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Phase II Trial of Amrubicin for Second-Line Treatment of Advanced Non-small Cell Lung Cancer

Results of the West Japan Thoracic Oncology Group Trial (WJTOG0401)

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Background: Amrubicin is a synthetic anthracycline drug that is a potent inhibitor of topoisomerase II. We have performed a multicenter phase II trial to evaluate the efficacy and safety of amrubicin for patients with previously treated non-small cell lung cancer (NSCLC).

Methods: Patients with advanced NSCLC who experienced disease recurrence after one platinum-based chemotherapy regimen were eligible for enrollment in the study. Amrubicin was administered by intravenous injection at a dose of 40 mg/m^2 on 3 consecutive days every 3 weeks.

Results: Sixty-one enrolled patients received a total of 192 treatment cycles (median, 2; range, 1–15). Response was as follows: complete response, 0; partial response, seven (11.5%); stable disease, 20 (32.8%); and progressive disease, 34 (55.7%). Median progression-free survival was 1.8 months, whereas median overall survival was 8.5 months, and the 1-year survival rate was 32%. Hematologic toxicities of grade 3 or 4 included neutropenia (82.0%), leukopenia (73.8%), thrombocytopenia (24.6%), and anemia (27.9%). Febrile neutropenia occurred in 18 patients (29.5%). One treatment-related death due to infection was observed. Nonhematologic toxicities were mild.

Conclusions: Amrubicin is a possible alternative for second-line treatment of advanced NSCLC, although a relevant hematological toxicity is significant, especially with a febrile neutropenia.

Key Words: Amrubicin, Non-small cell lung cancer (NSCLC), Platinum refractory, Second-line chemotherapy.

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Non-small cell lung cancer (NSCLC) is the leading cause of death related to cancer worldwide.[1] The first-line platinum-based chemotherapy confers a moderate improvement in survival and quality of life in individuals with advanced NSCLC.[2,3] It has recently become generally accepted that the second-line chemotherapy also has beneficial effects on survival and quality of life in such patients.[3–5] Despite the availability of several options for the second-line treatment of NSCLC,[6] however, the life expectancy of patients with advanced disease remains short, highlighting the urgent need for new treatments.

Amrubicin is a fully synthetic anthracycline anticancer drug with a similar structure to doxorubicin and is a potent inhibitor of topoisomerase II.[7–9] Two phase II trials of amrubicin administered as a single agent yielded response rates of 18.7 to 27.9% with acceptable toxicities in chemotherapy-naive patients with advanced NSCLC,[10,11] suggestive of promising activity for such patients. However, the activity and safety of amrubicin for patients with NSCLC whose

disease progresses after first-line chemotherapy have not been previously described.

Therefore, we conducted a multicenter phase II trial of amrubicin in patients with NSCLC previously treated with platinum-based chemotherapy. This trial was designed to determine the antitumor activity and toxicity of amrubicin in the second-line setting.

PATIENTS AND METHODS

Patient Selection

The eligibility criteria for participation of subjects in the trial included histologic or cytologic evidence of NSCLC; stage IV or stage IIIB disease (including only patients with no indications for curative thoracic radiotherapy) at study entry; recurrent or refractory disease after one previous platinum-containing chemotherapy regimen; measurable disease; no chemotherapy or radiotherapy within the 4 weeks before study entry; an age of 20 to 74 years; an Eastern Cooperative Oncology Group performance status of 0 or 1; adequate bone marrow function (leukocyte count of $\geq$4000 and $\leq$12,000/mm^3, neutrophil count of $\geq$2000/mm^3, platelet count of $\geq$100,000/mm^3, and hemoglobin content of $\geq$9.5 g/dl); adequate other organ function (serum total bilirubin concentration of $\leq$1.5 mg/dl, serum aspartate aminotransferase and alanine aminotransferase levels of $\leq$2.5 times the upper normal limit, and normal serum creatinine concentration); partial pressure of arterial oxygen of $\geq$60 torr; no abnormality on the electrocardiogram requiring treatment; and a left ventricular ejection fraction of $\geq$60% on echocardiography. Patients were ineligible for participation in the study if they had undergone previous amrubicin therapy, a history of a cumulative doxorubicin dose >500 mg/m^2 (epirubicin >900 mg/m^2, pirarubicin >950 mg/m^2, and daunorubicin >25 mg/kg), symptomatic brain metastasis, third-space fluid collection requiring drainage, active concomitant malignancy, radiographic signs of interstitial pneumonia or pulmonary fibrosis, a serious or uncontrolled concomitant systemic disorder (active infection, active gastric or duodenal ulcer, heart disease, diabetes mellitus, or a condition requiring chronic systemic administration of corticosteroids), or a history of drug allergy, or if they were lactating or pregnant. This study was performed in accordance with the principles of the Declaration of Helsinki and the good clinical practice guidelines. Written informed consent was obtained from all patients before study entry. Trial document approval was obtained from the institutional review board of each participating institution.

Study Design and Sample Size

The study was a multicenter, open-label, single-arm, phase II study. The primary end point was the response rate for amrubicin in patients with recurrent or refractory NSCLC who experienced treatment failure with platinum-based chemotherapy, which determined the sample size based on an optimal two-stage design.[12] On the basis of the results of previous studies, the proposed regimen was to be considered worthy or not worthy for additional investigation in the selected patient population if a true response rate was obtained of $\geq$18 or $\leq$5%, respectively, with a power of 0.9 and an α error of 0.05. A total of 55 assessable patients was necessary for the study; 23 in the first stage and 32 in the second stage. Assuming a drop-out rate of 10%, we planned on enrolling 60 patients in the study.

Treatment

Amrubicin was reconstituted in 20 ml of physiological saline or 5% glucose solution and was administered intravenously for more than 5 minutes at a dose of 40 mg/m^2 per day on days 1 to 3 every 3 weeks. Patients with evidence of disease progression or who experienced unacceptable adverse events were withdrawn from the study. Other criteria for treatment discontinuation included treatment refusal by the patient, inadvertent enrollment in the study, use of excluded concomitant therapy, or a decision by the physician to stop treatment. Subsequent courses of treatment were withheld until the following criteria were satisfied: the leukocyte count was $\geq$3000/mm^3, the neutrophil count was $\geq$1500/mm^3, the platelet count was $\geq$100,000/mm^3, and the grade of any nonhematologic toxicity was $\leq$2. If these criteria were not satisfied within 43 days after the onset of the last treatment, the patient was removed from the study. The dose of amrubicin was reduced to 35 mg/m^2 per day if leukopenia or neutropenia of grade 4 for more than 4 days, febrile neutropenia, thrombocytopenia of grade 4, or nonhematologic toxicity of grade $\geq$3 (or of grade 4 for anorexia, nausea, body weight loss, or hyponatremia) occurred during the previous course. If these toxicities occurred after reduction of the amrubicin dose to 35 mg/m^2 per day, the dose was reduced further to 30 mg/m^2 per day. The third reduction of amrubicin dose was not allowed.

Evaluation

Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors.[13] Tumors were measured by computed tomography within 4 weeks before the first cycle of treatment. The same measurement was performed every 4 weeks from the onset of treatment. A central radiologic review was performed to determine the eligibility of patients and the response to treatment. Response was confirmed at least 4 (for a complete or partial response) or 6 weeks (for stable disease) after it was first documented. Progression-free survival was defined as the time from registration until objective tumor progression or death. Patients whose disease had not progressed at the time of discontinuation of the study treatment were assessed until progression was documented. If a patient died without documentation of disease progression, the patient was considered to have had tumor progression at the time of death, unless there was sufficient documented evidence to conclude otherwise. Overall survival was defined as the time from registration until death from any cause. Progression-free and overall survival and the 1-year survival rate were estimated by the Kaplan-Meier method. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria (version 3). All patients who received one dose of chemotherapy were assessable for toxicity. Clinical and laboratory assessment was performed at least once a week.

RESULTS

Patient Characteristics

Between February 2005 and March 2006, 61 patients were enrolled in the study at 12 participating institutions. All patients were eligible for the study and assessable both for the efficacy and safety of treatment and for survival. The characteristics of the study subjects are summarized in Table 1. Thirty-nine patients were men and 22 were women, and their median age was 63 years, with a range of 51 to 74 years. Histologic analysis revealed that 40 patients (65.6%) had adenocarcinoma, and 14 patients (23.0%) had squamous cell carcinoma. Forty-eight patients (78.7%) had stage IV disease, and the other 13 patients had stage IIIB disease at the time of enrollment in the study. All 61 patients had been previously treated with platinum-based chemotherapy, with eight and 22 patients having also undergone surgery or radiation therapy, respectively, before enrollment in the study.

Treatment Administered

Patients received a median of two cycles of treatment (range, 1–15), with 16 patients (26.2%) receiving at least four cycles. A total of 192 cycles of treatment was delivered overall. The mean relative dose intensity of amrubicin was 87.3%. Dose reduction of amrubicin was necessary according to the study protocol in 22 cycles (11.5% of total cycles). The major reasons for dose reduction were neutropenia or leukopenia of grade 4 (13 cycles of all cycles) and febrile neutropenia (nine cycles of all cycles). Treatment was discontinued in 14 patients after the first cycle and in 17 patients after the second cycle; the reasons for discontinuation included progressive disease (25 patients), toxicity (four patients), and patient refusal (two patients). Poststudy, 71% of patients eventually received subsequent therapies. Twenty-eight patients (46%) received docetaxel-containing chemotherapy, 18 (26%) received gefitinib or erlotinib, and 30 (49%) received other chemotherapy.

TABLE 1. Characteristics of the 61 Eligible Patients

Characteristic	No. of Patients (%)
Median age (yr)	
<70	48 (78.7)
≥70	13 (21.3)
Sex	
Male	39 (63.9)
Female	22 (36.1)
Performance status (ECOG)	
0	15 (24.6)
1	46 (75.4)
Disease stage	
III B	13 (21.3)
IV	48 (78.7)
Tumor histology	
Adenocarcinoma	40 (65.6%)
Squamous cell carcinoma	14 (23.0%)
Large cell carcinoma	3 (4.9)
NSCLC, not specified	4 (6.6)
Prior therapy	
Chemotherapy	61 (100)
Radiotherapy	22 (36.1)
Surgery	8 (13.1)
Time since last chemotherapy	
<3 mo	28 (46.0)
3–6 mo	16 (26.0)
≥6 mo	17 (28.0)
Response to prior chemotherapy	
Complete response	1 (1.6)
Partial response	36 (59.0)
Stable or progressive disease	19 (31.1)
Not evaluable	5 (8.2)

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer.

