Eligible patients had an ECOG performance status of 0–2 with measurable NSCLC. Patients received continuous infusion cisplatin 20 mg/m^2/day on 5 days and bolus docetaxel 60 mg/m^2/day (day 1; PiD therapy) at a 4-week interval. ***Results:*** Forty-three patients were enrolled. The mean number of cycles administered per patient was 2, and ranged from 1 to 4. The response rate was 49% (95% confidence interval, 33.9–63.8%). The median survival time was 47 weeks and the 1-year survival rate was 47%. The major toxic effects were grade 3 or 4, neutropenia (88%), leukopenia (81%), thrombocytopenia (14%) and anemia (42%). There were no treatment-related deaths. ***Conclusion:*** PiD therapy was a well-tolerated and active regimen for patients with advanced NSCLC. The major toxicity was neutropenia.

Introduction

Unresectable non-small-cell lung cancer (NSCLC) is known to have an extremely poor prognosis, and its standard treatment remains to be established. The most common chemotherapy for NSCLC is a combination treatment consisting of 2 or 3 drugs including cisplatin (CDDP) as a key drug. The combination treatments have response rates of 30–50%, and have been proven to prolong survival time in clinical stages III [1] and IV [2, 3]; however, the response is only limited.

In recent years, new anticancer drugs have been developed and used for the treatment of NSCLC. Docetaxel is a new hemisynthetic anticancer agent originating from its precursor, 10-deacytylbaccatin III, extracted from the needle leaves of the European yew tree, *Taxus baccata* L. Docetaxel affects microtubules, and shows its cytotoxicity by prematurely stabilizing mitotic microtubules. In phase II clinical studies for the treatment of NSCLC carried out in Europe and the USA, docetaxel showed a response rate of about 30% in previously untreated patients with a better survival time [4, 5]. A major side effect of docetaxel is dose-dependent edema that is proportional to bone marrow suppression. Since hypersensitivity is particularly limiting, it is worth noting that docetaxel can be given by intravenous infusion in a short period of time without any pretreatment.

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In the Japan phase I study, dose-limiting toxicity of docetaxel was found to be leukopenia (neutropenia), and its recommended dose was set at 60 mg/m^2 [6]. In the multicenter phase II clinical study for the treatment of NSCLC carried out in Japan, a response rate of 19% was shown in untreated patients with predominant toxicities of leukopenia and neutropenia [7].

Currently, cisplatin is the active agent for treating NSCLC, and combination chemotherapy consisting of 2 or 3 drugs based on CDDP is a major strategy [8]. CDDP can be administered by short-term intravenous infusion, a divided dosage method, continuous administration, and other methods [9, 10]. CDDP cytotoxicity is enhanced by prolonged exposure to low doses of this drug in in vitro studies [11, 12]. Belliveau et al. [13] reported that the area under the concentration-time curve (AUC) achieved for non-protein-bound CDDP was twice as high after 5-day continuous infusion than that observed when an equivalent dose of CDDP was given by short-term bolus infusion. These findings suggest that continuous infusion of CDDP might improve the therapeutic efficacy as compared with that resulting from conventional short-term bolus infusion. However, compared with short-term intravenous infusion, 5-day continuous infusion makes inpatient hospitalization for at least 5 days necessary, and the duration of confinement for the purpose of infusion is lengthy and therefore onerous for the patient. The efficacy and safety of a continuous infusion lasting 5 days (24 h a day) were confirmed in our facility and some other facilities [10, 14–16]. In addition, combination chemotherapy of infusional CDDP with vindesine or CPT-11 was found to have high response rates in treating NSCLC [17, 18].

Cisplatin and docetaxel show nonsynergistic and additive effects in vitro, no cross-resistance and have a relatively nonoverlapping toxicity profile [19]. Therefore, the development of docetaxel in combination with cisplatin is warranted. We conducted a phase II study of docetaxel and infusional cisplatin, in patients with previously untreated advanced NSCLC, and evaluated antitumor activity and the safety of this therapy.

