Fennelly *et al.* reported a recommended dose of 80 mg/m^2 administered weekly for 6 weeks of an 8-week cycle in patients with recurrent ovarian cancer (6).

Based on this evidence, a phase II trial of 80 mg/m^2 weekly paclitaxel as a 1-h infusion for 6 consecutive weeks followed by 2 weeks without treatment (8-week cycle) was conducted in patients with relapsed SCLC. The objective of this study was to evaluate the efficacy and safety of weekly paclitaxel in patients with relapsed and refractory SCLC. The primary end-point was the response rate, while the secondary end-points were the toxicity profile and survival rate.

Patients and Methods

Patient selection. Patients who met all of the following criteria were considered eligible: a) histological or cytological proof of SCLC with no response to prior chemotherapy or progression after chemotherapy, b) measurable disease, c) most recent cytotoxic treatment less than 4 weeks before entry, d) ECOG performance status 0-2, e) age ≤75 years, f) adequate bone marrow function (leukocyte count ≥4,000/μl, hemoglobin level ≥9.0 g/dl and platelet count ≥100,000/μl), hepatic function (transaminases ≤2.5 times the upper limit of normal, bilirubin level ≤1.5 mg/dl), and renal function (creatinine ≤1.5 times upper limit of normal) and g) arterial oxygen partial pressure ≥60 torr. Excluded patients were those with any active concomitant malignancy, symptomatic brain metastases, a past history of drug allergy reactions, complication by interstitial pneumonia, treatment with non-steroidal anti-inflammatory drugs or steroids or other serious complications such as uncontrolled angina pectoris, myocardial infarction within 3 months, heart failure, uncontrolled diabetes mellitus or hypertension, massive pleural effusion or ascites or serious active infection. All patients gave written informed consent and our institutional review board for human experimentation approved the protocol.

Treatment schedule. Paclitaxel was infused intravenously (*i.v.*). over a 1-h period at a dose of 80 mg/m^2 each week for 6 consecutive weeks followed by a 2-week break. This 8-week period comprised one treatment cycle. Premedication consisted of 20 mg dexamethasone, 50 mg ranitidine and 50 mg diphenhydramine given *i.v.* 30 min prior to paclitaxel.

If the leukocyte count fell below 2,000/μl or the neutrophil count fell below 1,000/μl, recombinant granulocyte colony-stimulating factor (rhG-CSF) at a daily dose of 2 μg/kg was administered until the leukocyte count recovered to ≥10,000/μl, except on the days of paclitaxel administration. The toxicity assessment was based on the National Cancer Institute – Common Toxicity Criteria version 2.0. If grade 3 leukopenia, grade 4 neutropenia, grade 2 neuropathy or other grade 3 non-hematological toxicities occurred, the dose of paclitaxel in subsequent cycles was reduced by 10 mg/m^2 from the planned dose. Paclitaxel was not administered if the leukocyte count was <2,000/μl, the platelet count was <5,000/μl, or if there was grade 3 nausea/vomiting, infection with a fever of more than 38°C, or other grade 2 non-hematological toxicities except alopecia. The treatment was discontinued if there was disease progression, grade 3 neuropathy, other grade 4 non-hematological toxicities or a 2 consecutive weeks without paclitaxel administration.

Evaluation of response and survival. The tumor response was classified according to the WHO criteria (7). A complete response (CR) was defined as the total disappearance of all measurable and assessable disease for at least 4 weeks. Partial response (PR) was defined as a ≥50% decrease in the sum of the products of the 2 largest perpendicular diameters of all measurable tumors lasting for at least 4 weeks without the appearance of any new lesions. No change (NC) was defined as a decrease of <50% or an increase of <25% in tumor lesions for at least 4 weeks with no new lesions. Progressive disease (PD) was defined as the development of new lesions or an increase of 25% in the sum of the products of the 2 largest perpendicular diameters of all measurable tumors. The overall survival was measured from the time of study entry until death.

Statistical methods. The median probability of survival was estimated by the method of Kaplan and Meier (8). This study was designed as a phase II study, with the response rate as the main end-point. According to the Simons minimax design, with a sample size of 20 our study had a 90% power to accept the hypothesis that the true response rate was greater than 25%, while a 10% significance sufficed for rejection of the hypothesis that the true response rate was less than 5% (9).

Results

Patient characteristics. Between December 1999 and February 2002, a total of 22 patients were enrolled in the study, 1 of whom was deemed ineligible due to age (>75 years), leaving a total of 21 patients assessable for toxicity, response and survival. The main demographic characteristics of the cohort are summarized in Table I. The patient cohort consisted of 1 female and 20 males with a median age of 66 years (range, 48 to 75). Four patients exhibited limited disease and 19 exhibited extensive disease at the start of treatment. The majority of the patients had received no prior surgical treatment, while 67% had received prior radiation therapy. All patients had been treated with some form of cisplatin- or carboplatin-based combination chemotherapy regimen. Eighteen patients had received prior etoposide-containing chemotherapy and 10 prior irinotecan-containing chemotherapy. The median number of previous chemotherapy regimens administered was 1 (range, 1 to 2). Among the 10 patients who proved refractory to chemotherapy, 5 had NC or PD on first- or second-line treatment, 2 had PR but experienced disease progression during treatment and 3 had a relapse within a 90-day treatment-free interval after completing their treatments.

Toxicity. The toxicity of the regimen is summarized in Table II. Neutropenia was the main toxicity, with 6 out of the 21 patients experiencing grade 4 neutropenia during the entire study. Grade 3 anemia was observed in 2 patients. One patient experienced grade 4 anemia, secondary to digestive tract bleeding. Thrombocytopenia remained infrequent throughout the study. No cases of grade 3 or 4 thrombocytopenia were observed and there was no evidence of cumulative hematological toxicity.

