and the added possibility of direct antitumor activity [4, 5]. More recently, there has been accumulating phase III evidence that concomitant chemoradiotherapy probably yields higher response rates and survival in patients with stage III disease [7, 8].

Several novel agents with remarkable radiosensitizing properties have recently been introduced in clinical practice. In preclinical studies the taxanes were found to be potent radiation-enhancers by virtue of their ability to cause cell cycle arrest in the radiosensitive G2/M phase [9, 10]. Preclinical studies further illustrated the taxanes' radiosensitizing effect in tumor-cell lines, with docetaxel exhibiting an effect ten times that of paclitaxel at equimolar concentrations [11]. Four phase I trials of docetaxel and concurrent radiation have been reported [12–15]. Mauer et al. [12] and Koukourakis et al. [14] conducted phase I trials of weekly docetaxel with concurrent thoracic radiotherapy and determined that the maximum-tolerated dose (MTD) of weekly docetaxel was 20–30 mg/m^2 with thoracic radiation. The dose-limiting toxicities (DLTs) were esophagitis and neutropenia. The phase II studies of docetaxel [16, 17] and thoracic radiotherapy have shown an encouraging, high response, but an increased incidence of esophagitis and asthenia was observed.

The use of low daily doses of cisplatin concomitantly with RT seems to be of particular interest, since clear synergism has been demonstrated in vitro [18]. In a European Organization for Research and Treatment of Cancer (EORTC) study, daily administration of cisplatin proved to be more effective than a weekly schedule in potentiating the local tumor control achievable with RT alone, although the difference between the two schedules were not statistically significant [4].

In view of these considerations, we planned this phase I study. The objectives of this study were to determine the MTD, recommended dose (RD) and DLT of cisplatin and docetaxel when given weekly concomitantly with conventional TRT, and evaluate the efficacy of this regimen.

Moreover, since it has reported that serum α-1-acid glycoprotein (AAG) combined with docetaxel extensively [19] and that the AAG levels were significantly associated with time to progression in NSCLC patients and febrile neutropenia [20]. The AAG levels were significantly associated with the toxicity of docetaxel because AAG strongly binds docetaxel in serum. Thus, we examined the relationship between serum AAG level and major toxicities in this regimen.

Patients and methods

Patient eligibility

Previously untreated patients with histologically or cytologically documented inoperable stage IIIA or IIIB NSCLC were eligible for this study. Patients with malignant pleural effusion or any disease that required irradiation of more than half of the hemithorax were ineligible. Other eligibility criteria included: (1) age less than 75, (2) Eastern Cooperative Oncology Group performance status equal to or less than 2, (3) evaluable or measurable disease, (4) no prior therapy, (5) adequate bone marrow function (leukocyte count ≥4,000/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥9.5 g/dl), renal function (serum creatinine ≤ 2.0 mg/dl), hepatic function (AST/ALT ≤ 2.5 times upper limit of normal, serum bilirubin ≤ 1.5 mg/dl), and pulmonary function (arterial blood gases PaO2 ≥70 mmHg), (6) absence of active infection, heart failure, or acute myocardial infarction within 3 months before study entry, no serious medical or psychiatric illness. All patients signed an informed consent form that was approved by each of the institutional review boards. Before entry into the study, all patients underwent an evaluation that consisted of a complete history and physical examination, chest X-ray, chest and upper abdomen (to include the liver and adrenals) computed tomography (CT) scan, brain CT or MRI, and a bone scan.

Chemotherapy

The treatment regimens are outlined in Fig. 1. The study was designed to fix the cisplatin dose at 25 mg/m^2/week and escalate docetaxel dose. The docetaxel and cisplatin administration schedules were: split schedule (SS), 3 out of every 4 weeks (day 1, 8, 15, 29, 36, and 43), continuous schedule (CS), weekly (day 1, 8, 15, 22, 29, 36). Docetaxel was administered as an intravenous (IV) infusion over 30 min and followed by cisplatin given as an IV infusion over 30 min. The participating investigators at each institution were allowed to decide the volume of fluid replacement and the antiemetic therapy to be administered, but adequate amounts of parenteral fluid and diuretics were given in order to prevent the renal toxicity of cisplatin. The patients did not receive steroids due to prevention of a hypersensitivity reaction. The starting dose of docetaxel was 20 mg/m^2/week, and the docetaxel dose was increased by 5 mg/m^2/week. There was no dose escalation in individual patients, and administration of cisplatin and docetaxel was cancelled if the leukocyte count fell below 2,000/mm^3 or any DLTs occurred.

At first, we planed only sequential schedule. However, as we thought that continuous schedule had a stronger radiosensitizing effect compared with sequential schedule, we amended protocol and added continuous schedule. After the MTD and RD of SS had been determined, we treated with CS using the RD of SS.

Thoracic radiation

Thoracic radiation therapy of 60 Gy in 2.0 Gy fractions was given concurrently with weekly docetaxel and

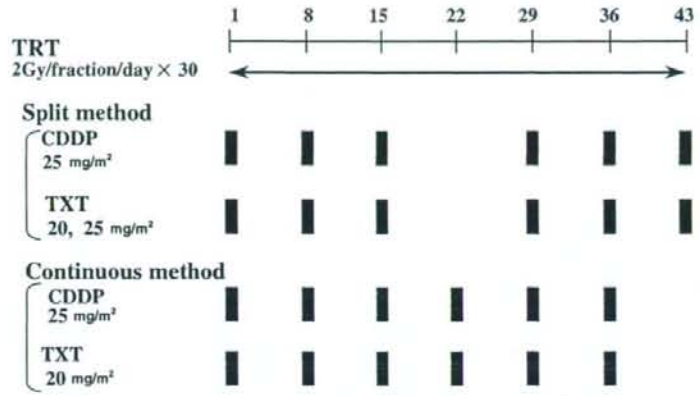

Fig. 1 Treatment regimens for weekly docetaxel and cisplatin concomitant with TRT

cisplatin infusion for 6 weeks. A 6- or 10-MV linear accelerator was used. Two-dimensional treatment planning of TRT was performed by conventional X-ray simulators. Inhomogeneity correction for lung tissues was not done. The initial planning target volume (PTV) consisted of the primary tumor, ipsilateral hilar nodes, and superior mediastinal nodes with 1–1.5 cm margin. If metastasis to supraclavicular nodes were found, they were also included in the initial PTV. This initial large field was treated by parallel-opposed anterior and posterior fields to 40 Gy in 20 fractions. The widths and lengths of the initial fields with appropriate trimming ranged from 10.5 to 16 cm (median; 14 cm) and 10.5–20 cm (median; 16 cm), respectively. After 40 Gy, oblique parallel-opposed fields were used to exclude the spinal cord. The angles of the oblique fields ranged from 15° to 45° with a median of 40°. In the boost fields, the primary tumors and the involved nodes were included with a margin of 0.5–1.5 cm. The total dose to the boost field was 60 Gy in 30 fractions. In the present study, patients were excluded if the initial radiation field exceeded half of the ipsilateral lung. However, no dose constraints on the normal tissues including the percentage of pulmonary volume irradiated to >20 Gy (V20) or esophageal length was determined, as three-dimensional treatment planning using a CT-simulator was not available.

If grade 4 hematologic toxicity occurred during the course of TRT, it was suspended and restarted after recovery to grade 3 or less. If grade 3 or greater esophagitis occurred and the physician decided that the TRT could not be continued, it was suspended and restarted after recovery to grade 2 or less. If PaO_2 fell to 10 torr and a patient had a fever of 38°C or higher, both TRT and chemotherapy were suspended and restarted immediately after recovery.