Patients and Methods

Patient Selection

All patients with histologically or cytologically confirmed advanced NSCLC were eligible for this phase II trial. The subjects of this study were patients in clinical stage IV or in stage III with unresectable disease or in whom radiotherapy with curative intent is not possible. Patients with unresectable disease or in whom radiotherapy with curative intent is not possible include those with pleural effusion and dissemination, those with intrapulmonary metastasis within the ipsilateral lobe, those in whom the irradiation field exceeds one half of one lung, those with metastasis to the contralateral hilar lymph nodes, and those with reduced lung function. None of the patients had received prior therapy. Other eligibility criteria included an expected survival of 12 weeks, age ≤75 years, Eastern Cooperative Oncology Group performance score of 0–2, measurable lesions, adequate hematological function (WBC ≥4,000/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥10 g/dl), renal function (serum creatinine ≤1.5 mg/dl, creatinine clearance ≥60 ml/min), and hepatic function (total serum bilirubin ≤1.5 mg/dl, glutamic oxaloacetic transaminase and glutamic pyruvic transaminase less than twice the normal range). The ethical committee of the Tochigi Cancer Center approved the protocols. Written informed consent was obtained in every case stating that the patient was aware of the investigational nature of this treatment regimen. Pretreatment evaluation included medical history, physical examination, complete blood count, bone marrow examination, serum biochemical analyses, chest roentgenogram, electrocardiogram, and urinalysis. All patients underwent a radionuclide bone scan, and computerized tomography of the brain, thorax and abdomen. Complete blood count, biochemical tests, serum electrolytes, urinalysis, and chest roentgenograms were obtained weekly during this phase II trial. Tests of measurable disease parameters such as computerized tomography were repeated every 4 weeks. Staging was according to the 4th edition of the UICC TNM classification.

Treatment

All patients were admitted to the Tochigi Cancer Center Hospital during this trial. The anticancer drug regimen consisted of a combined administration of docetaxel plus infusional cisplatin. Docetaxel was supplied, in concentrated form, in a sterile vial that contained 80 mg of the drug in 2 ml of polysorbate 80. Docetaxel (Taxotere; Aventis) 60 mg/m^2 was diluted in 250 ml of 5% glucose, and was infused over a 1-hour period on day 1. Three hours after completion of the docetaxel infusion, 20 mg/m^2 of cisplatin was given daily for 5 days by continuous intravenous infusion. One third of the daily dose was administered every 8 h dissolved in 800 ml of physiological saline [14]. The course was repeated every 4 weeks. Antiemetic drugs used were granisetron (3 mg/body/day, bolus infusion for 5 days), metoclopramide (3 mg/kg/day, continuous infusion for 5 days), methylprednisolone (125 mg bolus infusion every 8 h, days 1–5), diphenhydramine (30 mg orally, days 1–7) and alprazolam (1.2 mg orally, days 1–7) [15, 16]. In the first course, no routine premedication was given for hypersensitivity reactions or fluid retention. The reason for this was that the incidence of these events was low at the dose of docetaxel (60 mg/m^2) administered in the present study [7]. However, if hypersensitivity reactions or fluid retention occurred, premedications such as corticosteroids or antiallergic agents were allowed in the subsequent courses. Recombinant human granulocyte colony-stimulating factor was administered when leukopenia/neutropenia of grade 4 occurred.

Patients were treated with at least two cycles of therapy unless disease progression or unacceptable toxicity was encountered or the patients did not wish to continue. Patients who experienced grade 4 leukopenia or neutropenia that lasted for 3 or more days, or who experienced grade 4 thrombocytopenia or reversible grade 2 neurotoxicity or grade 3 liver dysfunction, received reduced doses of

both docetaxel and cisplatin (75% of the previous dose) for the next cycle. Patients who experienced stomatitis of grade 3 or more or renal dysfunction of grade 2 or more received a reduced dose of cisplatin (75% of the previous dose) for the next cycle. If neurotoxicity of grade 3 or more occurred, treatment was stopped. Subsequent courses of chemotherapy were started after day 28 when the leukocyte count was 4,000/mm^3 or more, the neutrophil count was 2,000/mm^3 or more, the platelet count was 100,000/mm^3 or more, serum creatinine was less than the upper limit of the normal range, creatinine clearance was 60 ml/min or more, GOT and GPT were 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, the patient was taken off the study, but still included in the analysis. In the case of stable or progressive disease after two courses of treatment, subsequent therapy was left to the discretion of the physician in charge of the patient.