Response and Survival

Among the 61 assessable patients, there were seven partial responses and no complete responses, for an overall response rate of 11.5% (95% confidence interval [CI], 4.7–22.2) (Table 2). Twenty patients (32.8%) had stable disease, yielding an overall disease control rate (complete response + partial response + stable disease) of 44.3% (95% CI, 31.5–57.6). Thirty-four patients had progressive disease as the best response. No correlation was apparent between the response rate and sex, age, tumor histology, disease stage, or smoking status.

Of the 61 subjects, 11 patients were still alive as of October 2008. The progression-free survival curve is shown in Figure 1; the median progression-free survival was 1.8 months (95% CI, 1.4–2.3). The curve for overall survival is shown in Figure 2; the median overall survival time was 8.5 months (95% CI, 7.7–10.4), and the 1-year survival rate was 32% (95% CI, 20.7–44.0).

Safety

The adverse events observed for all 61 treated patients are summarized in Table 3. The most frequent toxicity was myelosuppression, which mostly affected leukocytes. Neutropenia or leukopenia of grade ≥3 occurred in 82.0% and 73.8% of patients, respectively. Anemia and thrombocytopenia of grade ≥3 were relatively infrequent, occurring in 27.9% and 24.6% of patients, respectively. Eighteen patients (29.5%) developed febrile neutropenia. The most common

TABLE 2. Overall Response Rate for Amrubicin (Response Evaluation Criteria in Solid Tumors) as Determined by Independent Radiological Assessment

Response	No. of Patients
Complete response	0
Partial response	7 (11.5%; 95% CI, 4.7-22.2)
Overall response	7 (11.5%)
Stable disease	20 (32.8%)
Disease control	27 (44.3%; 95% CI, 31.5–57.6)
Progressive disease	34 (55.7%)

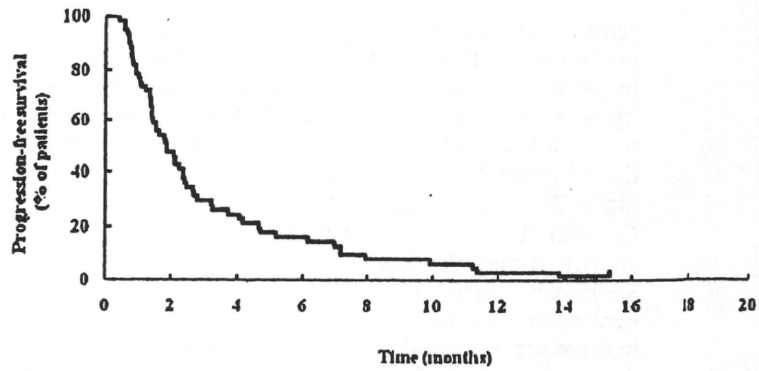

FIGURE 1. Kaplan-Meier analysis of progression-free survival for all 61 treated patients.

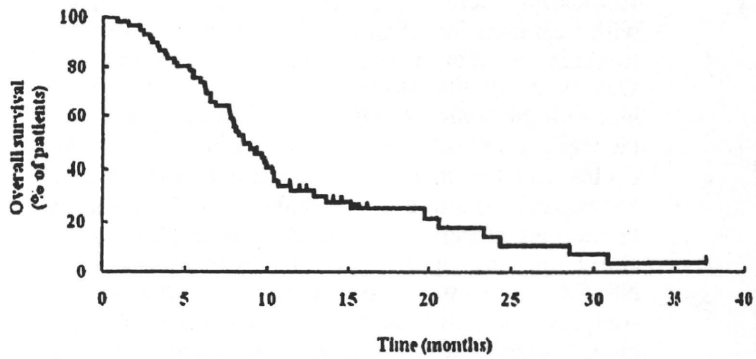

FIGURE 2. Kaplan-Meier analysis of overall survival for all 61 treated patients.

TABLE 3. Toxicity for all 61 Patients During Amrubicin Monotherapy According to the National Cancer Institute Common Toxicity Criteria (Version 3)

	Grade				Grade ≥3	
Toxicity	**1**	**2**	**3**	**4**	**No.**	**Percentage**
Leukopenia	5	8	24	21	45	73.8
Neutropenia	0	5	8	42	50	82.0
Anemia	16	27	13	4	17	27.9
Thrombocytopenia	25	7	7	8	15	24.6
Febrile neutropenia	0	0	18	0	18	29.5
Anorexia	19	9	5	1	6	9.8
Nausea	20	5	2	0	2	3.3
Vomiting	7	3	0	0	0	0
Asthenia	18	13	2	2	4	6.6
Infection	0	1	2	1	4[a]	6.6
Fever	10	6	1	0	1	1.6
Elevation of AST or ALT	15	3	1	3	4	6.6
Pneumonitis	1	0	1	0	1	1.6

[a] Includes one treatment-related death (grade 5).
AST, aspartate aminotransferase; ALT, alanine aminotransferase.

nonhematologic toxicities of grade 3 or 4 were anorexia (9.8%), asthenia (6.6%), an increase in serum alanine aminotransferase and aspartate aminotransferase levels (6.6%), and infection (6.6%), but most nonhematologic toxicities were mild. No cardiac toxicity was observed during the study. Pneumonitis of grade 3 occurred in one patient. One treatment-related death due to sepsis after febrile neutropenia occurred.

DISCUSSION

Amrubicin is a novel, fully synthetic anthracycline agent that is active against both NSCLC and small cell lung cancer (SCLC).[10,11,14–16] No prospective study evaluating the efficacy and safety of amrubicin for previously treated NSCLC has been reported. We have now demonstrated the efficacy of amrubicin monotherapy for patients with NSCLC previously treated with platinum-based chemotherapy, as shown by a response rate of 11.5%, median overall survival of 8.5 months, and 1-year survival rate of 32% in 61 patients. Previous phase III trials for second- or third-line treatment of NSCLC have shown response rates of 7.6 to 9.1%, median overall survival times of 6.7 to 8.3 months, and 1-year survival rates of 29.7 to 34%.[4,5,17–19] Amrubicin is a potent inhibitor of topoisomerase II, with its mechanism of action differing from those of currently available active agents for advanced NSCLC.[7–9] Given the encouraging results from our trial and the unique mode of action of amrubicin, this drug is a good candidate for the development of a new second-line treatment for NSCLC.

Treatment was discontinued in 14 patients after the first cycle and 17 patients after the second cycle. Of these 31 patients, 25 patients were withdrawn because of progressive disease. The study protocol required assessment of antitumor effect by computed tomography every 4 weeks. Such assessment, performed to avoid ineffective therapy, resulted in early discontinuation of treatment due to progressive disease and thereby yielded a median progression-free survival that was slightly shorter than otherwise might have been obtained.

Two recent phase II trials of amrubicin for previously treated SCLC, in which the drug was administered at the

same dose and according to the same schedule as in the present study, found that treatment was associated with a high incidence of bone marrow suppression, although drug toxicity was manageable.[20,21] Consistent with these results, the major adverse events in this study were hematologic toxicities of grade 3 or 4 including neutropenia (82.0%), leukopenia (73.8%), anemia (27.9%), and thrombocytopenia (24.6%). The incidence of these toxicities in this study was similar to that observed previously in the phase II trials for previously treated SCLC. However, the incidence of febrile neutropenia of grade 3 was higher in our study (29.5%) than in these previous trials (5–14%). One possible explanation for this difference is the frequent use of granulocyte colony-stimulating factor for treatment of SCLC, when compared with treatment for NSCLC. The incidents of significant neutropenia and febrile neutropenia were seen primarily in the first cycle. In this study, patients who experienced severe hematologic toxicities were not allowed to receive prophylactically granulocyte colony-stimulating factor in subsequent cycles. One treatment-related death due to sepsis after febrile neutropenia occurred in our study. Therefore, it is important to monitor closely leukocyte and neutrophil counts during amrubicin therapy in patients with previously treated NSCLC. Nonhematologic toxicity was manageable in this study. Another adverse event of particular concern for amrubicin is cardiac toxicity, given that the chemical structure of the drug is similar to that of doxorubicin, whose cardiac toxicity has been experimentally and clinically established. Indeed, cardiac toxicity was detected in previous trials of amrubicin, although its frequency (3.2%) was relatively low.[10,11] For safety reasons, this study allowed the enrollment only of patients with a left ventricular ejection fraction of ≥60% as determined by echocardiography. No cardiac toxicity was observed during our trial, even in the three patients who received more than eight cycles of amrubicin therapy.

In conclusion, in this first reported phase II study of the efficacy and safety of amrubicin monotherapy as a second-line treatment for advanced NSCLC previously treated with platinum-based chemotherapy, we obtained a response rate, overall survival, and 1-year survival rate comparable with those of other second-line treatment regimens. This activity despite a relevant hematological toxicity of amrubicin monotherapy is a possible alternative for second-line treatment of advanced NSCLC. Further evaluation of amrubicin for refractory or relapsed NSCLC in randomized phase III trials is warranted.

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Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial

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Summary

Background Patients with non-small-cell lung cancer harbouring mutations in the epidermal growth factor receptor (*EGFR*) gene respond well to the EGFR-specific tyrosine kinase inhibitor gefitinib. However, whether gefitinib is better than standard platinum doublet chemotherapy in patients selected by EGFR mutation is uncertain.