Definition of MTD, RD and DLT

Maximum-tolerated dose was defined as the dose level at which DLT occurs in more than 50% of the patients treated, and the preceding dose level was defined as RD. At least six patients were entered at each dose level. DLT was defined as grade 4 leukopenia or neutropenia lasting 3 days or more, a platelet count of $\leq 20{,}000/mm^3$, febrile neutropenia and grade 3 or greater non-hematologic toxicities other than nausea and vomiting. Suspension of docetaxel and cisplatin two or more times was also considered as a DLT.

Response evaluation and survival analysis

The criteria for assessing the response to treatment were as follows. Complete response (CR) was defined as total disappearance of all clinically detectable lesions for at least 4 weeks. Partial response (PR) was defined as a reduction of 50% or more in the sum of the products of the cross-sectional diameters of all measurable lesions for at least 4 weeks, without the development of new lesions. Stable disease (SD) was defined as a reduction of less than 50% or an increase of less than 25% in the sum of the products of the cross-sectional diameters of all measurable lesions, with no clear evidence of either regression or progression for at least 6 weeks. Progressive disease (PD) was defined as an increase of 25% or more 25% in the sum of the products of the cross-sectional diameters of all measurable lesions, together with an increase of assessable disease or the appearance of new lesions. Survival time was defined as the interval between the date of the start of treatment and the date of death due to any cause or the most recent follow-up evaluation. The survival curves were estimated by the Kaplan–Meier method.

Statistical analysis

The *T*-test was used to examine the relationship between serum AAG values and the categorical endpoints of major toxicities, such as grade of esophagitis. A *P*-value of 0.05 or less was considered statistically significant.

Results

Patient characteristics

Between April 1999 and April 2000, 21 patients were enrolled in the study, and their characteristics are listed in Table 1. All patients were eligible for evaluation of efficacy, but one who enrolled at a docetaxel dose of 20 mg/m^2/week in SS was excluded from the evaluation of toxicity because chemotherapy was suspended due to exacerbation of a gastric ulcer. That patient experienced no DLT. The 19 men and 2 women enrolled in the study had a median age of 65 (range: 51–75). Most patients had squamous cell carcinoma ($n=16$: 76%) and stage IIIB disease (n=17: 81%). Median performance status was 1 (range: 0–2), while only two patients had a performance status of 2.

Dose escalation

The DLTs encountered at each dose level are listed in Table 2. On the SS, six and seven patients were evaluable for toxicity at docetaxel doses of 20 and 25 mg/m^2/week, respectively. Two of the six patients at the 20 mg/m^2/week dose experienced DLTs consisting of grade 3 esophagitis in one patient and cancellation of chemotherapy twice because of grade 3 leukopenia in the other. At the 25 mg/m^2/week dose, four of the seven patients developed DLTs consisting of grade 3 esophagitis in two patients, grade 3 fatigue in one, and febrile neutropenia in one. Accordingly, the MTD and RD on the SS were concluded to be a dose of docetaxel 25 and 20 mg/m^2/week, respectively. The next cohort of patients was treated with a docetaxel dose of 20 mg/m^2/week in CS. However, four of the seven patients developed DLTs, consisting of grade 3 esophagitis in two patients, grade 3 fatigue in one patient, and cancellation of chemotherapy twice because of grade 3 neutropenia in one patient. Finally, we concluded that the dose level 1 in SS was the recommended dose for further study of this therapy.

Table 1 Patient characteristics

Characteristic	Number of patients
Total number of patients	21
Assessable for toxicity	20
Assessable for survival and response	21
Age, years	
Median (range)	65 (51–75)
Sex	
Male	19
Female	2
Performance status	
0	6
1	13
2	2
Histology	
Squamous cell carcinoma	16
Adenocarcinoma	5
Stage	
IIIA	4
IIIB	17

Toxicity

Hematologic and non-hematologic toxicities are summarized in Table. 3 and 4. Twenty patients could be assessed for toxicities. The hematologic toxicities were mild, and there were no grade 4 hematologic toxicities. Grade 3 neutropenia, decrease in hemoglobin, and thrombocytopenia were observed in 6 patients (30%), 6 patients (30%), and 1 patient (5%), respectively. Febrile neutropenia developed in only one patient, and it occurred at the 25 mg/m^2/week dose of docetaxel.

The principal toxicity on this regimen was esophagitis. Grade 2 or higher esophagitis occurred in 12 of the 20 (60%) patients enrolled, and in 5 cases (25%) it was of grade 3 and caused suspension of treatment in 2 patients and permanent discontinuation of treatment in one patient at 52 Gy. Another dose-limiting non-hematologic toxicity was grade 3 fatigue which occurred in one patient each at 25 mg/m^2/week dose of docetaxel on the SS and at the 20 mg/m^2/week dose of docetaxel on the CS. Other non-hematologic toxicities were mild and never greater than grade 2. Grade 2 nausea and pneumonitis occurred in five patients and two patients, respectively. No hypersensitivity reactions occurred. There were no treatment related deaths.

Treatment delivery

A total of 110 chemotherapy cycles were administered to 20 patients at three dose levels. Ten (9%) of the planned doses were omitted. The ratio of actual dose intensity to planned dose intensity of docetaxel and cisplatin at 20 and 25 mg/m^2/week docetaxel dose levels on the SS and at the 20 mg/m^2/week docetaxel dose level on the CS was 0.95, 0.93, and 0.88, respectively. A TRT dose of 60 Gy was administered to 18 of 20 (90 %) patients. TRT at the 25 mg/m^2/week dose of docetaxel on the SS and the 20 mg/m^2/week of docetaxel on the CS each one patient was discontinued at 58 and 52 Gy, respectively, because of grade 3 esophagitis.

Response and survival

Table 5 shows the responses observed at each dose level. All 21 patients enrolled were evaluable for response. CR was observed in 5 of the 21 (24%) patients, PR in 14 (67%) and SD in 1 (5%). The overall response rate was 90% (95% confidence interval: 69.6–98.8%). No significant differences in response were observed between the three dose levels of docetaxel.

Table 2 Dose limiting toxicity

Dose of docetaxel	Assessable patients	Dose limiting toxicitiy
Split schedule		
20 mg/m^2	6	2 1: Grade 3 esophagitis1: 2 times cancellation of chemotherapy due to grade 3 leukopenia
25 mg/m^2	7	4 2: Grade 3 esophagitis1: Grade 3 fatigue1: Febrile neutropenia
Continuous schedule		
20 mg/m^2	7	4 2: Grade 3 esophagitis1: Grade 3 fatigue1: 2 times cancellation of chemotherapy due to grade 3 neutropenia

Table 3 Hematologic toxicity

Dose level of docetaxel	No. of patients	ANC		Febrile neutropenia	Hb		Platelet	
		Grade			Grade		Grade	
		3	4		2	3	2	3
Split schedule								
20 mg/m^2	6	0	0	0	1	2	0	0
25 mg/m^2	7	2	0	1	3	2	1	1
Continuous schedule								
20 mg/m^2	7	4	0	0	2	2	0	0

ANC absolute neutrophil count, *Hb* hemoglobin

Figure 2 shows the overall survival for all 21 patients enrolled in the study; 16 patients (76%) had died at the time of the analysis. All survivors had a follow-up time of 30 months. Based on the Kaplan–Meier method, the 1-, 2-, and 3-year overall estimated survival rates were 71.4, 42.9, and 32.7%, respectively. The median overall survival time was 23.1 months.

Relationship between esophagitis and plasma AAG levels

The principle toxicity on this regimen was esophagitis. Another DLT, grade 3 fatigue occurred in only two patients, and hematologic toxicity was mild. We, therefore, examined the relationship between plasma AAG levels and grade of esophagitis. Plasma AAG was measured in 12 patients prior to the start of the treatment, and the baseline AAG level of the patients who experienced grade 2 or 3 esophagitis was significantly higher ($P=0.04$) than that of the patients who experienced grade 0 or 1 esophagitis (grade 0/1, mean AAG level = 168 pg/ml vs. grade 2/3, mean AAG level = 83 pg/ml: Fig. 3).