Assessment of Response to Treatment and Toxicity

The response to treatment was evaluated with WHO criteria. The criteria for response were as follows. Complete response was defined as the complete disappearance of all evidence of tumor for at least 4 weeks. Partial response was defined as a ≥50% reduction in the sum of the product of the two greatest perpendicular diameters of all indicator lesions for at least 4 weeks and no appearance of new lesions or progression of any lesion. Progressive disease was defined as a ≥25% increase in the tumor area or the appearance of new lesions. All other circumstances were classified as no change. Toxicity was graded according to the common toxicity criteria (version 2).

Statistical Analyses

The primary end point was the objective response rate. The duration of each response was defined as the number of days from the documentation of the response until tumor progression. Survival curves from registration until death were generated by the method of Kaplan and Meier. We chose a 40% response rate as a desirable target level, and a 20% response rate as undesirable. The study design had the power to detect a response of greater than 90%, with less than 5% error. Therefore, we needed 23 assessable patients in first stage and 20 in second stage, according to the mini-max design of Simon. We decided to stop the study if fewer than 5 patients responded in the first stage.

Results

Patient Characteristics

Forty-three patients were enrolled in this study from July 1997 to June 1999 and received 105 cycles of the regimen. Table 1 shows the patient characteristics. There were 14 women and 29 men with a median age of 61 years (range 34–75). One patient had stage IIIA, 7 patients stage IIIB, and 35 patients stage IV disease. In stage IIIA, 1 patient classified as c-T3N2M0 had lung cancer with a bulky tumor (10 cm), associated with extranodal and N2 involvement. Among the 7 stage IIIB patients, there were three T4 cases in which pleural effusion and pleural dissemination were present, two T4 cases of intrapulmonary metastasis in the ipsilateral lobe, and two T4N3 cases with mediastinal infiltration and supraclavicular fossa lymph node metastasis.

Table 1. Patient characteristics

Patients	43
Sex (M/F)	29/14
Age[1], years	61 (34–75)
Performance status: 0/1/2	9/30/4
Stage: IIIA/IIIB/IV	1/7/35
Histology: Ad/Sq/Other	27/14/2

Ad = Adenocarcinoma; Sq = squamous cell carcinoma.

[1]Value represents median with the range given in parentheses.

Treatments Administered

The mean number of cycles administered per patient was 2, and ranged from 1 to 4. In 99 of 105 cycles (94%), PiD was administered at 4-week intervals. In 5 of 6 cycles, in which cisplatin could not be administered at a 4-week interval, it was given a week later. As for the remaining cycle, it was administered 6 weeks later. The reason for the delay of the administration was the patient's request for 1 cycle and neutropenia in 5 cycles. Dosage was reduced in 7 cycles (7%). Reductions in dosage of docetaxel and cisplatin were made, respectively, in 6 cycles (6%) and 7 cycles (7%). The former reduction was made because 6 cycles showed neutropenia grade 4, and the latter reduction was made because 5 cycles showed neutropenia grade 4, and 1 cycle showed both neutropenia grade 4 and creatinine grade 3, and 1 cycle showed creatinine grade 2.

Response to Treatment and Survival

The response rate was 49% (95% confidence interval, CI, 33.9–63.8%); a complete response was observed in 1 and partial response in 20 patients (table 2). The median duration of the response was 39.2 weeks (range 5–147 weeks). The median survival time was 47 weeks (95% CI, 6–152 weeks) and the 1-year survival rate was 47% (fig. 1). Two patients are still alive.