Methods We did an open label, phase 3 study (WJTOG3405) with recruitment between March 31, 2006, and June 22, 2009, at 36 centres in Japan. 177 chemotherapy-naive patients aged 75 years or younger and diagnosed with stage IIIB/IV non-small-cell lung cancer or postoperative recurrence harbouring *EGFR* mutations (either the exon 19 deletion or L858R point mutation) were randomly assigned, using a minimisation technique, to receive either gefitinib (250 mg/day orally; n=88) or cisplatin (80 mg/m², intravenously) plus docetaxel (60 mg/m², intravenously; n=89), administered every 21 days for three to six cycles. The primary endpoint was progression-free survival. Survival analysis was done with the modified intention-to-treat population. This study is registered with UMIN (University Hospital Medical Information Network in Japan), number 000000539.

Findings Five patients were excluded (two patients were found to have thyroid and colon cancer after randomisation, one patient had an exon 18 mutation, one patient had insufficient consent, and one patient showed acute allergic reaction to docetaxel). Thus, 172 patients (86 in each group) were included in the survival analyses. The gefitinib group had significantly longer progression-free survival compared with the cisplatin plus docetaxel goup, with a median progression-free survival time of 9·2 months (95% CI 8·0–13·9) versus 6·3 months (5·8–7·8; HR 0·489, 95% CI 0·336–0·710, log-rank p<0·0001). Myelosuppression, alopecia, and fatigue were more frequent in the cisplatin plus docetaxel group, but skin toxicity, liver dysfunction, and diarrhoea were more frequent in the gefitinib group. Two patients in the gefitinib group developed interstitial lung disease (incidence 2·3%), one of whom died.

Interpretation Patients with lung cancer who are selected by EGFR mutations have longer progression-free survival if they are treated with gefitinib than if they are treated with cisplatin plus docetaxel.

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Introduction

Lung cancer is a major cause of cancer-related mortality worldwide.[1] However, current standard platinum doublet therapy seems to have reached a therapeutic plateau,[2] although it has recently been shown that patients with non-squamous histology who are treated with pemetrexed disodium have better survival than if they are treated with older drugs.[3]

Targeted therapies are actively being developed to improve efficacy in selected patient populations.[4] Small-molecule tyrosine kinase inhibitors (TKIs) that target the epidermal growth factor receptor (EGFR), such as gefitinib and erlotinib, are the first targeted drugs to enter clinical use for the treatment of lung cancer. Subgroups of patients of east-Asian origin, female sex, adenocarcinoma, and no history of smoking have been shown to be significantly associated with a favourable response to EGFR TKIs.[5,6] In 2004, researchers noted that activating mutations of the *EGFR* gene present predominantly in patients with the above-mentioned clinical characteristics, and determine sensitivity to EGFR TKIs.[7,8] *EGFR* mutations are present in the first four exons of the tyrosine kinase domain of the *EGFR* gene, and about 90% of these *EGFR* mutations are either short in-frame deletions in exon 19, or point mutations that result in a substitution of arginine for leucine at aminoacid 858 (L858R).[7–9] Subsequent retrospective and prospective trials confirmed that the response rate to gefitinib or erlotinib in patients with *EGFR* mutations is about 70–80%.[10–13] Furthermore, patients with *EGFR* mutations have a significantly longer survival than those with wild-type *EGFR* when treated

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with EGFR TKIs.[14,15] We proposed that the absence of any survival advantage conferred by gefitinib monotherapy in previous studies[16–18] is due at least in part to a lack of patient selection, and that gefitinib would confer a survival advantage compared with platinum doublet chemotherapy in a first-line setting if eligible patients were selected on the basis of *EGFR* mutation status. To address this issue, we did a phase 3 trial that compared gefitinib with cisplatin plus docetaxel in patients with an *EGFR* mutation.

Methods

Patients

This study (WJTOG 3405) was a multicentre, randomised, open-label, phase 3, trial of first-line treatment with gefitinib versus cisplatin plus docetaxel for patients with advanced or recurrent non-small-cell lung cancer (NSCLC) harbouring an activating mutation of the *EGFR* gene. We recruited patients between March 31, 2006, and June 22, 2009, at 36 centres in Japan. All centres were members of the West Japan Oncology Group (WJOG), which is a Japanese non-profit organisation for oncological clinical trials (formerly the West Japan Thoracic Oncology Group, or WJTOG).

Initially, only patients with postoperative recurrence were eligible, because these surgical specimens were expected to ensure good sample quality. However, because of the initial slow accrual, the protocol was amended on July 10, 2006, to include patients with stage IIIB/IV disease. Patients were eligible if they had histologically or cytologically confirmed NSCLC, harbouring activating *EGFR* mutations (either exon 19 deletion or L858R in exon 21), were aged 75 years or younger, had WHO performance status 0–1, had measurable or non-measurable disease according to the Response Evaluation Criteria in Solid Tumours (RECIST), and had adequate organ function. Patients with postoperative recurrence, treated with adjuvant therapy other than cisplatin plus docetaxel, were included when the interval between the end of adjuvant chemotherapy and registration exceeded 6 months for platinum-doublet

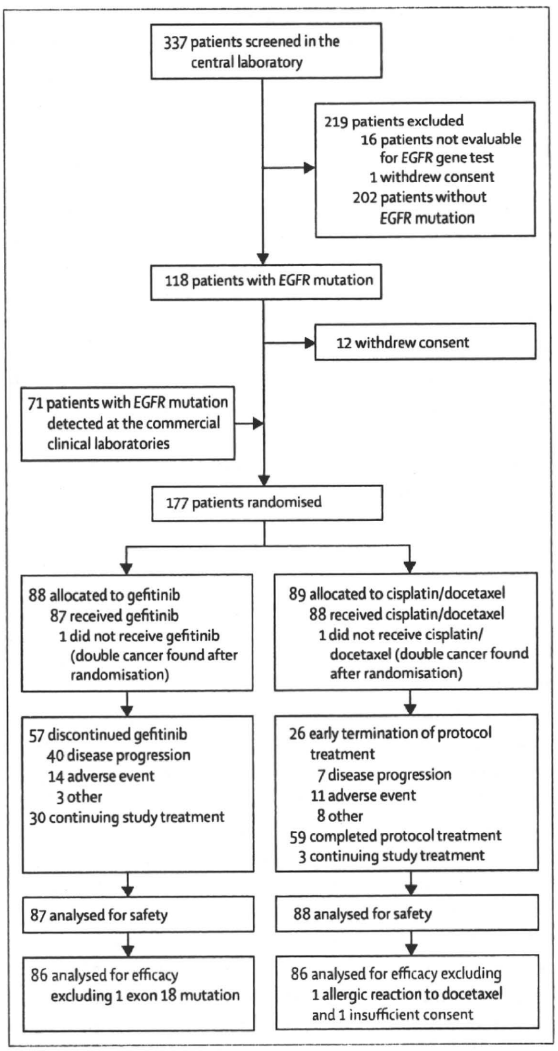

Figure 1: **Trial profile**

	Gefitinib (N=86)	Cisplatin plus docetaxel (N=86)
Sex		
Male	27	26
Female	59	60
Age (years; median; range)	64·0 (34–74)	64·0 (41–75)
Histological type		
Adenocarcinoma	83	84
Adenosquamous carcinoma	0	1
Squamous-cell carcinoma	1	0
Non-small-cell lung cancer; not otherwise specified	2	1
Smoking history		
Never	61	57
Former/current	25	29
Performance status		
0	56	52
1	30	34
Stage		
Postoperative recurrence	35	36
With postoperative adjuvant chemotherapy	19	23
Without postoperative adjuvant chemotherapy	16	13
IIIB	10	9
IV	41	41
EGFR mutation		
Exon 19 deletion	50	37
L858R	36	49

Table 1: **Demographic and baseline characteristics of the modified intention-to-treat population**

therapy and more than 1 month for oral tegafur plus uracil therapy. Patients were not eligible if they had received previous drug therapy that had targeted EGFR, had a history of interstitial lung disease, severe drug allergy, active infection or other serious disease condition, symptomatic brain metastases, poorly controlled pleural effusion, pericardial effusion or ascites necessitating drainage, active double cancer, or severe hypersensitivity to drugs containing polysolvate 80. Patients in pregnancy or lactation, or whose participation in the trial was judged to be inappropriate by the attending doctor, were not eligible. All patients provided written informed consent. Study approval was obtained from independent ethics committees at every institution. The study was undertaken in accordance with the Declaration of Helsinki.

Procedures

Patients were randomly assigned in a 1:1 ratio to receive gefitinib (250 mg/day, administered orally), or docetaxel (60 mg/m², administered intravenously over a 1 h period) followed by cisplatin (80 mg/m², administered intravenously over a 90-min period), with adequate hydration, in cycles of once every 21 days for three to six cycles.Treatment continued until progression of the disease, development of unacceptable toxic effects, a request by the patient to discontinue treatment, serious non-compliance with the protocol, or completion of three to six chemotherapy cycles. Further therapy after progression of the disease was at the physician's discretion. The primary endpoint was progression-free survival. Secondary endpoints included overall survival and response rate. Tertiary endpoints were disease control rate, safety, and mutation-type-specific survival.

Initially, patients were screened for *EGFR* mutation in a central laboratory at the Department of Molecular Diagnostics, Aichi Cancer Centre Hospital, Nagoya, Japan. The exon 19 deletion mutation was screened by fragment analysis and the L858R point mutation was screened by the Cycleave method, as described previously,[19] followed by confirmation by direct sequencing. On Feb 16, 2008, the protocol was amended to allow outsourcing of *EGFR* genetic testing from each institution to commercial clinical laboratories, either at SRL in Tokyo (direct sequencing), Mitsubishi Chemical Medience in Tokyo (peptide nucleic acid-locked nucleic acid PCR clamp[20]), or BML in Tokyo (PCR invader[21]), as this amendment would further facilitate patient accrual. The sensitivity of direct sequencing was anticipated to be less than that of other methods; however, false negativity was not a problem in this trial, since patients judged to lack EGFR mutations were not randomly allocated to a treatment.