Discussion

We conducted a phase I study of cisplatin and docetaxel administered in weekly infusions concomitant with conventional TRT in patients with unresectable stage IIIA/IIIB NSCLC. This is the first study that examined schedule and dose of weekly docetaxel in combination fixed dose of cisplatin 25 mg/m^2 concomitant with TRT. The recommended dose and schedule were determined to be cisplatin 25 mg/m^2 and docetaxel 20 mg/m^2 on days 1, 8, 15 of every 4 weeks, respectively. Esophagitis and neutropenia were by far the severest toxicities in this

Table 4 Non-hematologic toxicity

Dose level of docetaxel	No. of patients	Esophagitis		Fatigue		Nausea		Pneumonitis	
		Grade		Grade		Grade		Grade	
		2	3	2	3	2	3	2	3
Split schedule									
20 mg/m^2	6	3	1	0	0	2	0	1	0
25 mg/m^2	7	1	2	0	1	1	0	1	0
Continuous schedule									
20 mg/m^2	7	3	2	1	1	2	0	0	0

Table 5 Response at each dose level

Dose level of docetaxel	No. of patients	Response				Response rate
		CR	PR	SD	PD	
Split schedule						
20 mg/m^2	7	2	5	0	0	7/7100%
25 mg/m^2	7	2	5	0	0	7/7100%
Continuous schedule						
20 mg/m^2	7	1	4	1	0	5/771%
Total	21	5	14	1	1	19/2190%

study, while pulmonary toxicity was almost nonexistent. The pulmonary toxicity associated with concurrent chemoradiotherapy using third generation anticancer agents is frequently serious and fatal. When cisplatin and paclitaxel were combined with concurrent TRT, grade 3 or more late lung toxicity in 20%, including grade 5 in 8% was reported [21]. The incidence of grade 3 or more pulmonary toxicity in the studies of cisplatin and docetaxel concomitant with TRT has been low. Grade 3 pneumonitis occurred in 4.8% of patients in the study by Kiura et al. [22], and no grade 3 or more pulmonary toxicity was reported by Wu et al. [23].

Wu et al. [23] conducted a phase I study of weekly docetaxel and cisplatin concomitant with thoracic radiotherapy in stage III NSCLC and reported that the recommended dose was docetaxel 20 mg/m^2 plus cisplatin 20 mg/m^2 weekly. This dose is almost the same as in our study, but the dose intensity of docetaxel at the recommended dose was slightly lower in our study (docetaxel: 14 mg/m^2/week) than in the Wu study (docetaxel: 20 mg/m^2/week). The reason for this difference may be the dose of cisplatin.

Unfortunately, three-dimensional treatment planning and conformal radiotherapy were not available in the present study. Therefore, it was not possible to analyze a relationship between degree and frequency of toxicities and various dose-volume parameters including V20 or the maximum esophageal point dose. The acute toxicities are closely related to the dose-volume parameters of the normal tissues [24–26]. The degree and frequency of toxicities could be reduced by three-dimensional conformal radiation therapy, which can restrict the dose and volume of the normal tissues compared with conventional two-dimensional technique.

The response rate of 90%, median survival time of 23.1 months, and 2-year survival time of 42.9% obtained in our study are very encouraging. One reason for these favorable results may be that the weekly docetaxel and cisplatin not has only radiosensitizing activity but systemic chemotherapeutic activity. Ohe et al. [27] are currently evaluating docetaxel and cisplatin administered in three consecutive weekly infusions as systemic chemotherapy for advanced NSCLC. Thirty-three elderly patients with advanced NSCLC were enrolled in their phase II study of docetaxel 20 mg/m^2 and cisplatin 25 mg/m^2 on days 1, 8, and 15, doses which are similar to the recommended doses and schedule in our study. The overall response rate was 52%, the complete response rate was 6% and the median survival time was 12.4 months. Both response rate and median survival time in their study are promising and the results suggest that a docetaxel dose of 20 mg/m^2/week plus cisplatin dose of 25 mg/m^2/week has an antitumor effect as systemic chemotherapy.

The correlation with AAG was not a primary objective and this was not essential in this study. Thus, we could collect only 12 samples. The baseline AAG

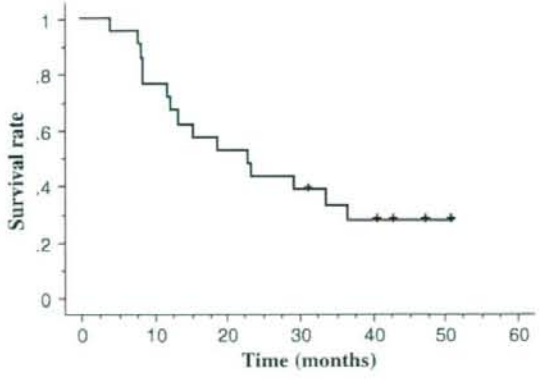

Fig. 2 Overall survival of patients treated with weekly docetaxel and cisplatin concomitant with TRT

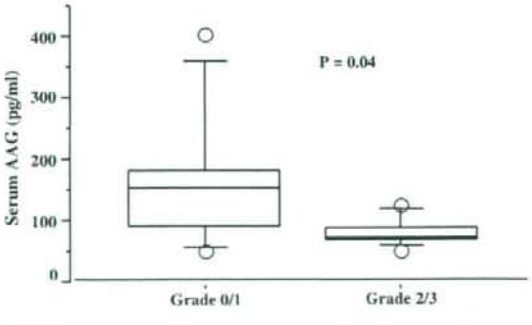

Fig. 3 Relationship between toxicity grade of esophagitis and serum AAG level

levels correlated significantly with the intensity of esophagitis in this study. The plasma AAG level was shown to be a significant predictor of pharmacodynamics in docetaxel treatment of NSCLC by Bruno et al. [20]. Since AAG strongly binds docetaxel, high AAG levels result in a lower free docetaxel fraction, and, therefore, decreased toxicity. The finding that high AAG decreased the grade of esophagitis was not unexpected.

In conclusion, the weekly combination of cisplatin and docetaxel concurrently with TRT is well tolerated and the recommended dose and schedule were determined to be cisplatin 25 mg/m^2 and docetaxel 20 mg/m^2 on days 1, 8, 15 of every 4 weeks, respectively. Because of favorable survival and acceptable toxicity profile, we consider this chemoradiotherapy as a warrant for further evaluation in phase II trials.

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

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ABSTRACT

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

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

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

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

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INTRODUCTION

The discovery that signaling by the epidermal growth factor receptor (EGFR) plays an important role in tumorigenesis prompted efforts to target this receptor in anticancer therapy, leading to the development of inhibitors of its tyrosine kinase activity.[1-3] Gefitinib, an orally active inhibitor of the EGFR tyrosine kinase, is a leading agent in the field of EGFR-targeted therapy.[4,5] Two large phase II trials involving previously treated patients with advanced non–small-cell lung cancer (NSCLC) revealed that gefitinib monotherapy was well tolerated and manifested clinically meaningful antitumor activity.[6,7] Objective responses that were both rapid and persistent were apparent at a dose of 250 mg/d in 12% to 18% of patients; the median survival time was 7 to 8 months, with a 1-year survival rate of 27% to 35%, and the most common adverse effects were rash and diarrhea, which were generally mild. Similar response and survival rates were apparent at a dose of 500 mg/d but were accompanied by a higher frequency of adverse events. Higher response rates were apparent in women, Japanese patients, patients with no history of smoking, and patients with adenocarcinoma.[6-8]