Table I. *Baseline characteristics of all patients.*

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

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

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

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

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

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

Table III. *Response data.*

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

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

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

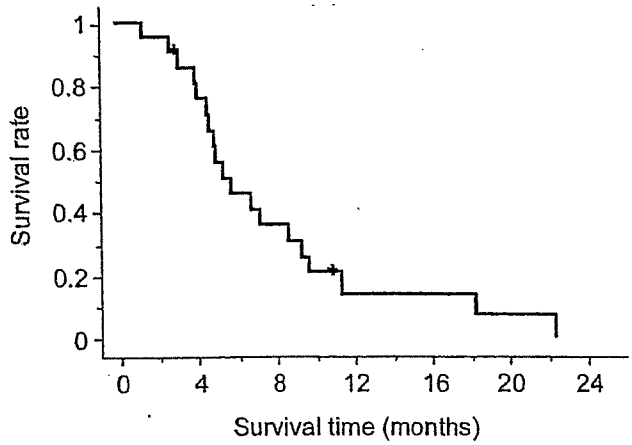

Figure 1. *Overall survival.*

Discussion

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

Single-agent paclitaxel, at a dose of 175 mg/m^2 as a 3-h infusion every 3 weeks in patients with previously treated SCLC, produced a response rate of 29% and an MST of 100 days (4). The results of our phase II study demonstrated that weekly paclitaxel at a dose of 80 mg/m^2 yielded a similar response rate of 23.8% and a much better MST of 5.8 months than that of paclitaxel given every 3 weeks. Because the antiproliferative activity of paclitaxel is cell-specific, prolonging patient exposure to a low dose of the drug beyond a threshold concentration is ultimately more efficacious than a short-term exposure to higher drug concentrations, a hypothesis supported by *in vitro* experiments with a variety of cell lines and suggested by the results of clinical studies. As clinical experience with paclitaxel treatment of various types of tumors has progressed, so has the use of weekly regimens at lower doses administered as 1-h infusions, as opposed to standard higher doses delivered once every 3 weeks as 3-h infusions.

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

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

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

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

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

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ORIGINAL ARTICLE

Nobuyuki Yamamoto · Yasumasa Nishimura
Kazuhiko Nakagawa · Kaoru Matsui
Masahiro Fukuoka

Phase I/II study of weekly docetaxel dose escalation in combination with fixed weekly cisplatin and concurrent thoracic radiotherapy in locally advanced non-small cell lung cancer

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Abstract *Purpose*: We conducted a phase I study to determine the maximum-tolerated dose (MTD) and dose-limiting toxicities (DLT) of weekly docetaxel and cisplatin (DOC/CDDP) with concurrent thoracic radiotherapy (TRT) in patients with unresectable stage III non-small-cell lung cancer (NSCLC). *Materials and methods*: The DOC/CDDP administration schedules consisted of a split schedule (SS) with administration in 3 out of every 4 weeks, and a continuous schedule (CS) with administration every week. TRT was given to a total dose of 60 Gy at 2 Gy per fraction over 6 weeks. *Results*: Twenty-one patients entered the study. The patient characteristics were: PS 0/1/2, 6/13/2; Sq/Ad, 16/5; stage IIIA/IIIB, 4/17. The principal DLT was grade3 esophagitis. The MTD of DOC on the SS and CS in combination with CDDP (25 mg/m2/week) was 25 and 20 mg/m^2/week, respectively. We determined the RD and schedule of DOC/CDDP on the SS to be 20/25 mg/m^2/week. The serum α-1-acid glycoprotein (AAG) concentration values were found to be negatively correlated with the grade of esophagitis. The median survival time was 23.1 months. *Conclusion*: The chemoradiation regimen tested in this study has promising activity and manageable toxicity. The continuous schedule could not be recommended due to excessive toxicity. The main DLT was esophagitis, and it significantly correlated with the plasma AAG concentration.

Keywords Docetaxel · Cisplatin · Chemoradiation · AAG

Conflicts of interest: The authors indicated no potential conflicts of interest

N. Yamamoto (✉) · K. Nakagawa · M. Fukuoka
Medical Oncology, Kinki University School of Medicine, Osaka, Japan
E-mail: n.yamamoto@scchr.jp
Tel.: +81-55-9895222
Fax: +81-55-9895634

Y. Nishimura
Radiology, Kinki University School of Medicine, Osaka, Japan

N. Yamamoto
Thoracic Oncology Division, Shizuoka Cancer Center, 1007 Naga-izumicho Shimonagakubo, Sunto-gun, 411-8777 Shizuoka, Japan

K. Matsui
Department of Thoracic Oncology, Osaka Prefectural Hospital for Pulmonary and Allergic Disease, Osaka, Japan

Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers, and although surgery offers the best chance of cure and long-term survival, only a small percentage of patients present with resectable disease. In fact, 25–30% of patients with NSCLC present with locally or regionally advanced unresectable tumors. Chest irradiation with modern megavoltage equipment plays a critical role in the treatment of these patients, since it assures good local control of the tumor in most patients. However, the development of distant metastases also affects their prognosis, and the addition of chemotherapy to thoracic radiation therapy (TRT) has been proposed in an attempt to reduce the risk of distant metastases.

Recent studies support the benefit of combined modality therapy in stage III NSCLC. The results of randomized studies that used sequential or concomitant chemotherapy for unresectable non-small cell lung cancer have shown significant differences in survival, local control rates, and distant metastasis rates for chemoradiotherapy over radiotherapy alone [1–5], and a recent meta-analysis of all randomized trials that compared TRT alone with the combined approach showed an unequivocal, although modest, survival advantage when cisplatin-based chemotherapy was added to TRT [6]. Concomitant chemoradiotherapy offers the potential advantage of synergistic interactions for local control

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

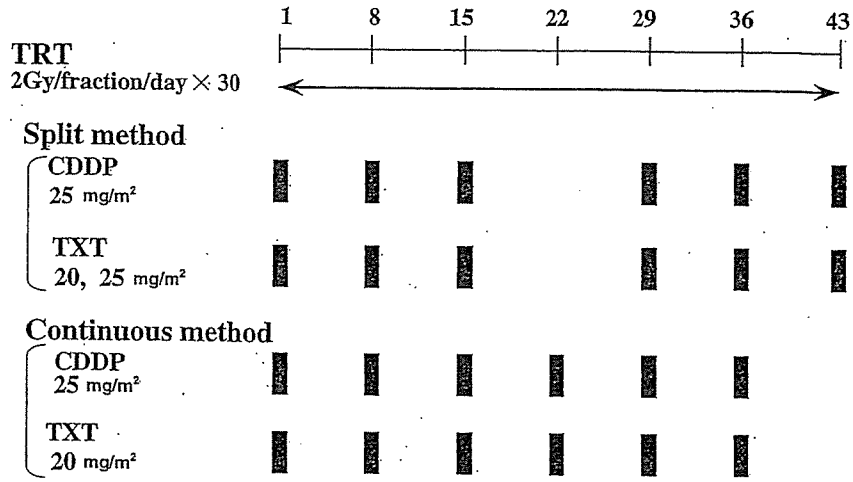

Fig. 1 Treatment regimens for weekly docetaxel and cisplatin concomitant with TRT