Progression-free survival was assessed from the date of randomisation to the earliest sign of disease progression as determined by CT or MRI imaging using RECIST criteria, or death from any cause. Overall survival was assessed from the date of randomisation until death from any cause. Tumour response was assessed every 2 months

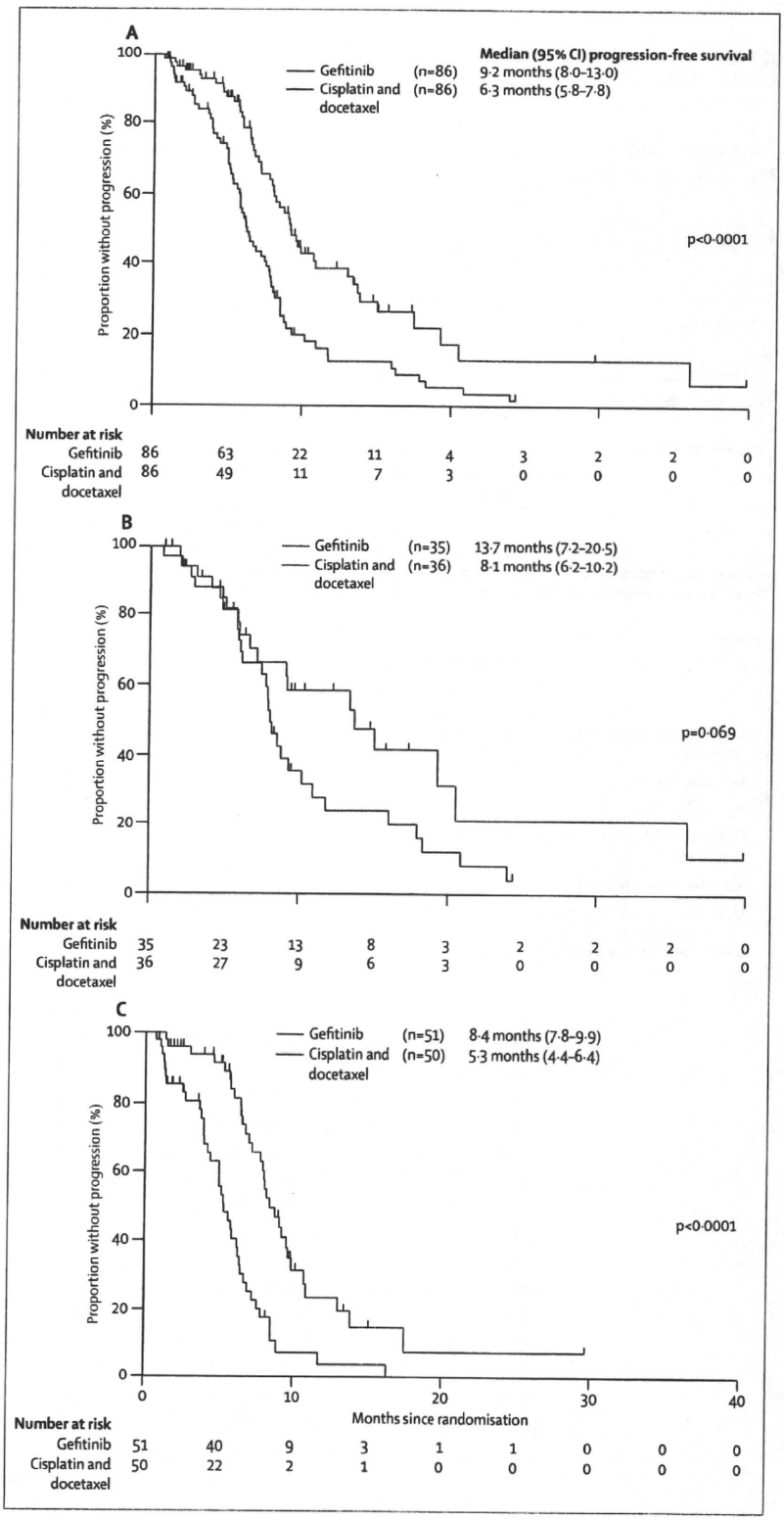

Figure 2: **Progression-free survival in the overall population (A), in patients with postoperative recurrence (B), and in patients with stage IIIB/IV disease (C)**

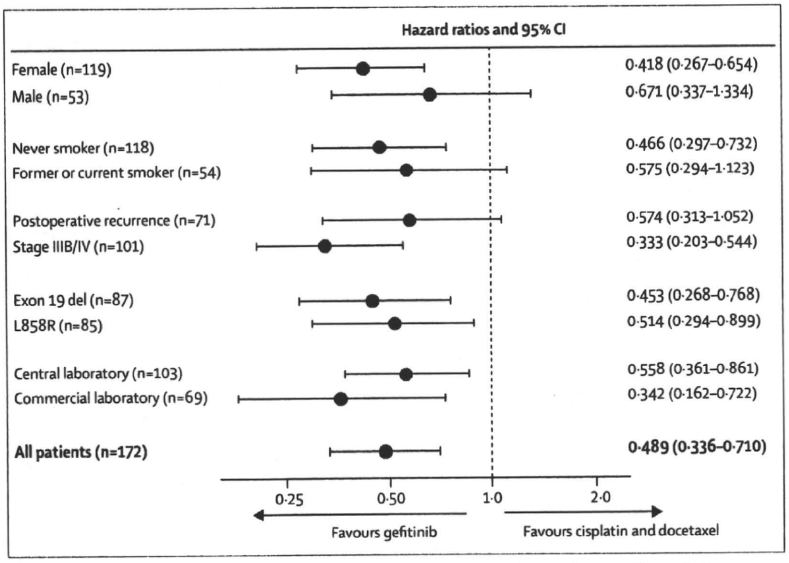

Figure 3: **Hazard ratios for progression-free survival using subgroup analysis in the overall population**
The shaded band represents the 95% CI of the hazard ratio for the overall population of patients.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Group (gefitinib/cisplatin plus docetaxel)	0·489 (0·336–0·710)	0·0002	0·258 (0·385–0·575)	<0·0001
Sex (male/female)	0·935 (0·625–1·398)	0·742	0·628 (0·361–1·092)	0·099
Age (<65 years /≥65 years)	1·091 (0·757–1·572)	0·641	1·183 (0·813–1·721)	0·380
Smoking history (never/former or current)	0·801 (0·541–1·186)	0·268	0·646 (0·378–1·105)	0·111
Stage (recurrence/IIIB–IV)	0·463 (0·220–0·976)	0·043	0·433 (0·290–0·649)	<0·0001
Mutation (exon 19 del/L858R)	1·001 (0·694–1·444)	0·996	1·135 (0·777–1·658)	0·514

Table 2: **Univariate and multivariate analysis of progression-free survival**

during the first year after randomisation, every 3 months between 12 and 18 months, and thereafter the interval of assessment was at the physician's discretion. Safety and tolerability were assessed according to National Cancer Institute Common Terminology Criteria (CTC) for Adverse Events, version 3.0. All events were confirmed via source-document verification at site visits to each participating institution by members of the WJOG data centre and the investigators.

Randomisation and masking

The investigator provided the necessary information to personnel at the WJOG data centre by fax. After an eligibility check, patients were allocated at the WJOG data centre to each treatment group using a desktop computer programmed for the minimisation method.[22] In this way, patient allocation was concealed from the investigator.

Because of the nature of treatment in each group, the study was open label. Stratification factors were: institution; postoperative adjuvant chemotherapy (presence *vs* absence); interval between surgery and recurrence (≥1 *vs* <1 year) for patients with postoperative recurrent disease; and institution; stage (IIIB *vs* IV); and sex (male *vs* female) for patients with stage IIIB/IV disease.

Statistical analysis

In previous studies the progression-free survival of patients harbouring EGFR mutations and treated with gefitinib was reported as 12·6 months,[15] compared with 6·6 months for patients harbouring EGFR mutations treated with carboplatin plus paclitaxel.[23] Assuming a progression-free survival for gefitinib and platinum doublet chemotherapy of 12·5 and 7 months, respectively, would yield a hazard ratio (HR) of 0·56. Taking this HR into consideration, 146 patients would be required to achieve 90% power to show superiority with α=0·05 (two-sided). Therefore, sample size was initially set at 200 patients. While this trial was ongoing, the results of the Iressa Pan-Asia Study (IPASS) were presented at the annual meeting of the European Society for Medical Oncology (Stockholm, Sweden, Sept 12–16, 2008), and were later published.[24] Subgroup analysis of patients with EGFR mutations using about a third of the patients showed that the HR of gefitinib compared with carboplatin plus paclitaxel for progression-free survival was 0·48. Similarly, the HR of gefitinib compared with carboplatin plus paclitaxel for progression-free survival in patients with EGFR mutations was 0·36 in the study done by the North East Japan (NEJ) 002 Gefitinib Study Group, which was presented at the annual meeting of the American Society of Clinical Oncology (Orlando, FL, USA, May 29–June 2, 2009).[25] NEJ 002 was a phase 3 trial that analysed 198 patients with EGFR mutation randomised either to gefitinib or carboplatin plus paclitaxel. 177 patients had been randomised in our trial as of June 13, 2009, and 79 events had been noted during the regular monitoring done in March, 2009. The number of events needed to detect a conservative HR of 0·48 was calculated to be 78, based on normal approximation of the logarithm of the hazard ratio under α=0·05 (two-sided) and 90% power. Therefore, further accrual of patients was considered to be futile and potentially unethical. Although interim analysis was originally planned to analyse progression-free survival, this analysis was not done. Instead, the steering committee held on June 13, 2009, proposed the amendment of the sample size and the final analyses be done using available data. This proposal was approved by the independent data and safety monitoring committee on Aug 28, 2009. The data were locked on June 30, 2009. Patient follow-up for safety and survival will continue until 1·5 years after the last patient entry, as originally described in the study protocol.

Progression-free and overall survival were analysed for the modified intention-to-treat population as defined previously.[26] They were analysed using the Kaplan-Meier method, and were compared using the log-rank test. Hazard ratios in the overall population and in patient

subsets were calculated using the Cox proportional hazards model. The χ^2 test was used to compare proportions. Differences were considered significant at a two-sided p value of 0·05 or less. All statistical analyses were done with SAS version 9.1. This study is registered with UMIN (University Hospital Medical Information Network in Japan), number 000000539.