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

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

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

PATIENTS AND METHODS

Study Patients

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

Confirmation of Gefitinib-Induced ILD

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

Demographic and Clinical Variables

The following pretreatment demographic and clinical information was obtained from case report forms and evaluated for its relationship to gefitinib-induced ILD: age, sex, smoking status, Eastern Cooperative Oncology Group performance status (PS), coincidental complications, histology, disease stage, body-surface area (BSA), and previous anticancer treatments. Smoking status was classified as no history of smoking (smoking a total of < 100 cigarettes) or a positive history. With regard to coincidental complications, we assessed the presence of pulmonary diseases, diabetes mellitus, and sequelae of previous treatment such as radiation pneumonitis. Disease stage was determined according to the TNM system.[13] Previous anticancer treatment was classified as surgery, radiotherapy, or chemotherapy. We obtained additional information about the field, dose, and modality of radiotherapy and about the regimen, dose, and number of treatment cycles for chemotherapy. We also collected information about antitumor response and survival after the initiation of gefitinib treatment. We asked the participating institutions to report antitumor response according to the Response Evaluation Criteria in Solid Tumors Group criteria,[14] although it was not confirmed extramurally. Overall survival was calculated from the initiation of gefitinib treatment to the date of death. Patients still alive were censored as of the last known follow-up. Survival data were last updated on December 31, 2003.

Statistical Analysis

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

RESULTS

Prevalence and Mortality of Gefitinib-Induced ILD

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

Risk Factors for Gefitinib-Induced ILD

Of the 1,874 patients who did not develop pulmonary infiltrates, 245 individuals (13.1%) were excluded from further analysis because of insufficient clinical information (Fig 1). We also excluded the 11

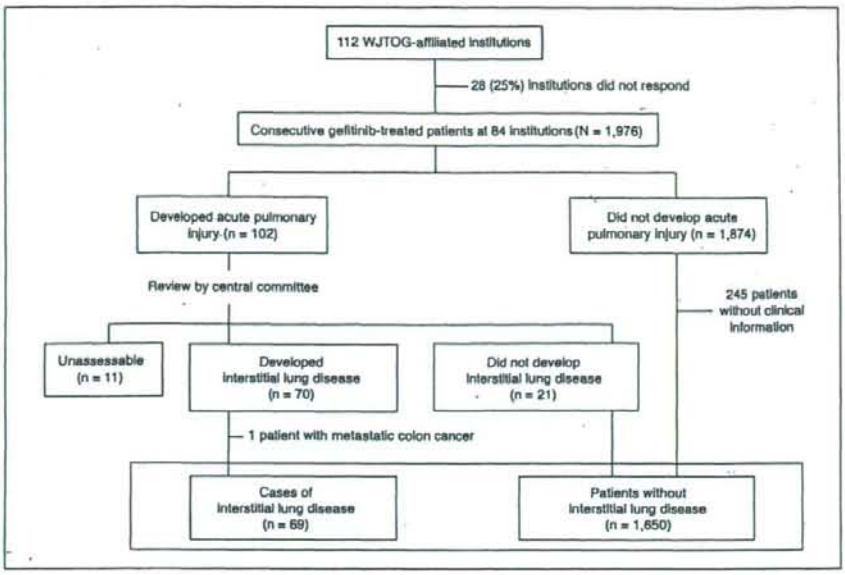

Fig 1. Outline of patient recruitment and classification. WJTOG, West Japan Thoracic Oncology Group.

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

Predictive Factors for Antitumor Response

An antitumor response was observed in 348 of the total of 1,976 patients (including 256 unassessable patients), corresponding to a response rate of 17.6% (95% CI, 16.0% to 19.4%). Univariate analysis revealed that an age of less than 70 years, female sex, no history of smoking, adenocarcinoma histology, metastatic disease, good PS, a history of chest surgery, no history of chest irradiation, the absence of interstitial pneumonia, and a BSA of less than 1.5 m^2 were associated with an antitumor response (Table 1). Multivariate logistic regression analysis revealed that sex, smoking status, histology, disease stage, and PS were independently associated with response rate (Table 4). No synergistic effect on antitumor response was apparent between sex and smoking status, sex and histology, or smoking status and histology ($P = .514$, .734, and .573, respectively). The adjusted odds ratio for an antitumor response was 9.2 (95% CI, 5.5 to 15.3) for women with adenocarcinoma and no history of smoking compared with male smokers with a nonadenocarcinoma histology.

Predictive Factors for Survival

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

DISCUSSION

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

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

Variable	ILD				Antitumor Response				Survival		
	Total No. of Patients	Patients With ILD		P	Total No. of Patients	Responders		P	Total No. of Patients	Median Survival (days)	P
		No.	%			No.	%				
Age, years											
< 70	1,047	39	3.7	.446	1,042	230	22.1	.024	1,044	296	.418
≥ 70	672	30	4.5		671	118	17.6		669	333	
Sex											
Female	631	6	1.0	< .001	627	222	35.4	< .001	631	499	< .001
Male	1,088	63	5.8		1,086	126	11.6		1,082	230	
Smoking status											
No smoking history	658	5	0.8	< .001	653	225	34.5	< .001	658	467	< .001
Positive smoking history	1,013	63	6.2		1,012	116	11.5		1,008	227	
Histology											
Adenocarcinoma	1,294	47	3.6	.130	1,288	311	24.2	< .001	1,291	362	< .001
Others	414	22	5.3		414	34	8.2		411	190	
Disease stage											
Metastatic	1,313	59	4.5	.069	1,310	296	22.6	< .001	1,309	280	< .001
Nonmetastatic	406	10	2.5		403	52	12.9		404	435	
Performance status											
0-1	1,161	44	3.8	.664	1,157	274	23.7	< .001	1,157	441	< .001
2	336	14	4.2		336	47	14.0		335	147	
3-4	216	11	5.1		214	26	12.2		216	67	
Previous chest surgery											
Yes	528	15	2.8	.093	527	128	24.3	.008	527	486	< .001
No	1,181	54	4.6		1,177	220	18.7		1,176	253	
Previous thoracic RT											
Yes	472	18	3.8	.767	471	73	15.5	.002	468	263	.005
No	1,235	51	4.1		1,230	273	22.2		1,233	335	
Previous chemotherapy											
Yes	1,356	57	4.2	.440	1,351	275	20.4	.937	1,353	301	.900
No	363	12	3.3		362	73	20.2		360	345	
Coincidence of IP											
Yes	36	5	13.9	.013*	36	1	2.8	.008	35	103	< .001
No	1,683	64	3.8		1,677	347	20.7		1,678	317	
Coincidence of diabetes											
Yes	85	5	5.9	.386*	85	12	14.1	.145	85	190	.002
No	1,634	64	3.9		1,628	336	20.6		1,628	322	
Coincidence of renal failure											
Yes	10	1	10.0	.333*	10	2	20.0	.99*	10	353	.588
No	1,707	67	3.9		1,701	346	20.3		1,701	312	
Body surface area, m²											
< 1.5	755	30	4.0	.796	751	197	26.2	< .001	755	355	< .001
≥ 1.5	875	37	4.2		874	135	15.5		872	290	

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

The present study constitutes the first large-scale survey designed to assess the prevalence of and risk factors for gefitinib-induced ILD during practical use of this drug in the Japanese population. The development of ILD subsequent to treatment with conventional cytotoxic chemotherapeutic agents has been recognized for many years, with the use of standard drugs for treatment of NSCLC being associated with ILD at a prevalence of up to 5%.[17,18] Drug-induced ILD in lung cancer patients is difficult to diagnose because of the high prevalence of pre-existing lung disease and respiratory tract infections as well as the progressive malignancy in such individuals. Clinical symptoms of ILD, such as escalating dyspnea, cough, and fever, may be indistinguishable from the symptoms of progressive tumor growth or infection. Computed tomographic features of ILD include pulmonary reticular changes and ground-glass opacity, which are also nonspecific and may not readily indicate a precise etiology.[18] Diagnosis of drug-induced ILD thus relies on rigorous exclusion of all other differential diagnoses, especially those of infection and tumor progression.