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

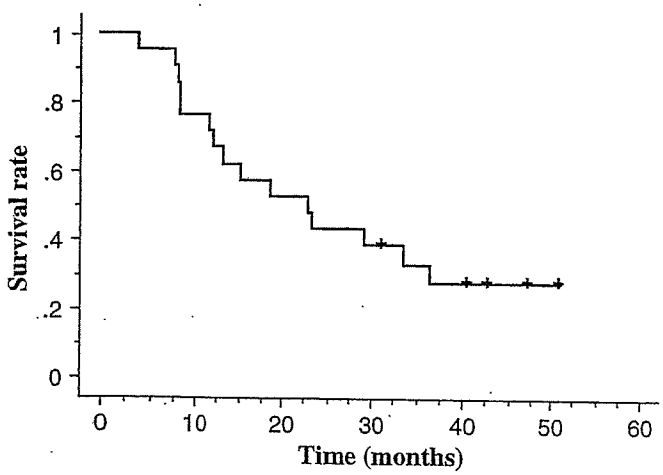

Fig. 2 Overall survival of patients treated with weekly docetaxel and cisplatin concomitant with TRT

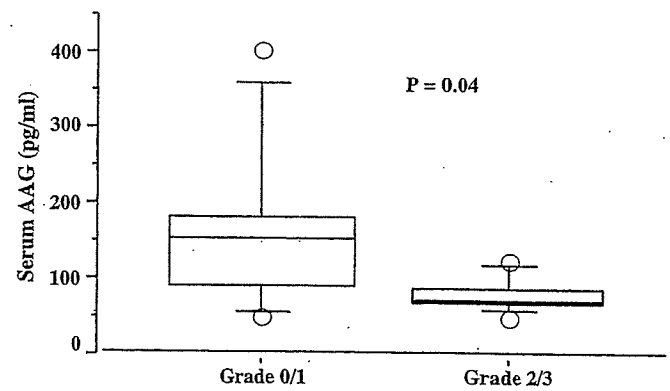

Fig. 3 Relationship between toxicity grade of esophagitis and serum AAG level

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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Phase I and Pharmacokinetic Study of Combination Chemotherapy Using Irinotecan and Paclitaxel in Patients with Lung Cancer

Gyo Asai, MD, PhD, Nobuyuki Yamamoto, MD,* Takayasu Kurata, MD, PhD,† Kenji Tamura, MD,† Hisao Uejima, MD, PhD,† Kazuhiko Nakagawa, MD, PhD,† and Masahiro Fukuoka, MD, PhD†*

The purpose of this study was to investigate the maximum tolerated doses, dose-limiting toxicities, efficacy, and pharmacokinetic profiles in the combination of irinotecan and paclitaxel. Eligibility criteria included age 75 years or younger, good performance status, adequate organ function, and unresectable non–small cell or extensive disease of small cell lung cancer. Irinotecan was administered on days 1 and 8 over 90 minutes, and paclitaxel was administered on day 8 over 3 hours after 90 minutes from the end of the irinotecan infusion. Irinotecan and paclitaxel were dose-escalated from 40 and 135 mg/m^2 and repeated every 4 weeks. The authors also administered a higher dosage with preventive granulocyte colony-stimulating factor support from day 9. Thirty-one patients were assessed for toxicities and responses. Dose-limiting toxicities were neutropenia and febrile neutropenia. The dose of irinotecan 60 mg/m^2 and paclitaxel 200 mg/m^2 with preventive granulocyte colony-stimulating factor support was tolerable and suitable for a phase II trial. Nine of 25 (36%) patients with non–small cell and all six patients with small cell carcinoma achieved partial response. The areas under the concentration versus time curves of irinotecan and its metabolites on day 8 were significantly higher than on day 1. This combination therapy must be planned only after careful consideration of the drug–drug interaction.

Key Words: Lung cancer, Irinotecan, Paclitaxel, Phase I, Pharmacokinetics.

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Chemotherapy for non–small cell lung cancer (NSCLC) has recently improved survival by using platinum compounds and new drugs (e.g., vinorelbine, gemcitabine, taxanes, and irinotecan).[1] Chemotherapy for extensive disease of small cell carcinoma (ED-SCLC) has also improved survival using cisplatin and irinotecan.[2] Although these regimens statistically improved survival, the benefits are far from satisfactory. There are comparatively few reports of nonplatinum regimens, and we do not have sufficient knowledge about these regimens regarding maximum tolerated doses (MTD), toxicities, responses, and pharmacokinetic profiles. However, irinotecan and paclitaxel have shown antitumor activity for both non–small cell and small cell carcinoma as a single agent.[3–6] This combination is also reported to have additive or supra-additive antitumor effects for lung cancer cells in vitro by using an isobologram.[7,8] Therefore, we conducted this combination phase I study to evaluate MTD, dose-limiting toxicities (DLTs), and pharmacokinetics in this combination therapy. We also evaluated the response rate and pharmacokinetic profiles.

Before planning this study, we performed this combination trial by another administration schedule.[9] In the prior trial, irinotecan was administered over 90 minutes on days 1, 8, and 15 and paclitaxel was given by infusion over 3 hours on day 2. Starting doses of irinotecan and paclitaxel were 50 and 135 mg/m^2, respectively. DLTs were neutropenia and febrile neutropenia, and MTD was the starting dose. Furthermore, most of the patients could not receive irinotecan on days 8 and 15 because of neutropenia. Although the neutropenia from this combination regimen was intolerable, an antitumor response was seen in the majority of the patients, suggesting that this combination might provide good antitumor activity and that an alternative administration schedule was needed to use these drugs. In this new trial, we therefore modified the administration schedule to escalate dose intensity while avoiding severe toxicities.

PATIENTS AND METHODS

Patient Selection

Patients with unresectable NSCLC or ED-SCLC were eligible for the trial. Pathologic confirmation and assessable lesions were necessary before study entry. Previous chemotherapy or radiotherapy, if given, must have been completed at least 4 weeks before entry. Other eligibility criteria included age 20 to 75 years, Eastern Cooperative Oncology Group performance status of 0 to 1, estimated life expectancy of at least 3 months, and adequate organ function defined as follows: white blood cell count greater than or equal to 4000 cells/μl, absolute neutrophil count greater than or equal to

*Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka; and †Department of Medical Oncology, Kinki University School of Medicine, Osaka, Japan.