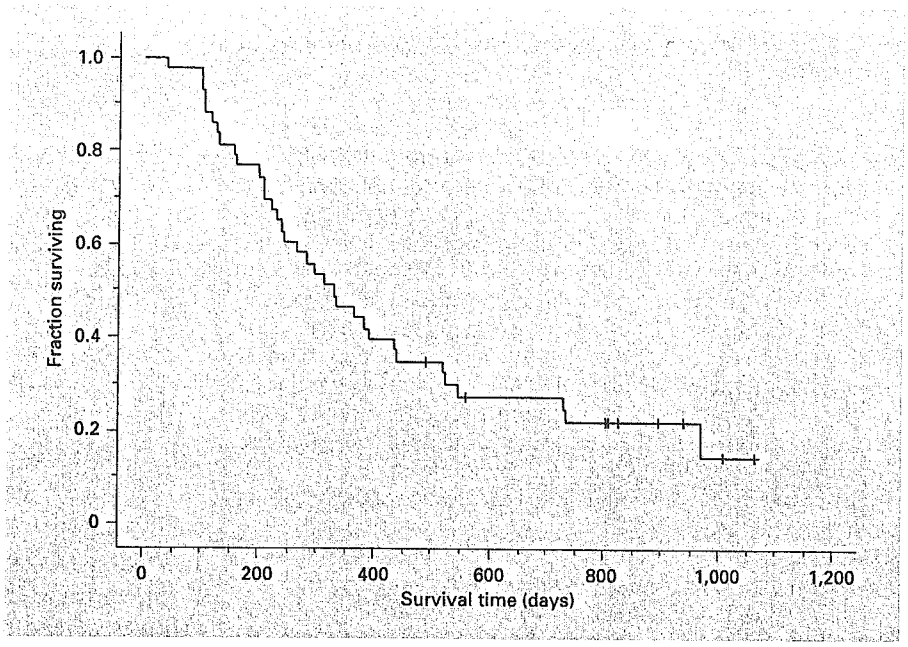

Fig. 1. Kaplan-Meier estimated overall survival curves. Median survival time was 47 weeks; 1-year survival rate was 47%.

Table 2. Chemotherapeutic evaluation (n = 43)

Cycles[1]	2 (1–4)
Response: CR/PR/NC/PD	1/20/20/2
Response rate, %	49
Response duration, weeks	
Average	39.2
Range	5–147
1-year survival rate, %	47

CR = Complete response; PR = partial response; NC = no change; PD = progressive disease.

[1]Value represents average with the range in parentheses.

Table 3. Toxicity (n = 43 patients)

	Maximum toxicity terms of CTC grade					Grade ≥3
	0	1	2	3	4	%
Leukopenia	1	1	6	29	6	81
Neutropenia	1	0	4	13	25	88
Anemia	1	6	18	18	–	42
Thrombocytopenia	25	5	7	6	0	14
Creatinine	23	18	1	1	0	2
SGOT/SGPT	30	12	1	0	0	0
Vomiting	5	7	31	0	–	0
Diarrhea	20	16	7	0	0	0
Alopecia	20	22	1	–	–	
Edema	36	6	1	0	–	0
Neuropathy	40	3	0	0	0	0

Figures represent number of patients. CTC = Common toxicity criteria; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

Toxicity

Table 3 shows the types and grades of toxicities resulting from the treatment, using the common toxicity criteria. All 43 patients could be evaluated for toxic reactions. The major toxicity was myelosuppression. Leukopenia <2,000/mm^3 (grade 3 or 4) was observed in 35 patients (81%), of whom 6 patients showed grade 4. Neutropenia <1,000/mm^3 (grade 3 or 4) was observed in 38 patients (88%), of whom 25 patients showed grade 4. Eight patients developed febrile neutropenia. Thrombocytopenia <5 × 10^4/mm^3 (grade 3 or 4) was observed in 6 patients (14%), and a hemoglobin nadir (grade 3) in 18 patients (42%). There were no episodes of bleeding or fluid overload.

Vomiting grade ≥2 occurred in 31 patients (72%). Diarrhea grade ≥2 was observed in 7 patients (16%). Grade 1 or 2 alopecia and edema were observed in 23 and 7 patients, respectively. In the first cycle, creatinine showed grade ≥2 in 2 patients, resulting in transient rises. In the following cycle, the creatinine level was kept at grade 1 by reducing the dosage of cisplatin. Grade 1 or 2 skin rash was observed in 3 patients. Finally, there were no treatment-related deaths.