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

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

Variable	Odds Ratio	95% CI	P
Male	3.10	1.15 to 8.36	.025
Positive smoking history	4.79	1.69 to 13.54	.003
Coincidence of IP	2.89	1.06 to 7.84	.038
BSA of < 1.5 m^2	1.67	0.98 to 2.83	.059

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

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

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

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

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

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

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

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

Abbreviation: ILD, interstitial lung disease.

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

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

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

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

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

Table 6. Median Survival Time and 1-Year Survival According to Clinical Factors

Variable	Chemotherapy Naive			Previously Treated With Chemotherapy		
	No. of Patients	Median Survival Time (days)	1-Year Survival Rate (%)	No. of Patients	Median Survival Time (days)	1-Year Survival Rate (%)
Sex						
Female	131	481	64.0	500	502	61.9
Male	229	263	36.8	853	217	33.8
Smoking status						
No smoking history	137	433	60.7	521	482	60.1
Positive smoking history	208	263	36.8	800	217	33.8
Histology						
Adenocarcinoma	266	378	51.8	1,025	358	49.2
Other	89	216	29.7	322	189	28.2
Disease stage						
Metastatic	254	299	41.4	1,055	274	40.8
Nonmetastatic	106	433	58.5	298	435	57.0
Performance status						
0-1	225	433	56.6	932	443	57.2
2	65	204	31.2	270	141	18.7
3-4	70	81	26.7	146	63	10.1
Previous chest surgery						
Yes	131	481	63.6	396	462	57.5
No	224	247	36.7	952	262	39.0

in all patients who received gefitinib after the failure of prior chemotherapy. Given that the present study included many elderly and patients with a poor PS, these survival data do not differ substantially from those obtained with the Japanese cohort of a phase II study (11.8 months and 50%, respectively).[6] These findings suggest that gefitinib treatment in clinical practice may lead to clinical benefit as it did in the clinical trials. Furthermore, the survival data in the present study are similar to those obtained with previously treated patients with a PS of 0 to 2 in a phase III trial of docetaxel (7.5 months and 37%, respectively), which is a standard second-line treatment for NSCLC.[30] These observations emphasize the importance of further comparison of gefitinib with docetaxel as a second-line treatment for NSCLC in ongoing phase III studies. In previous phase III clinical trials, however, gefitinib failed to prolong survival in unselected patients, suggesting

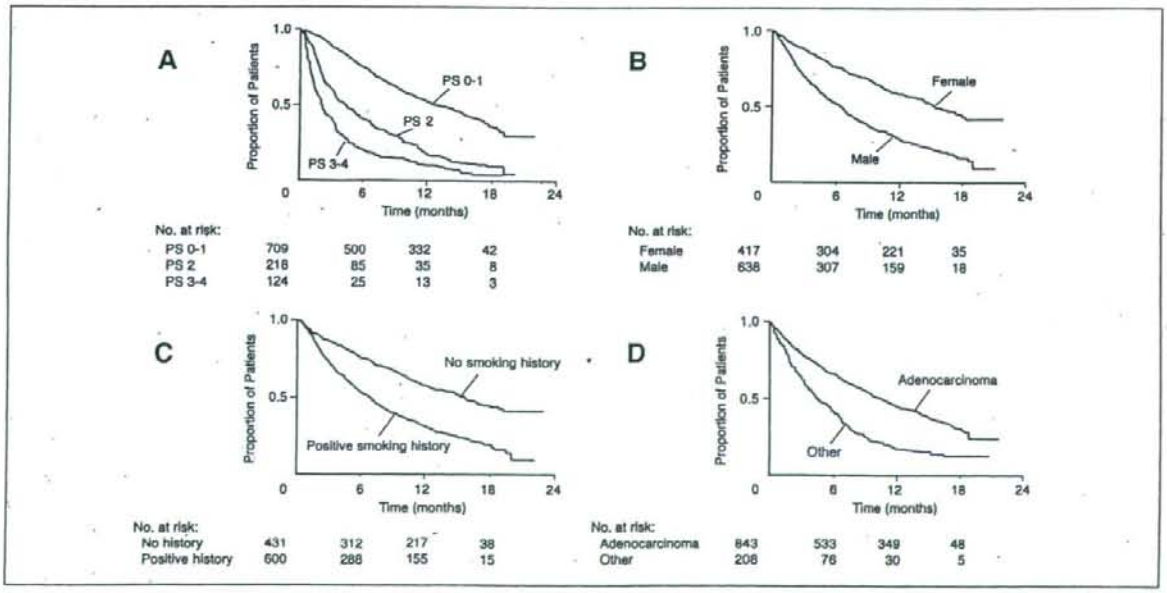

Fig 2. Kaplan-Meier plots of survival for patients with metastatic non–small-cell lung cancer previously treated with chemotherapy classified according to (A) performance status (PS), (B) sex, (C) smoking status, and (D) histology.

the necessity for patient selection on the basis of clinical or genetic factors if true clinical benefit is to be achieved from gefitinib treatment.[19,20,31] Indeed, a randomized phase III trial is now planned in Asian countries to assess the effect of gefitinib on survival in patients selected on the basis of clinical profile.

In conclusion, we have determined the prevalence of gefitinib-related ILD and identified risk factors for this life-threatening adverse event in a large population of Japanese patients with NSCLC treated with this drug. Our data confirmed an acceptable single-agent activity of gefitinib in routine clinical practice. We found that female sex and the absence of a history of smoking, which were known predictive factors for the efficacy of gefitinib, were also associated with a lower risk of gefitinib-induced ILD. Thus, our results indicate that patient selection on the basis of clinical factors can simultaneously minimize the risk of life-threatening ILD and maximize the clinical benefit of gefitinib treatment. They provide both important insight into individual risk-benefit assessment for gefitinib therapy in the practical setting as well as a basis for the planning of future clinical trials to accurately define the scope for gefitinib treatment in NSCLC patients.

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Appendix

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

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members 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. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Fractionated Administration of Irinotecan and Cisplatin in Japanese Patients With Extensive-Stage–Disease Small-Cell Lung Cancer

TO THE EDITOR: We read with great interest the recent article by Hanna et al,[1] in which they reported irinotecan and cisplatin (IP) regimen was not superior to the etoposide and cisplatin (EP) regimen for extensive-stage–disease (ED) small-cell lung cancer (SCLC), even though Noda et al[2] clearly showed the superiority of IP regimen over EP regimen. We previously fractionated the schedule of IP to obtain the synergistic effect of the two drugs and to reduce toxicities.[3] The recommended doses of irinotecan and cisplatin on days 1 and 8 were determined to be 50 mg/m^2 and 60 mg/m^2, respectively. However, the phase II study for ED SCLC was stopped early because of poor outcomes in the interim analysis.[4] Despite the small number of patients in our study, the median survival time and 1-year survival rates were similar to those reported in the study by Hanna et al (Table 1). The delivered doses of irinotecan and cisplatin in their study were 1.8 times and 0.7 times as much as those of our study, respectively (Table 1). In comparison to the study by Noda et al, we should have modified fractionated administration by escalating the dose of irinotecan and reducing that of cisplatin to improve the outcomes. However, both irinotecan and cisplatin in the Hanna et al study showed more dose intensity than that reported in the Noda et al study. Hanna et al suggested that IP might therefore be a better regimen for Japanese patients. We considered fractionated administrations of IP to be inferior to the original schedules of IP (cisplatin on day 1 and irinotecan on days 1, 8, and 15) for not only American but also Japanese patients with ED SCLC based on the findings of our study.