Address for correspondence: Gyo Asai, MD, PhD, Division of Thoracic Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi, Sunto-gun, Shizuoka 411-8777, Japan; email: gyoa@gmx.net.

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2000 cells/μl, platelet count greater than or equal to 100,000 cells/μl, serum creatinine less than or equal to 1.2 mg/dL, bilirubin less than or equal to 1.5 mg/dL, serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) less than twice the upper limit of normal, and PaO_2 greater than or equal to 60 mmHg. Patients with interstitial pneumonia, active infection, unstable cardiac disease, uncontrolled diabetes mellitus, pleural or cardiac effusion that required drainage, or symptomatic brain metastasis were ineligible. Our hospital institutional review committee approved this study, and all patients provided written informed consent.

Treatment

Irinotecan was administered on days 1 and 8 over 90 minutes, and paclitaxel was administered on day 8 over 3 hours after 90 minutes from the end of irinotecan infusion (Figure 1). All patients received premedication for paclitaxel and vomiting. The treatment was repeated every 4 weeks. The latter therapy was permitted using preventive granulocyte colony-stimulating factor (G-CSF) support from day 9 if patients experienced DLT of leukopenia or neutropenia and achieved partial response or stable disease on the previous course. The criteria for administration on day 8 were white blood cell count greater than or equal to 3000 cells/μl and other eligibility criteria before study entry. If patients did not clear this criteria for day 8, their treatment was cancelled and they were excluded from the evaluation of toxicities and responses.

Dose Escalation

The dose escalation schedule is shown in Table 1. Evaluation of DLTs for dose escalation was performed for the first course of chemotherapy. DLTs were defined using National Cancer Institute Common Toxicity Criteria (version 2.0)[10] as grade 4 neutropenia lasting 5 days or more, other grade 4 hematologic toxicities, neutropenic fever, or grades 3 and 4 toxicities in other organ systems except for nausea and vomiting. Three patients were assigned to each dose level. When all three patients did not experience DLT, we shifted to the next dose level. If one or two patients experienced DLT, an additional three patients were entered at the dose level before dose escalation. When at least three patients were found to have DLT, the dose was defined as the MTD. After the MTD was determined without preventive G-CSF support, we continued this study with preventive G-CSF support from day 9 until the recovery of neutropenia. We permitted the latter therapy by using preventive G-CSF support if patients who experienced DLT achieved stability or a partial response. Intrapatient dose escalation was not permitted. World Health Organization tumor evaluation criteria were used for tumor response evaluation.[11,12]

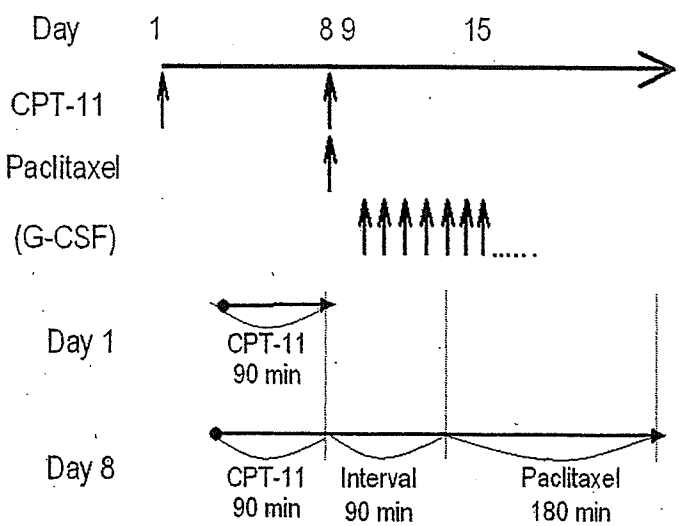

FIGURE 1. Treatment schedule of irinotecan and paclitaxel.

TABLE 1. Dose Escalation Schedule

Dose Level	CPT-11 (mg/m²)	Paclitaxel (mg/m²)
1	40	135
2	50	135
3	60	135
4	60	150
5	60	175
6	60	200

CPT-11, irinotecan.

Pharmacokinetic Analysis

Blood samples for pharmacokinetic analysis were obtained on days 1 and 8 in the first course. We collected samples by means of a peripheral venous catheter at the following times from the end of irinotecan infusion: 0, 15, 30, 90, 180, 240, 300, 420, 540, and 1410 minutes on day 1; and 0, 15, 30, 90, 180, 240, 270, 285, 300, 360, 420, 540, 630, and 1410 minutes on day 8, respectively. To analyze the pharmacokinetics of paclitaxel and the influence on the pharmacokinetics of irinotecan by paclitaxel, several processes were

TABLE 2. Patient Characteristics

Characteristic	Value
No. of patients enrolled	31
Median age (range) (yr)	62 (36–75)
Sex	
Male	23
Female	8
PS	
0	4
1	27
Prior chemotherapy	
Yes	2
No	29
Type of lung cancer	18
Adenocarcinoma	6
Squamous cell carcinoma	1
Large cell carcinoma	6
Small cell carcinoma	
Median no. of courses (range)	2 (1–5)

PS, performance status.

TABLE 3. Major Toxicities

	Level 1	Level 2	Level 3	Level 3' (G-CSF)	Level 4 (G-CSF)	Level 5 (G-CSF)	Level 6 (G-CSF)
No. of patients	3	6	3	2* + 1	6	6	6
Neutropenia							
G3	1	0	0	1	2	0	1
G4 (<5 days)	1	4	3	1	2	2	1
G4 (≥5 days)	0	0	0	0	0	0	0
Neutropenic fever	0	1	2*	0	1	1	1
AST or ALT							
G2	0	0	0	0	0	0	0
G3	0	1	0	0	0	0	0
Diarrhea							
G2	0	1	1	0	1	0	1
G3	0	0	0	0	0	1	0
DLT patients	0	2	2*	0	1	2	1

*Two patients who had neutropenic fever in level 3 were treated with preventive G-CSF support in second courses as level 3'. Level 3' was tolerable for them. G, National Cancer Institute Common Toxicity Criteria grade; DLT, dose-limiting toxicity.

added on day 8. Heparinized tubes were used, and the plasma was immediately separated by centrifugation and stored at –20°C until analysis. Plasma concentrations of irinotecan, its metabolites (SN-38 and SN-38G), and paclitaxel were measured using high-performance liquid chromatography on the reported conditions.[13,14]

The area under the plasma concentration-time curve (AUC) of irinotecan, its metabolites, and paclitaxel were calculated by the trapezoidal method with extrapolation to infinity using WinNonlin (version 1.1; Scientific Consulting, Inc., Apex, NC).