Discussion

Cisplatin is one of the key drugs for the treatment of NSCLC. Its high response rate of 40% and safety when it was given alone by continuous infusion over 5 days [14] are confirmed.

Docetaxel is also an active agent to treat NSCLC, and docetaxel of 60 mg/m^2/day (day 1), a recommended dose in Japan, showed a response rate of 19% [7]. Docetaxel has no cross-resistance with cisplatin, and in clinical practice, docetaxel was effective in some patients who were resistant to cisplatin [19]. In addition, additive effects are confirmed between cisplatin and docetaxel, and major side effects of the two drugs are different.

This was a phase II study to determine the usefulness and safety of combination chemotherapy of cisplatin (5-day continuous infusion) and docetaxel for the treatment of advanced NSCLC. The response rate in this study was 49%, which is higher than with docetaxel alone. In comparison with other combination therapies, response rates were 39–42% for cisplatin (bolus) and docetaxel [20, 21], and 58.5% for cisplatin (infusion) and irinotecan with G-CSF. In combination with cisplatin (bolus) and newly developed anticancer agents, the response rates were 44% with paclitaxel [22], 31% with gemcitabine [23], and 26% with vinorelbine [24]. Although these studies differed as regards patients' backgrounds, generally, combination therapies showed better response rates than docetaxel alone.

In our study, side effects predominantly involved hematological toxicity (leukopenia, neutropenia, and anemia). Fever associated with neutropenia was observed in 8 (23%) of 43 patients, and they were treated by administering antibiotics. Hematological toxicities were similar to those in other combination therapies [20, 21]. Nonhematological toxicities were mild, with only 1 patient showing an increased creatinine level of grade 3. The increase was transient, and soon returned to normal. Peripheral edema was observed in only 16%, which was markedly lower than the 24–46% found in other studies [5, 25, 26]. When accumulated doses of docetaxel exceeded 500 mg/m^2, the incidence of edema increased, and at a dose of 85 mg/m^2 or less, eruption was not observed [27]. The dosage was 60 mg/m^2 in our study, and no patients received 500 mg/m^2. There were no side effects concerning hypersensitivity or treatment-related deaths.

We carried out a phase II study of combination treatment of cisplatin (5-day continuous infusion) and docetaxel in 43 patients with NSCLC. The response rate was 49%, and median survival time was 47 weeks. A major side effect was neutropenia. A combination treatment of infusional cisplatin and docetaxel is a tolerable and active regimen for patients with advanced NSCLC. It is to be recommended as a candidate regimen in planning a phase III clinical study in advanced NSCLC, and this regimen will ultimately be evaluated in a phase III clinical study.

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References

1 Dillman RO, Seagren SL, Propert KJ, et al: A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. N Engl J Med 1990;323:940–945.
2 Rapp E, Pater JL, Willan A, et al: Chemotherapy can prolong survival in patients with advanced non-small cell lung cancer – Report of a Canadian multicenter randomized trial. J Clin Oncol 1988;6:633–641.
3 Pronzato P, Landucci M, Vaira A, Bertelli G: Carboplatin and etoposide as outpatient treatment of advanced non-small-cell lung cancer. Chemotherapy 1994;40:144–148.
4 Fossella FV, Lee JS, Murphy WK, et al: Phase II study of docetaxel for recurrent or metastatic non-small-cell lung cancer. J Clin Oncol 1994;12:1238–1244.
5 Francis PA, Rigas JR, Kris MG, et al: Phase II trial of docetaxel in patients with stage III and IV non-small-cell lung cancer. J Clin Oncol 1994;12:1232–1237.
6 Taguchi T, Furuse K, Niitani H, et al: Phase I clinical trial of RP 56976 (docetaxel), a new anticancer drug (in Japanese). Jpn J Cancer Chemother 1994;21:1997–2005.
7 Kunitoh H, Watanabe K, Onoshi T, et al: Phase II trial of docetaxel in previously untreated advanced non-small-cell lung cancer: A Japanese cooperative study. J Clin Oncol 1996; 14:1649–1655.