Role of the funding source

There was no sole study sponsor for this trial. The WJOG designed and did the trial independently of any pharmaceutical company. The report was written by the corresponding author, who had unrestricted access to the study data and is responsible for the accuracy and completeness of the reported analyses. The corresponding author had final responsibility for the decision to submit for publication.

Results

118 patients were positive for EGFR mutation at the central laboratory, 106 of whom were randomly allocated a treatment together with 71 patients with EGFR mutations who were tested at the commercial laboratories, giving a modified intention-to-treat population of 172 patients (figure 1). Baseline characteristics were well balanced between the two treatment groups (table 1), with the exception that the gefitinib group had an excess of exon 19 deletion mutations (50 of 86; 58·1%) compared with the cisplatin plus docetaxel group (37 of 86; 43·0%). Most of the patients had adenocarcinoma. 71 of 172 (41·3%) patients had postoperative recurrent disease, and 54 of 172 (31·4%) of the patients had a history of smoking. At the data collection cut-off time, the median follow-up was 81 days (range 74–1253 days), the median exposure to gefitinib was 165 days (range 22–1100 days), and the median number of cycles of cisplatin plus docetaxel chemotherapy was four, or 64 days (range one to six cycles, or 1–106 days).

Median progression-free survival was 9·2 months (95% CI 8·0–13·9) in the gefitinib group and 6·3 months (5·8–7·8) in the cisplatin plus docetaxel group (p<0·0001; figure 2A). Gefitinib treatment resulted in significantly longer progression-free survival than cisplatin plus docetaxel (HR 0·489; 95% CI 0·336–0·710; p<0·0001). Progression-free survival can be affected by the schedule of clinic visits and the interpretation of evidence of disease progression. We were able to confirm that the time schedule for clinic visits was almost the same in the two treatment groups (data not shown). In our trial, 71 patients had postoperative recurrent disease, and the remaining 101 patients had stage IIIB/IV disease. In both patient subsets, progression-free survival in the gefitinib group was longer than that in the cisplatin plus docetaxel group (figure 2B, 2C), although this was not a pre-specified analysis and was non-significant for those patients with postoperative recurrence. We noted that curves for each treatment group in the postoperative recurrence subgroup (figure 2B) overlapped during the first 6 months, while the separation was clear during this time in the stage IIIB/IV group (figure 2C).

Patients treated with gefitinib had better progression-free survival than patients treated with cisplatin plus docetaxel in all subgroup analyses (figure 3). Additionally, gefitinib was better than cisplatin plus docetaxel, irrespective of where EGFR genetic testing was done. Exploratory analyses for progression-free survival showed that, in addition to the treatment group, patients with postoperative recurrent disease had a significantly better prognosis than those with stage IIIB/IV disease (table 2). We did a pre-planned comparison of exon 19 deletion with L858R in each treatment group. As shown in figure 4, mutation type was not prognostic. Therefore,

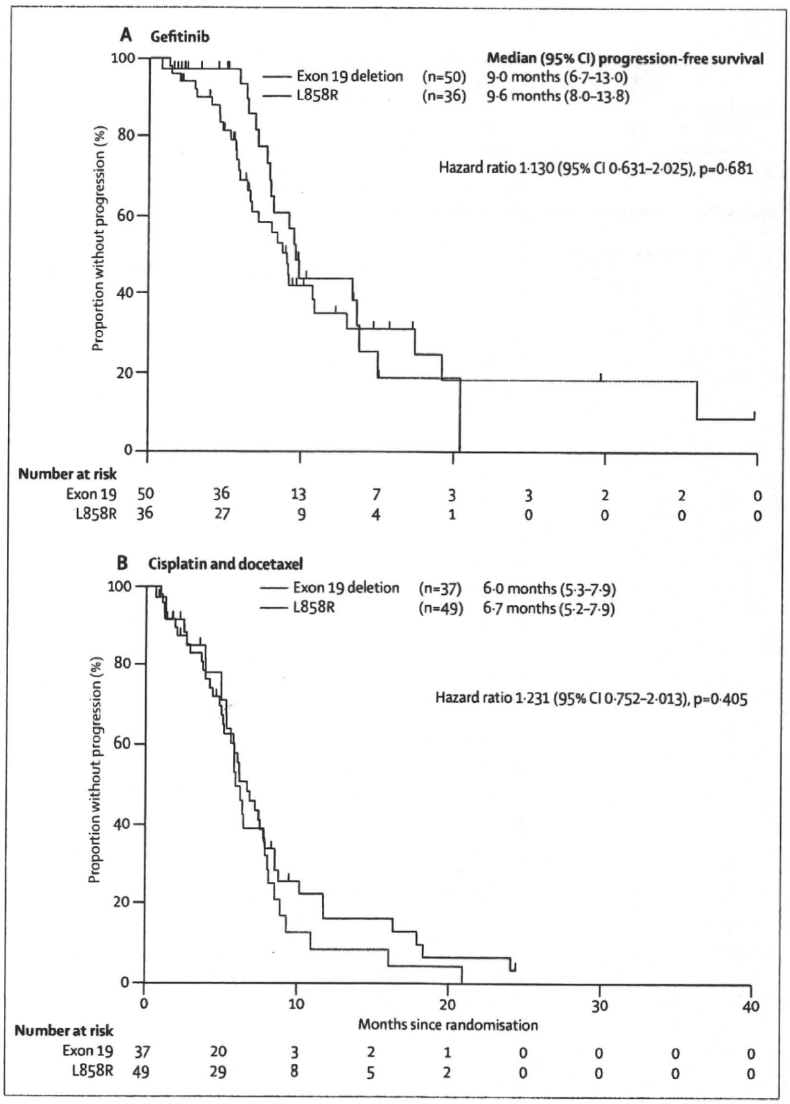

Figure 4: **Progression-free survival in (A) the gefitinib group and (B) the cisplatin plus docetaxel group according to type of the EGFR mutation**

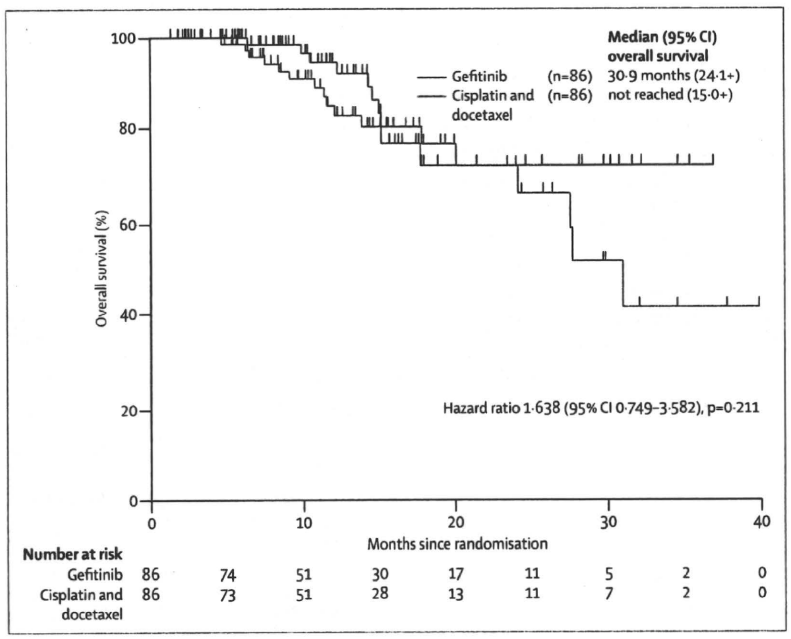

Figure 5: **Overall survival in the overall population**

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	Gefitinib (n=87)		Cisplatin plus docetaxel (n=88)	
	All	CTC grade ≥3	All	CTC grade ≥3
Non-haematological toxicity				
Rash*	74	2	7	0
AST*	61	14	17	1
ALT*	61	24	35	2
Dry skin*	47	0	3	0
Diarrhoea	47	1	35	0
Fatigue*	34	2	73	2
Paronychia*	28	1	1	0
Stomatitis	19	0	13	0
Nausea*	15	1	83	3
Constipation*	14	0	39	0
Alopecia*	8	0	67	0
Sensory disturbance*	7	1	23	0
Haematological toxicity				
Leucocytopenia*	13	0	82	43
Thrombocytopenia*	12	0	29	0
Neutropenia*	7	0	81	74
Anaemia*	33	0	79	15

ALT=alanine aminotransferase. AST=aspartate aminotransferase. CTC=National Cancer Institute Common Terminology Criteria. *p<0·001.

Table 3: **Adverse events occurring in more than 10% of either of the treatment groups listed according to incidence in the gefitinib group**

imbalance of mutation types was not likely to affect the interpretation of the overall results.

The objective response rate in the overall population with measurable disease (n=117) was 62·1% (36 of 58 patients) in the gefitinib group and 32·2% (19 of 59 patients) in the cisplatin plus docetaxel group (p<0·0001). The difference was significant (29·9%, 95% CI 12·6–47·1%; p<0·0001). The disease control rate was also higher in the gefitinib group (54/58, 93·1%) than in the cisplatin plus docetaxel group (46/59, 78·0%; difference in disease control rate 15·1%, 95% CI 2·7–27·6, p=0·020; webappendix). Because of frequent and detailed postoperative follow-up, which is standard practice in Japan, only 28 of 71 patients were found to have recurrent disease that met criteria for RECIST—ie, greater than 1 cm in the largest diameter. At the data cut-off, only 27 patients (15·7%) had died. Therefore, data for overall survival were immature, with follow-up still ongoing; 17 events (deaths) in the gefitinib group versus 10 events in the chemotherapy group—with an HR for gefitinib of 1·638 (95% CI, 0·75–3·58; figure 5). 51 patients in the chemotherapy group received an EGFR-TKI after they completed the study; 17 patients in the gefitinib group received post-protocol platinum doublet chemotherapy.

Adverse events occurring in more than 10% of either of the treatment groups are listed (table 3). The most common adverse event in the gefitinib group was skin rash followed by liver dysfunction, dry skin, and diarrhoea. However, adverse events with CTC grade 3 or more were infrequent, with the exception of liver dysfunction. By contrast, the most common adverse events in the cisplatin plus docetaxel group, which occurred in more than half of patients, were nausea, myelosuppression, fatigue, and alopecia.