The AUC of irinotecan, SN38, and SN-38G on day 1 were compared with those on day 8 using paired *t* test and Wilcoxon matched-pairs signed ranks test. Clearance of paclitaxel was compared with reported data in monotherapy.

RESULTS

Patient Characteristics

Twenty-six men and eight women were enrolled in the study and were treated between March of 1999 and November of 2002 at Kinki University Hospital in Osaka, Japan. Two men in level 3 and one man in level 4 were excused because of the criteria for administration of day 8. One showed grade 3 elevation of ALT and ileus, another showed grade 2 elevation of ALT, and the other exhibited grade 2 rash. These patients were excluded from evaluation of toxicities and responses at each dose escalation. Finally, 31 patients were evaluated for their toxicities and responses, and blood samples were drawn on both day 1 and day 8 from 31 patients. The characteristics of the 31 patients are listed in Table 2.

Toxicities and Dose Escalation

Major toxicities are hematologic toxicities, diarrhea, and elevation of AST and ALT. Other nonhematologic toxicities are mild. Details are listed in Table 3. In level 2, one patient developed grade 3 liver dysfunction and the other developed neutropenic fever. In level 3, all patients developed grade 4 neutropenia and two of three patients developed neutropenic fever. Although level 3 had not reached the definition of MTD at this point, we judged that the dose of level 3 was probably MTD, and that further continuation of level 3 was dangerous. However, two patients who had neutropenic fever did not develop DLT in the second course of level 3 with preventive G-CSF support. We decided, therefore, to continue this study with preventive G-CSF support from level 3. One patient added to level 3 with preventive G-CSF support did not develop DLT. Most patients received second or later courses on schedule in each level. Although the schedules were delayed in a few patients, the reasons were not toxicities. This study was subsequently continued until level 6, and the dose did not reach the MTD with preventive G-CSF support. Although level 6 with G-CSF support was tolerable, this phase I study was discontinued because each dose was close to the recommended dose for monotherapy in Japan. We estimated that the recommended dose for phase II study was irinotecan 60 mg/m^2 (days 1 and 8) and paclitaxel 200 mg/m^2 (day 8) with preventive G-CSF support from day 9.

TABLE 4. Tumor Responses

Level	Patients	PR	SD	PD
1	3		3	
2	6	2 + 1*	2	1
3	4	1	1	2
4	6	0 + 3*	2	1
5	6	4 + 2*		
6	6	2	2	2

*Patients with ED-SCLC. †NSCLC (25 patients): PR, 9 (36%; 95% CI, 18–57%). ED-SCLC (6 patients): PR, 6 (100%; 95% CI, 61–100%). PR, partial response; SD, stable disease; PD, progressive disease; CI, confidence interval.

TABLE 5. Comparison of AUCs of Day 1 and Day 8

	CPT-11	SN-38	SN-38G
Average (μg/min/ml) ± SD			
Day 1	223.3 ± 73.6	5.92 ± 5.30	70.24 ± 70.40
Day 8 (with paclitaxel)	296.3 ± 92.0	8.31 ± 7.13	102.71 ± 123.14
Paired *t* test (*p* value)	<0.0001	0.0271	0.0136
Wilcoxon matched-pairs signed ranks test (*p* value)	<0.0001	0.0044	0.0001

SD, standard deviation; CPT-11, irinotecan.

Tumor Responses

Nine of 25 (36%) patients with NSCLC achieved partial response, and all six patients with ED-SCLC achieved partial response (Table 4).

Pharmacokinetics

Pharmacokinetic analyses were conducted on 31 patient blood samples. AUCs of irinotecan and its metabolites on day 8 were significantly higher than on day 1 (Table 5). Clearance of paclitaxel (day 8) was 14.3 ± 5.3 liters/hr/m^2.

DISCUSSION

Several other studies of this combination were reported.[15–17] Both paclitaxel and irinotecan were administered weekly in some studies, and patients were given paclitaxel on day 1 and irinotecan on days 1, 8, and 15 in some studies. DLTs and other major toxicities were hematotoxicities and diarrhea. These toxicities were similar to those in this study. Administration of irinotecan on day 8 or 15 was generally skipped in the weekly schedule, or administration of paclitaxel on day 1, because of hematotoxicities. This study schedule was designed to avoid skipping administration on day 8 and to elevate dose intensity and its efficacy by using G-CSF without any risky administration on day 15. Other studies did not increase the dosage with G-CSF and did not treat patients with ED-SCLC. This combination showed comparatively stronger hematologic toxicity than the other platinum combination regimens or nonplatinum regimens as indicated from our results and the other reports on this combination.

Platinum-based combinations with third-generation drugs are standard regimens in the treatment of advanced NSCLC.[1,18,19] However, a recent meta-analysis has reported that 1-year survival was not significantly prolonged when platinum-based therapies were compared with third-generation–based combination regimens.[20] Platinum-free doublet regimens are expected to offer improved survival without decreasing quality of life. Although this trial showed a response rate similar to other nonplatinum regimens, hematotoxicities were stronger than those of the other regimens. Therefore, this combination therapy might not be suitable for the treatment of NSCLC.

In the treatment of small cell lung cancer, the regimen of cisplatin and irinotecan ensures better survival than the regimen of cisplatin and etopside.[2] There have been very few reports of platinum-free doublet regimens based on third-generation drugs in small cell lung cancer. The response rate of this study regimen was noteworthy. Although the number of patients with small cell carcinoma was limited, all patients achieved partial response (95% confidence interval, 61–100%). This combination showed similar or better response than the combination of cisplatin and etoposide, and this regimen might be as effective as the combination of cisplatin and irinotecan. Therefore, this combination is proposed as an attractive regimen for small cell lung cancer chemotherapy.