Another explanation for the negative results of the Hanna et al study might be due to salvage chemotherapy. More patients on the IP arm received subsequent treatment with etoposide (47.2% *v* 22.6%) whereas more patients on the EP arm received subsequent treatment with topoisomerase I inhibitors including irinotecan or topotecan (33% *v* 24.1%).[1] Noda et al did not describe the use of salvage chemotherapy, which might have affected the survival difference in both arms. Because chemotherapy with fluorouracil, leucovorin, and irinotecan (FOLFIRI), followed by fluorouracil, leucovorin, and oxaliplatin (FOLFOX), had almost the same efficacy as that with FOLFOX followed by FOLFIRI in the treatment of advanced colorectal cancer,[5] IP followed by EP might therefore have had the same efficacy as EP followed by IP in the treatment of ED SCLC. To achieve a prolonged survival, the administration of all three active cytotoxic drugs (cisplatin, irinotecan, and etoposide) during the treatment course may thus be necessary.

Table 1. Irinotecan and Cisplatin for the Treatment of Extensive-Stage–Disease Small-Cell Lung Cancer

Characteristic	Study		
	Noda et al[2]	Hanna et al[1]	Takigawa et al[4]
Age, years			
Median	63	63	61
Range	30-70	37-82	41-74
Performance status 0 or 1, %	92.2	92.3	100
Delivered dose, mg/m^2/wk			
Irinotecan	36.2	39	21.4
Cisplatin	14.3	18	25.7
Median survival, months	12.8	9.3	9.4
1-year survival rate, %	58.4	35	40
Time to progression, months	6.9	4.1	5.6

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IN REPLY: Takigawa and colleagues consider the fractionated schedule of irinotecan and cisplatin (IP) to be inferior to the original schedule given in the study by Noda et al[1] and point to this as one possible explanation for the lack of survival advantage for the IP regimen in our study[2] published in the May 1, 2006, issue of the *Journal of Clinical Oncology*. A second point raised by these authors is that salvage chemotherapy may have affected the survival outcomes and suggest the best outcomes may be achieved with the combination of all three agents (cisplatin, etoposide, and irinotecan).

Regarding the first point, we acknowledged in our paper that the fractionated regimen of IP may be inferior to the regimen in the study by Noda et al.[1] The authors cite their own study of fractionated IP as evidence of this point.[3] However, the response rate of 80% and median time to progression of 5.6 months in their study (n = 15) was similar to that seen with the Noda IP regimen. In addition, as the authors acknowledge the dose intensity of irinotecan was 1.8 times greater with irinotecan in our study compared with theirs. The Southwest Oncology Group is completing a much larger trial in patients with extensive disease small-cell lung cancer utilizing the two arms of the Noda trial.[1] The results from this trial will provide the answer to this question of dose/schedule of IP. However, given the lack of positive phase III trials testing a number of active agents in various combinations, schedules, and dosages in extensive disease small-cell lung cancer over the last 25 years, it seems unlikely that a change in schedule of IP which provides less dose intensity (as does the original schedule of IP compared with our regimen) will positively affect survival outcomes.

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A phase I and pharmacological study of amrubicin and topotecan in patients of small-cell lung cancer with relapsed or extensive-disease small-cell lung cancer

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Summary Cisplatin-based chemotherapy is considered to be a standard treatment in patients with relapsed or extensive-disease (ED) small-cell lung cancer (SCLC), the survival benefit remains modest. Relapsed or ED-SCLC patients were enrolled. Topotecan and amrubicin were administered on Days 1–5 and on Days 3–5, respectively. Nine patients received a total of 24 cycles. Since all three patients experienced dose-limiting toxicity (grade 4 neutropenia lasting for more than 4 days, grade 3 febrile neutropenia, and grade 4 thrombocytopenia) at the third dose level (topotecan: 0.75 mg/m^2, amrubicin 40 mg/m^2), the maximum tolerated dose was determined to be this dose level. Objective response was observed in six patients (67%). The maximum concentration (C_{max}) and area under the plasma concentration–time curve (AUC) of amrubicin increased in a dose-dependent manner. Amrubicin did not influence the pharmacokinetics of topotecan. The C_{max} and AUC of amrubicin were correlated with the duration of grade 4 neutropenia. The mean C_{max} of topotecan on day 2 in responders (22.9 ± 3.6) was significantly higher than that in non-responders (10.9 ± 0.4). This phase I study showed the safety and activity of two-drug combination of amrubicin and topotecan in patients with relapsed or ED-SCLC.

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1. Introduction

Recently, therapy with a cisplatin (CDDP)-based two-drug combination has been used as the standard treatment for small-cell lung cancer (SCLC) cases with extensive-disease (ED). In particular, the combination of irinotecan (CPT-11) and CDDP has been reported to be highly effective in previously untreated patients with ED-SCLC [1]. However, since the majority of responders showed early relapse, and salvage chemotherapy for SCLC usually yields disappointing results, the long-time survival rate was extremely low [2–5]. Accordingly, in order to achieve better treatment results for SCLC, new effective combination regimens need to be sought for patients with relapsed or refractory SCLC after standard chemotherapy. Recently, several new agents with novel mechanisms of actions have been developed and been shown to be highly effective for the treatment of SCLC [6].

Amrubicin (AMR), a novel and entirely synthetic anthracycline, inhibits DNA topoisomerase II activity. It has been shown to be active against previously untreated SCLC, with an overall response rate and median survival time (MST) of 78.8% and 11.0 months, respectively [7].

Topotecan (TOP), a unique semi-synthetic water-soluble analog of camptothecin, exhibits inhibitory activity against DNA topoisomerase I, and has been shown to have favourable anti-tumour activity against SCLC, with a response rate of 39% and MST of 9.0 months [8].

DNA topoisomerases I and II are functionally correlated and act in concert. Both enzymes are believed to be essential for the maintenance of cell viability. Therefore, combined use of agents targeted against the DNA topoisomerases I and II may be expected to completely inhibit both DNA and RNA synthesis and exert synergistic cytotoxicity [9–11]. There have been some reports of the effectiveness of such a combination of drugs, namely, irinotecan (CPT-11) and etoposide (VP-16), in patients with SCLC [12].

Based on these results, we conducted a phase I trial of the two-drug combination chemotherapeutic regimen of AMR and TOP in patients with relapsed or ED-SCLC. The primary objective of this trial was to determine the maximum tolerated dose (MTD) of the two-drug regimen. The secondary objectives were to investigate the anti-tumour activity of the regimen and influence of the administration sequence of the two drugs on the pharmacokinetics and clinical toxicity of the combination regimen.

2. Materials and methods

2.1. Eligibility criteria

Patients were recruited based on the following eligibility criteria: pathologically proven SCLC; relapsed disease or ED-SCLC; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1 or 2; age $\leq$75 years; presence of evaluable lesion; no chemotherapy within 4 weeks prior to study entry; adequate haematological (WBC count $\geq$3000/μL, neutrophil count $\geq$1500/μL, haemoglobin level $\geq$9.5 g/dL, platelet count $\geq 15 \times 10^4/\mu$L), renal (serum creatinine $\leq$ 1.5 mg/dL), hepatic (total bilirubin $\leq$ 1.5 mg/dL, serum transaminases $\leq$2.5$\times$ upper limit of normal range) and pulmonary function ($PaO_2 \geq 60$ Torr) reserves; receipt of written informed consent. Patients with symptomatic brain metastasis or evidence of preexisting interstitial pulmonary disease on the chest radiograph were excluded from the study. Pretreatment evaluations included a complete history, physical examination, laboratory tests, chest radiography, electrocardiography, computed tomography (CT) of the chest and abdomen, magnetic resonance imaging (MRI) of the brain, and a radionuclide bone scan. Staging was conducted according to the tumour, node, metastasis system [13]. The protocol was approved by the institutional review board of the NHO Minami-Okayama Hospital and Okayama University Medical School.