Other potentially treatment-related toxicities included allergic reaction (one in gefitinib group, four in cisplatin plus docetaxel group) and oedema (one in gefitinib group, seven in the cisplatin plus docetaxel group). Two patients in the gefitinib group developed interstitial lung disease. There was one treatment-related death in the gefitinib group due to interstitial lung disease; there were no deaths in the cisplatin plus docetaxel group. There were no other serious adverse events.

Discussion

Our results show that first-line treatment with gefitinib conferred longer progression-free survival than treatment with cisplatin plus docetaxel in a molecularly defined (ie, EGFR mutation positive) group of patients with NSCLC.

In the IPASS study for patients with lung adenocarcinoma with no or former light smoking history, the progression-free survival of patients treated with gefitinib was significantly longer.[25] However, the curves crossed at the 6-month timepoint (initially chemotherapy was better, while gefitinib was better later). Molecular analysis for about a third of the patients suggested that the benefit of gefitinib was limited to patients with EGFR mutations with an HR of 0·48 (95% CI 0·36–0·64) and that gefitinib treatment was detrimental for patients without mutations (HR 2·85).[25] This result might seem similar to ours; however, the primary objective of the IPASS study was to assess gefitinib treatment in clinically selected patients,

	Patient group	N	Median progression-free survival (months)			Median overall survival (months)	
			Gefitinib	Chemotherapy	HR (95% CI)	Gefitinib	Chemotherapy
Non-randomised pooled analysis							
I-CAMP[11]	Japanese, *EGFR* mutation	148	10·7	6·0	0·35 (0·23–0·52)	27·7	25·7
Subset analyses of the phase 3 trials for patients selected according to clinical backgrounds							
IPASS[25]	East Asian, light-non-smoker, adenocarcinoma	261	9·5	6·3	0·48 (0·36–0·64)	~20	~20
First SIGNAL[33]	Korean, non-smoker, adenocarcinoma	42	8·4	6·7	0·61 (0·31–1·22)	30·6	26·5
Phase 3 trials of patients selected according to *EGFR* mutation status							
NEJ 002[26]	Japanese, *EGFR* mutation	194	10·4	5·5	0·357(0·252–0·507)	28·0	23·6
WJTOG3405	Japanese, *EGFR* mutation	172	9·2	6·3	0·489 (0·336–0·710)	..	..

Table 4: Recent clinical trials assessing EGFR mutations as predictors of efficacy of gefitinib compared with chemotherapy

and not in molecularly selected patients, as was the case in our trial. In this context, a HR of 0·36 (95% CI 0·25–0·51)[26] for gefitinib compared with carboplatin plus paclitaxel in patients selected by EGFR mutation is highly relevant. Furthermore, our pooled analyses based on individual patient data from seven Japanese phase 2 studies that assessed prospectively the efficacy of gefitinib for patients with EGFR mutations (I-CAMP study)[11] and the pooled analysis of 1006 patients enrolled in a phase 3 trial of gefitinib[27] also showed similar progression-free survival of about 10 months for patients harbouring an EGFR mutation who were treated with gefitinb, while the median progression-free survival of patients treated with chemotherapy was 6·0 months (table 4).[11] These results strongly suggest that the presence of EGFR mutations, and not the clinical background of patients, determines clinical efficacy, and this knowledge should lead to molecularly based, personalised treatment of lung cancer.

Since the median duration of each treatment was quite different (165 days for gefitinib compared with 64 days for chemotherapy), one interpretation might be that a maintenance effect of gefitinib therapy contributed to the positive progression-free survival outcome, at least in part. Indeed, the progression-free survival curves of both groups in IPASS were initially similar, and then separate at about the time that chemotherapy stops. However, this was not the case in our trial, especially in patients with stage IIIB/IV disease. Furthermore, the SATURN[28] and the FAST-ACT[29] trials that tested maintenance erlotinib after chemotherapy showed that progression-free survival (both trials) and overall survival (SATURN) was prolonged. The benefit was much greater in patients with an *EGFR* mutation than in those without it in the SATURN trial.[28]

According to analyses of five US and European clinical trials that assessed first-line TKI treatment,[12] patients with the exon 19 deletion have a significantly longer progression-free and overall survival than patients with L858R (30·8 *vs* 14·8 months; p<0·0001). A similar trend was shown in a recent Spanish study.[13] In IPASS, the HR for progression-free survival for gefitinib versus chemotherapy was 0·38 (95% CI 0·25–0·56) in the subgroup of patients with exon 19 deletions, and 0·55 (95% CI 0·35–0·87) in the L858R mutation subgroup, although a direct comparison between exon 19 deletion and L858R in the gefitinib group was not done.[30] However, recent Japanese trials, including I-CAMP[11] and this study, did not detect any difference. The reason for this discrepancy is not clear, although it might be attributable to ethnic differences or difference of EGFR-TKI used between study populations.

Two patients in the gefitinib group (2·3%) developed interstitial lung disease, one of whom died. This incidence was low compared with previous Japanese reports of 4·0% (59/1482)[31] and 3·5% (70/1976).[32] Selecting patients according to EGFR mutation status is expected to reduce the risk of interstitial lung disease, because risk factors for interstitial lung disease include smoking, male sex, and squamous histology, all of which are negative predictors of the presence of EGFR mutations.[31,32]

Our study indicates that EGFR genetic testing is feasible and should be done when possible. Although patients without EGFR mutations were not included in our study, potential harm of first-line gefitinib therapy compared with chemotherapy for patients without EGFR mutation shown in the IPASS[25] and the First-SIGNAL[33] study indicate the necessity of patient selection by EGFR mutation.

Clinical background might help identify patients who have a higher chance of carrying EGFR mutations. However, it should be noted that in a previous study,[9] eight of 37 (22%) patients with lung adenocarcinoma with a history of heavy smoking (>50 pack-years) harboured EGFR mutations.[9]

In conclusion, gefitinib significantly prolonged the progression-free survival of patients with NSCLC who carry EGFR mutations compared with cisplatin plus docetaxel. It is not yet known whether the prolonged progression-free survival conferred by gefitinib will translate into prolonged overall survival; we will continue to carefully follow-up our patients to determine its long-term effects. Considering the efficacy and toxicity of gefitinib, it is a reasonable option for the first-line treatment of patients with activating EGFR mutations.

Contributors

TM, SM, SN, TS, MS, NK, and KN were involved in the conception and design of the study. KN and MF supervised the study. TM, IO, TS, MS, HT, TH, KA, NK, MT, HY, KS, SK, ES, HS, and ST were involved in the

provision of study material, patients, and data acquisition. TM, SM, YY, SN, IO, JT, TH, NK, MT, HY, KS, ES, HS, ST, and KN were involved in data analysis and interpretation. SM was in charge of the statistical design of the study. YY was in charge of *EGFR* gene testing at the central laboratory. All authors were involved in writing the report and approved the final version.

Conflicts of interest

TM has received lecture fees from AstraZeneca, Chugai, and Boehringer-Ingelheim. SN has received honoraria from AstraZeneca and Sanofi-Aventis. MS has received honoraria from AstraZeneca. HT has received honoraria from AstraZeneca and Sanofi-Aventis. ST has received honoraria from AstraZeneca and Chugai. KN has received lecture fees from AstraZeneca, Chugai, and Boehringer-Ingelheim. MF has received lecture fees from AstraZeneca, Chugai, and Boehringer-Ingelheim. All other authors declared that they have no conflicts of interest.

Acknowledgments

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Randomized Phase II Study of Two Different Schedules of Gemcitabine and Oral S-1 in Chemo-naïve Patients with Advanced Non-small Cell Lung Cancer

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Introduction: This study was conducted to evaluate the efficacy and safety and to compare dosing schedules of gemcitabine combined with S-1 in chemo-naïve non-small cell lung cancer patients.

Methods: Patients with chemo-naïve stage IIIB/IV non-small cell lung cancer were randomized into two treatment arms. Patients were given oral S-1 (60 mg/m^2/d, twice a day) from days 1 to 14 with gemcitabine (1000 mg/m^2/d) on days 1 and 8 (arm A) or on days 8 and 15 (arm B). This cycle was repeated every 21 days.

Results: A total of 80 patients were entered in this trial. The primary end point of this study was response rate. The response rates of arm A and arm B were 22.0 and 28.9%, respectively (p = 0.606). Median time to treatment failure in arm A was 3.6 months and 4.8 months in arm B. Median time to progression in arm A was 4.1 months and 5.5 months in arm B. Median survival time in arm A and arm B was 15.5 months and 18.8 months, respectively. The toxicity profile was relatively mild and did not differ very much between two arms.

Conclusion: The combination of gemcitabine and S-1 was determined to be feasible and effective for advanced non-small cell lung cancer. We selected arm B for further studies because of its higher response rate and survival data.

Key Words: S-1, Gemcitabine, Non-small cell lung cancer (NSCLC), Phase II study, Dosing schedule.

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Lung cancer is one of the leading causes of cancer-related mortality worldwide. Patients suffering from non-small cell lung cancer (NSCLC) mainly presented an advanced stage of the disease at diagnosis.[1] Standard chemotherapy for favorable patients with advanced NSCLC is the platinum-based doublet regimen.[2] Considering the toxicities of cisplatin-based chemotherapy and the poor prognosis of advanced NSCLC, explorations of active and less toxic substitutable combinations that include new, active compounds with novel mechanisms of action are urged.

Gemcitabine (GEM), a deoxycytidine analog structurally resembling cytosine arabinoside (Ara-C), has been shown to have a high antitumor activity and favorable toxicity profile.[3] Monotherapy of GEM has demonstrated significant improvement of symptoms,[4] and the combination of platinum and GEM has shown the best progression-free survival outcome of any platinum regimen in advanced NSCLC in meta-analysis to date.[5]

S-1 is a novel oral derivative of the 5-fluorouracil (5-FU) prodrug to which tegafur was combined with two modulators.[6] One of the modulator is gimeracil, which increase concentrations of 5-FU in blood, and the other is oteracil potassium, which reduce gastrointestinal toxicity. S-1 has shown its antitumor activities with relatively mild adverse effects in a variety of solid tumors. A phase II study in Japan showed 22% of response rate (RR) and median survival time (MST) with 10.2 months for monotherapy.[7] Moreover, RR of 47% and MST of 11 months have been reported in a combination with cisplatin,[8] contributing to use in Japan on NSCLC.