In this trial, three persons were withdrawn from treatment by the criteria of day 8 and thus excluded from evaluation. We know from our previous study that this combination may cause severe neutropenia and that some patients occasionally show stronger toxicities for irinotecan than most. For example, it has been suggested that the polymorphism of UDP-glucuronosyltransferase might raise severe toxicities.[21,22] If only single administration of low-dose irinotecan produced toxicities that conflicted with the criteria of day 8, we can regard that patient as an anomaly regarding irinotecan. At this point, our administration schedule seems to be safe for this combination.

In the pharmacokinetic study, AUCs of irinotecan and its metabolites on day 8 were significantly higher than those of day 1. Clearance of paclitaxel was similar to that in many previously reported studies. We observed a 90-minute interval between irinotecan infusion and paclitaxel infusion to avoid severe drug interactions. We concluded that the mechanism of drug elimination is competitive because we had found indications of interaction from the pharmacokinetic investigation in our previous study. Irinotecan and its metabolite are mainly excreted by P-glycoprotein and cMORT in the liver, and paclitaxel or its vehicle (Cremophor EL) will compete in some stage of excretion. Noninterval administration of paclitaxel and irinotecan would heighten the AUC and the risk of toxicities. It has been advised in phase II trials that the administration time schedule of a phase I study be retained because it is very likely that the MTDs are different in each administration schedule. If the interval between irinotecan and paclitaxel administration is shorter or the order of administration is reversed, the possible pharmacokinetic interaction and toxicities might be much stronger. This combination therapy must be planned carefully with due consideration of the drug–drug interaction.

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Imaging of gefitinib-related interstitial lung disease: Multi-institutional analysis by the West Japan Thoracic Oncology Group

Masahiro Endo[a,*], Takeshi Johkoh[b], Kazuhiko Kimura[c], Nobuyuki Yamamoto[d]

[a] *Division of Diagnostic Radiology, Shizuoka City Hospital, Shizuoka, Japan*
[b] *Department of Medical Physics, Osaka University Graduate School of Medicine, Oasaka, Japan*
[c] *Department of Radiology, Kawasaki Hospital, Kobe, Japan*
[d] *Division of Thoracic Oncology, Shizuoka Cancer Center, Nagaizumi, Japan*

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Summary Gefitinib (Iressa™) is an epidermal growth factor receptor tyrosine kinase inhibitor that has been approved for the treatment of lung cancer in Japan, however, after marketing several cases of severe pulmonary toxicity were reported. The West Japan Thoracic Oncology Group conducted an independent survey of acute pulmonary toxicity and interstitial lung disease (ILD) caused by gefitinib in its member's institutions. The purpose of this study was to clarify the image characteristics of ILD caused by the molecular-targeting drug gefitinib. A total of 1976 patients had been treated with gefitinib between August and December 2002, and 102 of them were suspected of having acute pulmonary toxicity and ILD. A final definite diagnosis of gefitinib-induced ILD was made by at least three radiologists based on a review and analysis of the chest radiography and CT findings plus the clinical data in the medical records. The imaging findings were classified into four patterns: (A) a nonspecific area with ground-glass attenuation, (B) a multifocal area of airspace consolidations, (C) patchy distribution of ground-glass attenuation accompanied by interlobar septal thickening, and (D) extensive bilateral ground-glass attenuation or airspace consolidations with traction bronchiectasis. CT as well as chest radiography had been performed in 65 of the 102 patients at the onset of ILD, and chest radiography alone had been performed in 26. After excluding 11 cases with insufficient data and 21 cases

Abbreviations: AEP, acute eosinophilic pneumonia; AIP, acute interstitial pneumonia; BOOP, bronchiolitis obliterans organizing pneumonia; CT, computed tomography; DAD, diffuse alveolar damage; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; WJTOG, West Japan Thoracic Oncology Group

* Corresponding author. Present address: Division of Endoscopy, Shizuoka Cancer Center, Nagaizumi, Japan. Tel.: +81 55 989 5222; fax: +81 55 989 5783.
E-mail address: m.endo@scchr.jp (M. Endo).

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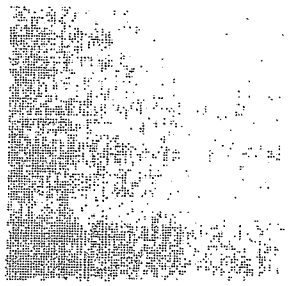


concluded to be other pulmonary diseases, 70 patients were diagnosed with gefitinib-induced ILD. Finally, the diagnostic image findings were classified as pattern A in 29 cases, pattern B in 7 cases, pattern C in 3 cases, pattern D in 20 cases and others in 11 cases. The CT images were classified as pattern A, B, C, and D in 24, 7, 1, and 12 cases, respectively. The mortality rate was significantly higher in the patients with pattern D than the other patterns. Pattern D were thought to represent the features of diffuse alveolar damage. In conclusion, the molecular-targeting drug gefitinib induces pulmonary toxicity at a certain rate and the imaging findings of ILD induced by gefitinib are similar to those of pulmonary toxicity induced by conventional antineoplastic agents.

1. Introduction

Lung cancer is the leading cause of cancer deaths among both females and males in Japan and worldwide. The epidermal growth factor receptor tyrosine kinase inhibitor gefitinib (Iressa™) was recently approved in Japan for the treatment of recurrent non-small cell lung cancer, before being approved in the United States. Clinical trials have revealed significant variability in response to gefitinib, showed higher response rate in Japanese patients than in a predominantly European-derived population (27.5% versus 10.4%, respectively in a multi-institutional phase II trial) [1]. The good responders in Japan were women, patients with adenocarcinoma, and non-smokers. Adverse drug reactions in the pre-approved trials were frequent, but mild, and included an acne-like skin rash and diarrhea. However, some cases of gefitinib-related life-threatening interstitial lung disease (ILD) have been reported since the marketing of the drug [2–6], and the incidence of ILD was considered higher than that of ILD caused by pre-existing anticancer drugs. Based on these considerations, the West Japan Thoracic Oncology Group (WJTOG) independently investigated the incidence of acute pulmonary toxicity and ILD, the risk factors for their development, and the outcome. The radiological diagnosis of acute pulmonary toxicity and ILD in that survey was made by the participating radiologists. The purpose of this study was to clarify the characteristics of pulmonary toxicity induced by the molecular-targeting drug gefitinib based on an analysis of diagnostic images alone.

2. Materials and methods

We observed the guidelines for the retrospective epidemiological analysis in Japan using encoded data of patients in order to survey the incidence and risk factors of gefitinib-related ILD, and the survey by the WJTOG was approved by the review board of each institution.