2.2. Treatment scheme

TOP, diluted in 100 mL of physiological saline, was administered by intravenous infusion over 1 h on days 1–5. AMR, diluted in 20 mL of physiological saline, was administered as a bolus intravenous injection over 5 min on days 3–5, after completion of the TOP infusion. Each patient was premedicated with i.v. dexamethasone (8 mg) and granisetron (3 mg). The starting doses of TOP and AMR were 0.75 and 30 mg/m^2, respectively, which were 60–70% of the recommended doses in previous phase II monotherapy studies [8,14–16]. The following five dose escalations of TOP/AMR (mg/m^2) were planned: 0.75/30, 0.75/35, 0.75/40, 1.0/40 and 1.0/45.

The treatment was repeated every 4 weeks at the same dose levels up to four cycles, unless disease progression or unacceptable toxicity was observed, or the patient refused further treatment. Initiation of the next cycle of chemotherapy was delayed until recovery of the WBC count to $\geq$3000/μL, neutrophil count to $\geq$1500/μL, platelet count to $\geq 15 \times 10^4/\mu$L, and resolution of non-haematologic toxicities to $\leq$grade 1. After completion or discontinuation of this regimen, patients were permitted to receive standard chemotherapy for SCLC.

2.3. Assessment of toxicity and dose escalation

Toxicity was graded according to the National Cancer Institute-Common Toxicity Criteria ver 2.0 [17]. Dose-limiting toxicity (DLT) was defined as development of at least one of the following adverse events: any non-haematologic toxicities $\geq$grade 3, except for alopecia, nausea, vomiting and general malaise; platelet count $\leq 2 \times 10^4/\mu$L; grade 4 leukopenia; persistence of grade 4 neutropenia for more than 4 days; grade 3 or more severe neutropenia with fever $\geq$38 °C or evidence of infection; failure to recover sufficiently from toxicities by Day 29, before beginning the next cycle of treatment.

Initially, three patients were enrolled at each dose level. If fewer than two patients experienced DLT, the next group of patients was treated at the next higher dose level. If all three patients developed the DLT, the dose level was determined to be the MTD. The recommended dose was also defined as one below the MTD. If two patients experienced the DLT, six patients in total were administered the same dose level. If half or more of these six patients developed DLT, the dose was determined to be the MTD. Dose escalation above the starting dose in individual patients was

not allowed. If grade 4 leukopenia, grade 4 neutropenia, or febrile neutropenia was noted, the use of granulocyte colony-stimulating factor (G-CSF) was permitted.

2.4. Assessment of antitumour activity

The standard response evaluation criteria in solid tumors was used to evaluate the responses [18]. Complete and partial response (PR) were confirmed by two observations not less than 4 weeks apart.

2.5. Pharmacokinetic analysis

Blood samples for pharmacokinetic analysis were obtained during the second and third days of the first cycle, from an indwelling venous catheter placed in the arm contralateral to that used for the drug infusion. Five milliliters of blood were collected in heparinised tubes before the drug administration, at the end of the TOP infusion, and 0.5, 3, 8 and 23 h after the end of the TOP infusion on both Days 2 and 3 in the first cycle. After centrifugation, the plasma specimens were stored at −80 °C until the assays. The plasma concentrations of AMR, amrubicinol (13-OH-AMR: active form of AMR) and TOP were measured by high-performance liquid chromatography (HPLC). The area under the plasma concentration–time curve (AUC) was calculated using WINNONLIN Standard Edition, Version 1.5. Differences in the pharmacokinetic parameters among three dose levels in the first cycle were evaluated by the Kruskal–Wallis test, and those between Days 2 and 3 in the first cycle were evaluated by Mann–Whitney's *U*-test. The correlations between the pharmacokinetic parameters and the clinical toxicities or responses were assessed with Spearman's rank test. Statistical analyses were performed using the STATVIEW 5.0 program (Brainpower, Calabasas, CA). A *p*-value of less than 0.05 was considered to denote statistical significance.

3. Results

3.1. Patients' characteristics

Nine patients with relapsed or ED-SCLC were enrolled between April and November 2003. There were eight men and one woman, with a median age of 62 years (range, 51–75 years). All patients had a good performance status (PS 0 in five patients and PS 1 in four patients). Five patients (56%) had received prior chemotherapy (CDDP + VP-16 in three, CDDP + CPT-11 in one, and carboplatin + VP-16 in one). Three patients had sensitive disease and two had refractory disease.

A total of 24 chemotherapy cycles were administered. Three patients (33%) received only one cycle of chemotherapy, because of unacceptable toxicity (two patients) or the patient's refusal to undergo further treatment (one patient). At the first dose level (TOP 0.75 mg/m^2, AMR 30 mg/m^2), one patient developed DLT (grade 3: diarrhoea, stomatitis and febrile neutropenia, grade 4: leukopenia, neutropenia lasting for more than 4 days and thrombocytopenia). At the second dose level (TOP 0.75 mg/m^2, AMR 35 mg/m^2), one patient developed DLT (grade 4 neutropenia lasting for more than 4 days). At the third dose level (TOP 0.75 mg/m^2, AMR 40 mg/m^2), all three patients experienced DLT (grade 4 neutropenia lasting for more than 4 days in one, grade 4 neutropenia lasting for more than 4 days and grade 3 febrile neutropenia in one patient each, and grade 4 thrombocytopenia in one). Therefore, the third dose level was deemed to be MTD, and the recommended doses for the phase II study were the second dose levels, that is, 0.75 mg/m^2 for TOP, and 35 mg/m^2 for AMR.

Table 1 Grade 2 or more severe haematological toxicity (all courses)

Toxicity	Grade	Dose level		
		1	2	3
No. of treated patients		3	3	3
No. of courses evaluated		7	9	8
No. of courses in which toxicity was encountered (%)				
Leukopenia	2	0	1 (11%)	1 (13%)
	3	6 (86%)	8 (89%)	3 (38%)
	4	1 (14%)	0	4 (50%)
Neutropenia	2	1 (14%)	0	2 (25%)
	3	2 (29%)	3 (33%)	0
	4	4 (57%)	6 (67%)	6 (75%)
Thrombocytopenia	2	1 (14%)	4 (44%)	0
	3	1 (14%)	0	5 (63%)
	4	1 (14%)	0	0
Anaemia	2	1 (14%)	5 (56%)	3 (38%)
	3	1 (14%)	2 (22%)	2 (25%)
	4	2 (29%)	0	1 (13%)

3.2. Haematological toxicity

The main toxicity of this drug combination was myelosuppression. Analysis of the toxicity during all courses of chemotherapy is shown in Table 1. Grade 3 or 4 leukopenia was observed during all the seven courses (100%) at the first dose level, eight courses (89%) at the second dose level, and seven courses (88%) at the third dose level. Similarly, grade 3 or 4 neutropenia was also frequently observed, necessitating G-CSF administration in eight patients. Grade 3 or 4 thrombocytopenia was observed less frequently at the first and second dose level, however it was observed during five courses (63%) at the third dose level, with two patients requiring platelet transfusion. Although grade 3 or 4 anaemia was observed less frequently, three patients required red blood cell transfusion.

3.3. Non-haematological toxicity

The non-haematological toxicities observed are summarised in Table 2. Febrile neutropenia occurred during one course (14%) at the first dose level, two courses (22%) at the second dose level, and four courses (50%) at the third dose level, however, it was reversible in all cases with only appropriate supportive care. Other toxicities, including diarrhoea, were mild, and did not require any intensive management.