The combination of GEM and 5-FU demonstrates a marked synergistic cytotoxic effect in a sequence-dependent manner in the in vitro assay.[9] It has also shown a significant increase in hENT1, a major modulator of cellular uptake of GEM, and GEM cellular uptake after S-1 or 5-FU treatment in pancreatic cancer cell lines.[10] Significant tumor growth inhibition has been reported in mice treated with S-1 followed by GEM compared with both untreated and S-1/GEM-treated mice in other schedules.[10] A phase I/II trial using combination therapy with S-1/GEM in advanced pancreatic cancer demonstrated mild toxicity and favorable efficacy at the recommended dose of S-1 (60 mg/m^2 on days 1 to 14) and GEM (1000 mg/m^2 on days 8 and 15).[11] The combination may result in a synergistic effect by sequence-dependent manner. This synergistic effect, however, has some concerns

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about increased toxicity. This study, therefore, was conducted to evaluate the efficacy and safety and to compare dosing schedules of GEM combined with S-1 in chemo-naïve NSCLC patients.

PATIENTS AND METHODS

Eligibility

Patients were considered eligible if they met the following criteria: histologically or cytologically proven NSCLC, stage IIIB disease who were not candidates for thoracic radiation or stage IV disease or postoperative recurrence, naïve to chemotherapy, at least one measurable lesion, age more than 20 years, Eastern Cooperative Oncology Group performance status (PS) of 0 to 1, life expectancy of more than or equal to 3 months, ability to take oral medication, and adequate organ function defined as leukocyte count more than or equal to 4000/mm^3, platelet count more than or equal to 10,000/mm^3, hemoglobin more than or equal to 9.0 g/dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels less than twofold the upper limit of normal, total bilirubin less than 1.5 mg/dl, serum creatinine less than the upper limit of normal or creatinine clearance more than or equal to 60 ml/min, and partial pressure of arterial oxygen more than or equal to 60 torr. Patients were excluded if they had interstitial pneumonia, history of severe allergic reactions to drugs, severe infections or other complications, judged as seriously interfering with this treatment. Symptomatic brain metastasis or active concurrent malignancies were also excluded. All patients provided written informed consent, and the Institutional Review Board for Human Experimentation approved the protocol and conducted in accordance with the Declaration of Helsinki.

Protocol Treatment

Patient were assigned randomly to arm A or B and were stratified by disease stage (stage IIIB versus IV [including postoperative recurrence]), PS (0 versus 1), gender (female versus male), and age (75 $\leq$ versus $<$ 75).

Patients received 60 mg/m^2 S-1 orally twice daily on days 1 to 14. S-1 was available as capsules containing 20 or 25 mg of tegafur, so that patients were treated with the following doses: 60 mg (body surface area [BSA] $<$1.25m,^{2} dividing 40 and 20 mg), 80 mg (1.25 $<$ BSA $<$ 1.50 m^2), and 100 mg (BSA $>$1.50 m^2). GEM was administrated at a dose of 1000 mg/m^2 as a 30-minute intravenous infusion on days 1 and 8 (arm A) or on days 8 and 15 (arm B). Treatment was cycled at 3-week intervals. The scheduled treatment of GEM was delayed for up to 1 week until recovery if a patient presented a leukocyte count less than 2000/mm^3, platelet count less than 75,000/mm^3, AST/ALT more than or equal to 100 IU/liter, T-bilirubin more than or equal to 1.5 mg/dl, and/or other non-hematologic toxicities grade more than or equal to 3. The subsequent cycles were begun if a patient presented a leukocyte count more than or equal to 3000/mm^3, platelet count more than or equal to 100,000/mm^3, AST/ALT less than 100 IU/liter, T-bilirubin less than 1.5 mg/dl, creatinine less than 1.5 mg/dl, and/or other non-hematologic toxicities grade less than or equal to 2. A 2-week delay in initiating the subsequent course was allowed. Otherwise, the patient was withdrawn from the study. Patients were scheduled to receive at least three cycles and up to a maximum of six cycles.

In regard to dose modification of GEM in the subsequent cycles in both arms, if, during the previous course, the patient presented grade 4 leukopenia sustained for more than or equal to 4 days, febrile neutropenia, thrombocytopenia less than or equal to 25,000/mm^3, non-hematologic toxicities grade more than or equal to 3, or cancellation of GEM administration, the dose of GEM was reduced to 800 mg/mm^3. Any patients with non-hematologic toxicities grade more than or equal to 4 or interstitial pneumonia grade more than or equal to 2 were withdrawn from the study. If more than three of the first six patients experienced the following toxicities—grade 4 leukopenia sustained for more than or equal to 4 days, febrile neutropenia, and delay of starting a subsequent course by more than 14 days—then patient recruitment for the treatment group was stopped early.

Response and Toxicity Evaluation

The pretreatment evaluation consisted of complete medical history and physical examination, complete blood count, blood chemistry, blood gas analysis, chest x-ray, electrocardiography, computed tomography (CT) scans of the chest, magnetic resonance imaging or CT scan of the brain, CT scans or ultrasound examination of the abdomen, and bone scintigram. Throughout the treatment period, patients were monitored weekly through physical examination, in which toxic effects, complete blood count, and blood chemistry were recorded. Studies of drug-related toxicities were evaluated according to National Cancer Institute Common Toxicity Criteria (version 3.0) and standard RECIST was used for response evaluation. We obtained CT scans for the evaluation of measurable lesion every 1 to 2 cycles. A confirmatory scan was performed at least 4 weeks after any assessment showing an initial partial response or complete response. After the study treatment, all patients were observed with chest x-ray (every 1 month) and CT scans (every 3 months) until disease progression. An extramural review was conducted to validate staging and responses.

Statistical Methods

This study was designed as a multicenter randomized phase II trial. The primary end point was objective RR. According to the criteria of Simon et al.,[12] the required sample size was established as 40 patients per arm to allow selection of the better treatment with 90% accuracy if absolute RR difference of the better treatment is at least 15% and expected baseline RR, 30%. Secondary end points were treatment completion rate, safety, time to progression (TTP), and overall survival (OS). Randomization was performed centrally using the minimization method of balancing disease stage, PS, gender, age, and institution. Fisher's exact test was used to compare patient characteristics, RR, treatment completion rate, and adverse effects. TTP and OS were estimated using the Kaplan-Meier method and compared between treatment arms using the log-rank test. Two-tailed p values less than 0.05 were considered statistically significant. Statistical

TABLE 1. Patients Characteristics According to Treatment Group

Characteristic	Arm A (n = 41) n	%	Arm B (n = 38) n	%	p
Gender					
Male	22	53.7	23	60.5	0.65
Female	19	46.3	15	39.5	
Age (yr)					
Median	64		65		0.30
75≥	3	7.3	6	15.8	
<75	38	92.7	32	84.2	
Cell type					
Adeno	37	90.2	27	71.1	0.07
SCC	4	9.8	10	26.3	
Others	0	0.0	1	2.6	
Stage					
IIIB	9	22.0	9	23.7	1.00
IV	28	68.3	25	65.8	
Postoperative recurrence	4	9.8	4	10.5	
ECOG PS					
0	13	31.7	8	21.1	0.32
1	28	68.3	30	78.9	

Adeno, adenocarcinoma; SCC, squamous cell carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status.

TABLE 2. Treatment Delivery and Dose Intensity

Measure	Arm A n	%	Arm B n	%	p
No. receiving treatment	41		38		—
No. of cycles (median)	4.0		4.0		—
No. of cycles (range)	1–22		1–15		
No. completing ≥3 cycles	29	70.7	26	68.4	—
Dose reductions (GEM)	2	4.9	2	5.3	1.00
Cycle delayed	25	61.0	29	78.9	0.16
Length of cycles (median, days)	22.3		26.4		<0.0001
Length of cycles (range, days)	21–29		20–35		
Median relative dose intensity					
GEM	0.93		0.80		0.0010
S-1	0.91		0.83		0.0105

GEM, Gemcitabine.

analysis was performed using JMP version 7.0.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Patient Characteristics

Between June 2005 and November 2006, 80 patients were enrolled (41 in arm A and 39 in arm B). One in 39 patients in arm B showed rash before any study treatment and withdrawn from this study. This patient was reassigned to the study after rash was recovered. The patient demographics are summarized in Table 1. In the study population, randomization was well balanced across patient characteristics.

Treatment Delivery

Treatment administration is summarized in Table 2. The median number of cycles of chemotherapy administrated was four in both arms. Three or more cycles were delivered to 70.7 and 71.1% of patients in arm A and B, respectively. Five of the patients were administered more than 6 courses (7 to 22) until progressive disease on their request (3 in arm A, 2 in arm B). More patients in arm B required a delay in the initiating of subsequent cycles because of slow recovery of hematologic toxicities than the patients in arm A. The relative dose intensity (RDI) delivered on an mg/m^2/wk basis of GEM, and S-1 was significantly greater in arm A than in arm B (GEM, p = 0.0010; S-1, p = 0.0105).

Toxicity Results

Hematologic and non-hematologic toxicities are summarized in Table 3. The grade 3 or 4 hematologic toxicities were neutropenia (56%), febrile neutropenia (6%), thrombocytopenia (11%), and anemia (4%). A higher rate of grade 3 or 4 thrombocytopenia was observed in arm B. Grade 3 pneumonitis was observed in 2 patients in arm A, infection in 4 patients in both arms, and mild rash in 42 patients (53.2%), with a similar incidence in both arms.

Efficacy Results

Four of the 79 patients did not undergo response assessment because of a decrease in PS (n = 2), the use of radiation therapy (n = 1), or complication in the form of severe pneumonia (n = 2). Table 4 lists the efficacy data. The RR was 22.0% (95% confidence interval [CI] = 10.6–37.6%) in arm A and 28.9% (95% CI = 15.4–45.9%) in arm B (p = 0.606).