2.1. Patients

The chest computed tomography (CT) scans and chest radiographs obtained in the 102 patients with suspected gefitinib-related ILD were retrospectively reviewed. The patients were identified as follows.

We requested to examine the number of patients who had begun to receive gefitinib between August 31, 2002 (when the drug was put on the National Health Insurance Drug List) and December 31, 2002, and the number of patients who were suspected of acute pulmonary toxicity and ILD to the 112 centers that were members of the WJTOG at the end of December 2002, and responses were obtained from 84 centers. A total of 1976 patients had been treated with gefitinib, and 102 of them were suspected of having acute pulmonary toxicity and ILD. In addition, a thorough clinical history and record of the patients and their chest radiography and CT scans taken about 1 month before the onset of ILD, at the onset, and serially after the onset, were obtained from each institution. Chest radiography and CT scans taken about 1 month before the onset were obtained for 97 and 92 patients, respectively, and chest radiography and CT scans taken at the onset were obtained for 92 and 65 patients, respectively. Serial chest radiography and CT scans after the onset were obtained for 89 and 32 patients, respectively. The patients consisted of 15 females and 87 males, and their mean age was 67 years (range, 38–90 years). All patients had non-small cell lung cancer including adenocarcinoma in 69 patients, squamous cell carcinoma in 27 patients, large cell carcinoma in 2 patients, and others in 4 patients. No patients had undergone lung biopsy and/or bronchoalveolar lavage to diagnose ILD.

2.2. Radiography and CT scanning methods

The chest radiographs obtained were the original films taken at each institution and included conventional films and computed radiographs. The CT scans were performed with a CT unit at each institution. All CT scans were obtained with 5–10 mm collimation at 5–10 mm intervals and with the patient in the supine position and at maximal inspiration. In 40 cases thin-section CT was performed with 1–2 mm collimation at 10 mm intervals at the onset of ILD. Scanning extended from the apices of lungs to the costophrenic angles. Thin-section CT images were reconstructed with a high-spatial-frequency algorithm. CT scans were obtained with window settings for lung parenchyma (window width, 1600–1800 HU; window level, −600 to −700 HU) and mediastinum (window width, 300–350 HU; window level, 25–40 HU).

2.3. Image analysis

The chest radiography and CT images were reviewed by at least three chest radiologists together, and final decisions regarding the findings were made by consensus, in conference with pulmonary physicians and medical oncologists. Gefitinib-related ILD was defined as an acute respiratory disorder that developed during gefitinib therapy in which ILD

was suspected on the basis of the imaging findings and other diseases, such as pneumonia, could be ruled out based on the clinical information.

The confirmation of the diagnosis was categorized like this: (1) proofless ILD, as defined by no chest radiography and CT at the onset of the disease, (2) non-ILD, as defined by pneumonia, progression of lung cancer, radiation pneumonitis, organizing pneumonia, and non-gefitinib related ILD, and (3) confirmed ILD, as defined by a confirmation of gefitinib-related ILD.

The CT findings were assessed for distribution and patterns of such as ground-glass attenuation, airspace consolidation, interlobular septal thickening, and traction bronchiectasis. Ground-glass attenuation was defined as an area of slightly increased attenuation in which the bronchial walls and vessels remained visible. Airspace consolidation was defined as an area of increased attenuation with obscuration of the adjacent bronchial wall and vessels, and traction bronchiectasis was defined as irregular bronchial dilatation within areas with ground-glass attenuation or airspace consolidation. Based on these findings, the CT images of gefitinib-induced ILD were classified into four patterns [7], and we defined the plain-film findings corresponding to them.

Pattern A was defined as a pattern of only nonspecific area with ground-glass attenuation, and it corresponded to diffuse and faint opacity without lung volume loss on chest radiography. Pattern B was defined as a pattern of multifocal areas of airspace consolidation such as in cryptogenic organizing pneumonia or bronchiolitis obliterans organizing pneumonia (BOOP), and it corresponded mainly to peripheral consolidations on chest radiography. Pattern C was defined as a pattern of patchy distribution of areas with ground-glass attenuation accompanied by interlobular septal thickening, such as in acute eosinophilic pneumonia (AEP), and it corresponded to patchy or diffuse faint, linear opacities on chest radiography. Pattern D was defined as a pattern of extensive bilateral ground-glass attenuation or airspace consolidations with traction bronchiectasis, such as in acute interstitial pneumonia (AIP), and it corresponded to diffuse faint opacities or consolidations with lung volume loss on chest radiography. Pre-existing lung lesions such as emphysema, IPF, old inflammation, and lung resection, etc., were also recorded.

2.4. Statistical analysis

The differences in frequency of each category in each subgroup were evaluated by the Fisher exact test or the χ^2-test with continuity correction, probability values less than 0.05 were considered significant.

3. Results

The images and data in the medical records of the 102 patients with suspected ILD were analyzed. Sixty-five patients had been examined by CT as well as chest radiography at the onset of ILD, but 26 patients had been examined by chest radiography alone. Eleven patients were considered as indeterminate for pulmonary toxicity, because no chest radiographs or CT scans at the onset were submitted, or they were insufficient. We analyzed the chest radiographs and/or CT scans of the other 91 patients in the context of the clinical course, and made a diagnosis of gefitinib-related ILD in 70 of them. The remaining 21 patients were diagnosed with other diseases; pneumonia in 9, progression of lung cancer in 4, radiation pneumonitis in 3, and other conditions in 5 (Table 1).