There seemed to be different severity in toxicity profiles in patients with or without prior chemotherapy; grade 4 neutropenia and leucopenia were observed in 5 (38%) of 13 courses versus none of 11 courses in previously treated and untreated patients, respectively. Additionally, febrile neutropenia occurred in only patients with prior chemotherapy (7 [54%] of 13 courses versus none of 11 courses, respectively). However, in our study, pretreated patients tended to be incidentally accrued at higher dose level, which might be rather contributed to the difference in severity of toxicity profiles than prior chemotherapy itself was.

3.4. Antitumour activity

All patients were assessable for response. Although none of the cases showed complete response, six patients (67%),

Table 2 Grade 2 or more severe non-haematologic toxicity (all courses)

Toxicity	Grade[a]	Dose level		
		1	2	3
No. of treated patients		3	3	3
No. of courses evaluated		7	9	8
No. of courses in which toxicity was encountered (%)				
Febrile neutropenia	3	1 (14%)	2 (22%)	4 (50%)
Nausea/vomiting	2	0	1 (11%)	0
	3	0	0	0
Hepatotoxicity	2	1 (14%)	0	0
	3	0	0	0
Infection	2	0	0	0
	3	0	1 (11%)	0
Diarrhoea	2	0	1 (11%)	0
	3	1 (14%)	0	0

[a]No grade 4 or more severe toxicities were observed.

Table 3 Pharmacokinetic parameters of the drugs at dose levels 1–3

		Level 1 (AMR 30 mg/m^2) [number of points: 3]	Level 2 (AMR 35 mg/m^2) [number of points: 3]	Level 3 (AMR 40 mg/m^2) [number of points: 3]	p
AMR	C_{max} (ng/mL)	319.4 ± 109.5	401.6 ± 76.1	447.5 ± 33.5	0.49
	AUC (ng h/mL)	1195.6 ± 445.5	1615.1 ± 194.6	1849.8 ± 90.2	0.58
13-OH-AMR	C_{max} (ng/mL)	23.2 ± 13.3	28.9 ± 2.5	28.3 ± 2.5	0.73
	AUC (ng h/mL)	196.2 ± 169.7	191.2 ± 95.3	299.4 ± 88.2	0.67
TOP (day 2)	C_{max} (ng/mL)	20.3 ± 2.9	21.6 ± 7.9	18.8 ± 7.5	0.73
	AUC (ng h/mL)	64.2 ± 5.1	54.3 ± 15.7	45.1 ± 5.9	0.25
TOP (day 3)	C_{max} (ng/mL)	22.1 ± 1.7	15.0 ± 1.1	16.8 ± 1.7	0.09
	AUC (ng h/mL)	71.4 ± 6.7	53.2 ± 6.2	56.5 ± 1.9	0.19

Each data represents the mean values and standard errors. *Abbreviations*: AMR, amrubicin; TOP, topotecan; C_{max}, maximum concentration; AUC, area under the plasma concentration–time curve.

Table 4 Pharmacokinetic parameters of topotecan on days 2 and 3

	Day 2 (topotecan alone) [number of points: 9]	Day 3 (topotecan combined with amrubicin) [number of points: 9]	p
Parameters			
T_{max} (h)	0.5	0.5	
C_{max} (ng/mL)	20.2 ± 3.3	18.0 ± 1.3	0.83
AUC (ng h/mL)	54.5 ± 5.8	60.4 ± 3.9	0.23

Each data represents the mean values and standard errors. Abbreviations: C_{max}, maximum concentration; AUC, area under the plasma concentration–time curve.

including one receiving only the first dose level, showed PR. It is worthy of note that 4 out of the 5 (80%) relapsed patients showed PR, although only 2 out of 4 (50%) chemo-naïve patients showed PR. The median time to progression was 4.0 (95% CI: 0.8–6.8) months.

3.5. Pharmacokinetic and pharmacodynamic analysis

Pharmacokinetic parameters were determined in samples obtained on the second and third days of the first cycle in all nine patients. The maximum concentration (C_{max}) and AUC of AMR increased in a dose-dependent manner, although statistical significance was not reached (Table 3). The C_{max} and AUC of TOP were almost comparable among the first three dose levels, suggesting that the AMR dose did not influence the pharmacokinetics of TOP (Table 3). The C_{max} and AUC of

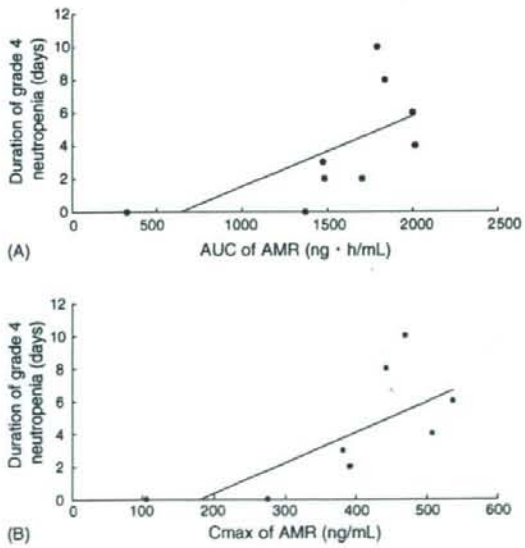

Fig. 1 (A) The correlation between the area under the plasma concentration–time curve (AUC) of AMR (amrubicin) on day 2 and the duration of grade 4 neutropenia in the first cycle (Spearman rank test, $p = 0.0288$), and (B) the correlation between the maximum concentration (C_{max}) of AMR on day 2 and the duration of grade 4 neutropenia in the first cycle (Spearman rank test, $p = 0.0225$).

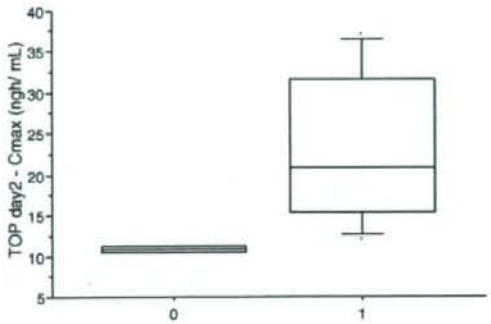

Fig. 2 Correlation between the maximum concentration (C_{max}) of topotecan on day 2 and objective tumour response in the first cycle. "0" denotes stable disease and progressive disease and "1" denotes partial response. The mean C_{max} of seven responders and two non-responders were 22.9 ± 3.6 and 10.9 ± 0.4, respectively (Mann–Whitney's U-test, $p = 0.0404$).

13-OH-AMR were not significantly different even with dose escalation of AMR. 13-OH-AMR was not detectable in any of the samples collected from the first patient and two of the samples collected from the second patient at the first dose level, in three samples collected from the two patients at the second dose level, and in one sample collected from the patients at the third dose level, although AMR was detectable in all of these samples. However, the serum concentrations of 13-OH-AMR were higher than 20 ng/mL (minimum detectable value) in all the other patients. We also evaluated differences in the pharmacokinetic parameters of TOP between Day 2 (TOP alone) and Day 3 (TOP plus AMR), in order to investigate the effect of concurrent administration of AMR on the pharmacokinetics of TOP. As listed in Table 4, there were no significant differences. In the correlation of toxicity profiles with the pharmacokinetic parameters, the AUC and C_{max} of AMR were correlated with the duration of grade 4 neutropenia ($p = 0.0288$ and 0.0225, respectively; Fig. 1A and B). In addition, the mean C_{max} of TOP on Day 2 in 7 responders (22.9 ± 3.6) was significantly higher than that in 2 non-responders (10.9 ± 0.4, $p = 0.0404$; Fig. 2).

4. Discussion

Although the combined use of DNA topoisomerase I and II inhibitors is theoretically attractive, preclinical studies have demonstrated mixed results [19,20–23]. There have been