The OS, TTP, and time to treatment failure (TTF) curve for the two treatment arms are shown in Figure 1. Median TTF in arm A was 3.6 months (95% CI = 2.8–5.6) and arm B, 4.8 months (95% CI = 3.8–6.3). Median TTP in arm A was 4.1 months (95% CI = 2.8–5.6) and arm B, 5.5 months (95% CI = 3.8–6.3). MST in arm A was 15.5 months (95% CI = 8.0–23.1) and arm B, 18.8 months (95% CI = 11.7–24.5). The 1-year survival rate was 53.8% (95% CI = 38.4–68.9%) in arm A versus 65.8% (95% CI = 50.7–80.9%) in arm B, and 2-year survival rate was 34.2% (95% CI = 19.6–48.7%) in arm A as opposed to 31.6% (95% CI = 16.8–46.4%) in arm B.

Additional Treatment Provided Poststudy

After the study treatment, 60 patients (75.9%) received chemotherapy. Thirty-six patients were put on a platinum doublet (17 in arm A and 19 in arm B) for 2nd-line chemotherapy. Fifteen patients were put on gefitinib (10 in arm A and 5 in arm B). Four patients were given a 3rd-generation drug (1 in arm A and 3 in arm B), and three were added to

TABLE 3. Adverse Events According to Treatment Group

Toxicity	Arm A (n = 41) All, n (%)	Arm A (n = 41) Grade, ¾ n (%)	Arm B (n = 38) All, n (%)	Arm B (n = 38) Grade, ¾ n (%)	p (Grade 3/4)
Hematologic					
Leukocytes	36 (87.8)	11 (26.8)	33 (86.8)	11 (28.9)	1.00
Neutrophils	40 (97.6)	25 (61.0)	36 (94.7)	19 (50.0)	0.37
Platelets	33 (80.5)	2 (4.9)	33 (86.8)	7 (18.4)	0.08
Hemoglobin	33 (80.5)	1 (2.4)	33 (86.8)	2 (5.3)	0.61
Febrile neutropenia	3 (7.3)	3 (7.3)	2 (5.3)	2 (5.3)	0.61
Non-hematologic					
GOT	14 (34.1)		13 (34.2)		—
GPT	17 (41.5)		20 (52.6)	1 (2.6)	0.48
Bilirubin	9 (22.0)		16 (42.1)		—
Creatinine	2 (4.9)		1 (2.6)		—
Nausea	22 (53.7)	1 (2.4)	19 (50.0)	2 (5.3)	0.61
Anorexia	25 (61.0)	2 (4.9)	24 (63.2)	2 (5.3)	1.00
Diarrhea	9 (22.0)		6 (15.8)		—
Constipation	27 (63.4)	1 (2.4)	23 (60.5)	1 (2.6)	1.00
Fatigue	33 (80.5)	2 (4.9)	32 (84.2)	3 (7.9)	0.67
Infection	7 (17.1)	4 (9.7)	11 (28.9)	4 (10.5)	1.00
Rash	20 (48.8)		22 (57.9)		—
Pneumonitis	3 (7.3)	2 (4.9)			0.49
Stomatitis	3 (7.3)		6 (15.8)		—

Adverse events were graded by National Cancer Institute Toxicity Criteria version 3.0.
GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase.

TABLE 4. Response and Survival According to Treatment Group

Measure	Arm A (n = 41)	Arm B (n = 38)
No. receiving treatment	41	38
No. not assessable	2	2
No. assessable	39	36
Response		
Response rate (%)	22.0	28.9
95% CI (%)	10.6–37.6	15.4–45.9
Complete response (n)	0	1
Partial response (n)	9	10
Stable disease (n)	22	19
Disease control rate (%)	75.6	78.9
Progressive disease (n)	8	6
Time to progression		
Median (mo)	4.1	5.5
95% CI	2.8–5.6	3.8–6.3
Time to treatment failure		
Median (mo)	3.6	4.8
95% CI	2.8–5.6	3.6–6.3
Overall survival		
Median (mo)	15.5	18.8
95% CI	8.0–23.6	11.7–23.9
1-yr survival rate (%)		
Rate	53.7	65.8
95% CI	38.4–68.9	50.7–80.9
2-yr survival rate (%)		
Rate	34.2	31.6
95% CI	19.6–48.7	16.8–46.4

S-1/GEM rechallenge regimen (1 in arm A and 2 in arm B). Most patients (41; 51.9%) ultimately received a platinum doublet in their subsequent poststudy treatment regimens.

DISCUSSION

This study is the first evaluation of the safety and efficacy of combination with a new agent, S-1, with GEM in the population of NSCLC patients. The key goal of this study was to conduct a comparative examination as to which combination schedule could be used in further studies.

Although the RR in both arms were lower than the expected value, given that single agent S-1 produced 22% RR in the previous phase II study,[7] it is still possible that the combination regimen has a synergistic effect. The disease control rate (complete response + partial response + stable disease) of our study ranging between 75 and 79% was favorable and higher by 15 to 20% than that of S-1 monotherapy. The RR in arm B was similar to the RR in platinum doublet arms of two recent Japanese phase III studies (Four-Arm Cooperative Study [FACS][13] and West Japan Thoracic Oncology Group Trial 0203[14]) and an S-1 non-platinum doublet.[15]

Majority of the patients showed rash, which was an adverse effect particularly observed in combination therapy used in this study. It was, however, mild and did not increase its severity with the repeated administrations. We expected the advantage of this non-platinum regimen, S-1 plus GEM, to be the facilitation of favorable maintenance of quality of living because of the low incidence of toxicity in terms of gastrointestinal, renal, and hematological toxicities. Although the S-1 plus GEM combination showed higher rates of

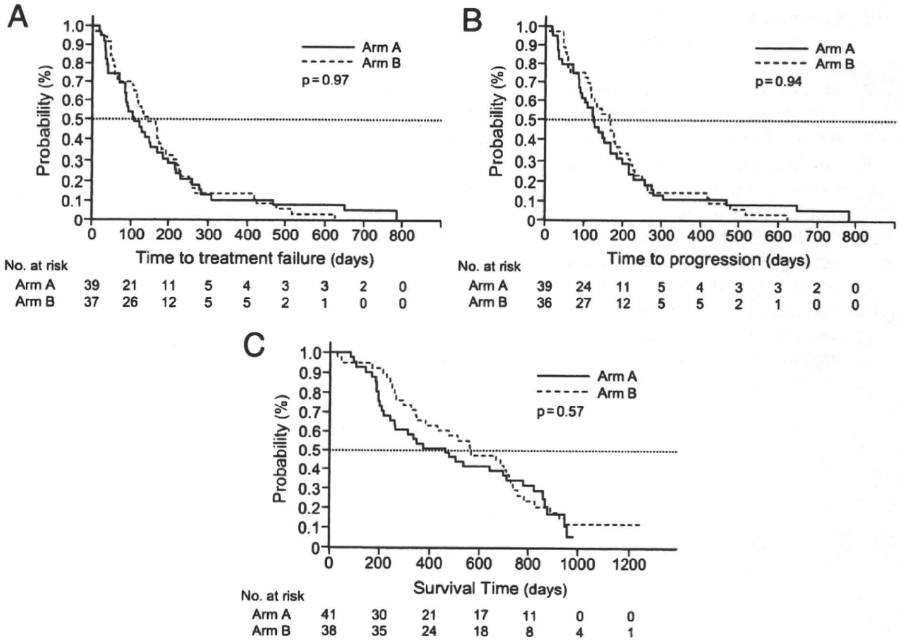

FIGURE 1. Kaplan-Meier curves for time to treatment failure (*A*), time to progression (*B*), and overall survival (*C*). Median follow-up: 1056 days.

leukopenia and neutropenia than S-1 plus cisplatin[8] or S-1 plus irinotecan,[15] the incidence of febrile neutropenia was similar to that of S-1 plus irinotecan[15] and grade 3 or 4 neutropenia, lower than the platinum doublet arms in the FACS[13] and West Japan Thoracic Oncology Group Trial 0203[14] studies. And, incidence of grade 3 or 4 non-hematologic toxicity in terms of diarrhea, anorexia, and fatigue was lower than that reported in the abovementioned studies. Although the incidence of hematologic toxicity appears relatively higher, the toxicity profile indicates that it is a regimen that is easy to continue without adversely affecting the patient's condition. Grade-3 pneumonitis was observed in 2 patients; however, no other severe non-hematologic toxicities were confirmed. There were many cases of delay to initiate the subsequent treatment courses because of prolonged hematologic toxicity in arm B, resulting in a significant decrease in RDI. Regardless of the lower RDI, favorable trends were observed in the arm B efficacy-related end points. Both the depressed RDI and better efficacy in arm B suggest that the preclinical sequence-dependent synergistic effect reported by Nakahira et al.[10] may also be present in the actual clinical setting and may substantiate the relatively favorable efficacy observed with the combination therapy used in our study.

Our study demonstrated relatively favorable TTP and TTF, and very favorable OS. The OS of both arms of this study were superior to the OS observed in each arm in the FACS study. Most patients were followed up with platinum-based doublets 2nd line. This may have led to the favorable OS. The combination therapy used in the study seems to be not very toxic and does not worsen activities of daily living. Thus, this suggests that a major advantage of the therapy is that it allows them to maintain a favorable systemic condition conducive to subsequent therapy in which platinum is combined. Use of less toxic regimens from 1st-line that allow for the continuation of a maintained PS level and effective subsequent treatments may be a treatment option in the future.

Our study showed the S-1/GEM combination therapy not only to be relatively non-toxic but also have a favorable MST of 18.8 months, particularly in arm B. These findings suggest that this combination therapy may be a promising substitute for platinum-based doublet in 1st-line treatment in NSCLC.

In conclusion, the combination of GEM and S-1 was determined to be feasible and effective for advanced NSCLC. We determined the arm B dosing schedule to be a reasonable treatment regimen for future studies because of the better RR, median TTF, and MST.

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