Table 1 Confirmation of the diagnosis of interstitial lung disease (ILD) induced by gefitinib

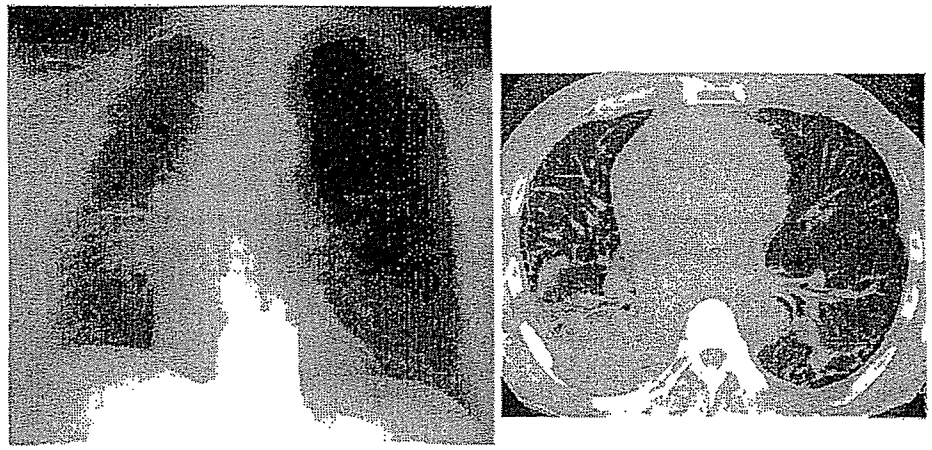
Category	Number of patients
Proofless ILD	11
Non-ILD	21
(1) Pneumonia (infectious disease)	9
(2) Progression of lung cancer	4
(3) Radiation pneumonitis	3
(4) Others	5
Confirmed ILD	70
Total	102

Chest radiographs of the 70 patients diagnosed with gefitinib-related ILD were classified as pattern A in 29 patients (43.8%; Fig. 1a), pattern B in 7 (10.0%; Fig. 2a), pattern C in 3 (4.3%), pattern D in 20 (28.6%; Fig. 3a), and other patterns in 11 (15.7%). The CT images were classified as pattern A, B, C, D, and other patterns in 24 patients (47.1%; Fig. 1b), 7 patients (13.7%; Fig. 2b), 1 patient (2.0%), 12 patients (23.5%; Fig. 3b), and 7 patients (13.7%), respectively. The number of deaths in each pattern was 9, 2, 0, 15, and 5, respectively, and the mortality rate was 31.0%, 28.6%, 0%, 75.0%, and 45.5%, respectively. It was significantly higher in patients with pattern D than in patients with other patterns (75.0% versus 32.0%, $p = 0.001$).

In addition, we analyzed associations between the frequency of pre-existing lung lesions and the fatal cases. There were 52 (74.1%) patients with various grades of pulmonary emphysema, 14 (20.0%) with IPF, and 20 (28.6%) with old inflammation, such as pleural thickening and/or fibrous change. Thoracic irradiation was performed in 16 (22.9%) patients, and lung resection in 17 (24.3%). No associations were found between the frequency of pre-existing lung lesions and the fatal cases (Tables 2 and 3).

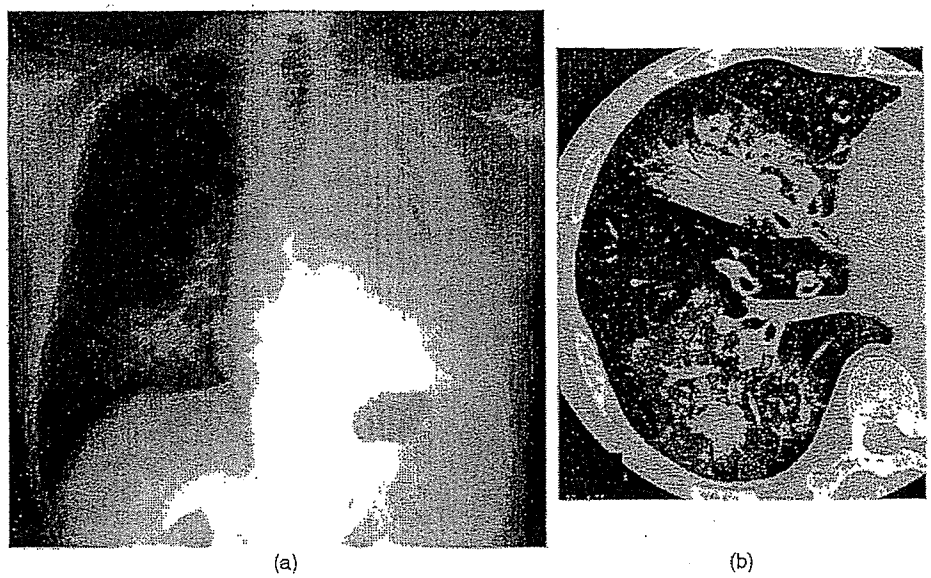
Table 2 Frequency of radiological patterns of ILD induced by gefitinib and mortality

Radiological pattern	Frequency		Mortality
	Chest radiography	CT	
A	29 (43.8%)	24 (47.1%)	9 (31.0%)
B	7 (10.0%)	7 (13.7%)	2 (28.6%)
C	3 (4.3%)	1 (2.0%)	0 (0.0%)
D	20 (28.6%)	12 (23.5%)	15 (75.0%)
Others	11 (15.7%)	7 (13.7%)	5 (45.5%)
Total	70	51	31 (44.3%)



(a) (b)

Fig. 1 A 60-year-old male with stage IV non-small cell lung cancer who had been treated with platinum-based chemotherapy developed mild dyspnea on day 10 after administration of gefitinib. The chest radiography reveals a mass opacity in the right hilum and diffuse ground-glass density over the entire lung field against a background of emphysema and fibrosis (a). The CT scan shows nonspecific areas with ground-glass attenuation throughout the lung parenchyma (b).



(a) (b)

Fig. 2 A 70-year-old male with stage IIIB adenocarcinoma who had been treated with platinum-based chemotherapy was started on gefitinib, and developed a severe cough and mild dyspnea on day 30 of gefitinib therapy. The chest radiography shows areas of consolidation on the upper and lower field of the right lung (a), and multifocal areas of airspace consolidation are seen on the thin-section CT scan (b).

4. Discussion

After gefitinib was approved on July 5, 2002, some cases of severe pulmonary toxicity were come to light in Japan, and AstraZeneca organized an Expert Committee analyzed about gefitinib-related ILD [8]. The WJTOG also independently conducted a survey of patients with acute pulmonary toxicity caused by gefitinib. Then we participated in a survey and had an opportunity to review the chest radiographs and CT images suspected gefitinib-related ILD.

In this study nonspecific areas with ground-glass attenuation (pattern A, 47.1%) and extensive bilateral ground-glass attenuation or airspace consolidation with traction bronchiectasis (pattern D, 23.5%) were observed on chest CT images in the majority of patients, and it was considered that the molecular-targeting drug gefitinib also showed radiological appearances of pulmonary toxicity similar to those reported to be caused by conventional antineoplastic drugs [9–13]. Those drugs are known to induce a variety of pathological reactions in the lung, such as noncardiogenic