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 II Study of 3-Week Scheduling of Irinotecan in Combination With Cisplatin in Patients With Advanced Nonsmall-Cell Lung Cancer

Hiroshi Saito, MD, Shinzoh Kudoh, MD,† Kazuhiko Nakagawa, MD,‡ Shunichi Negoro, MD,§ Kaoru Matsui, MD,¶ Hiroshi Semba, MD,‖ and Minoru Takada, MD***

Objectives: The combination of irinotecan and cisplatin given every 4 weeks is one of the standard treatments for advanced nonsmall-cell lung cancer (NSCLC) in Japan. The purpose of this study is to evaluate the efficacy, safety and dose-intensity as a measure of the feasibility of 3-week scheduling of irinotecan and cisplatin in patients with advanced NSCLC in phase II study.

Methods: Previously untreated patients with stage IIIB and IV NSCLC were treated intravenously with irinotecan (60 mg/m^2) on days 1 and 8 and cisplatin (60 mg/m^2) on day 1 of a 3-week cycle.

Results: Of the 28 patients enrolled, 27 were evaluable for response and toxicity. The response rate was 30% (95% confidence interval, 14–50%). The median duration of response was 16 weeks (range, 10–26 weeks). The median survival time for all patients was 52 weeks and the 1-year and 2-year survival rates were 48% and 29%, respectively. The dose-intensity of irinotecan was 34 mg/m^2/wk (range, 19–40). The major toxicities observed were neutropenia (grade 3, 30%; 4, 30%), leukopenia (grade 3, 30%), and diarrhea (grade 3, 22%). Other toxicities were generally mild.

Conclusions: Three-week scheduling of irinotecan and cisplatin is effective and feasible in advanced NSCLC.

Key Words: irinotecan, cisplatin, nonsmall-cell lung cancer

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Lung cancer is the leading cause of cancer mortality. Nonsmall-cell lung cancer (NSCLC) accounts for 80% to 85% of patients with lung cancer and approximately two-thirds of them are inoperable at the time of diagnosis. Therefore, chemotherapy is a mainstay of the treatment of advanced nonsmall-cell lung cancer (NSCLC).[1] Recent meta-analyses have shown that cisplatin-based chemotherapy produces improved survival in advanced NSCLC.[2,3] Several new agents including irinotecan, taxanes, vinorelbine, and gemcitabine are active as single agents against NSCLC with the response rate ranging from 20% to 27%.[4] Among these, irinotecan hydrochloride, a camptothecin derivative, is active against NSCLC with a response rate of 32% as a single agent when given on a weekly basis.[5] The combination of irinotecan and cisplatin is considered to be synergistic and is active against advanced NSCLC.[6,7] A phase III study performed in Japan has revealed that a combination therapy with irinotecan and cisplatin given every 4 weeks produced comparable survival to a combination of cisplatin and vindesine in patients with advanced NSCLC.[8] In the subgroup analysis, the combination of irinotecan and cisplatin was also superior to the combination of cisplatin and vindesine in terms of survival prolongation in patients with stage IV disease.[8] Based on these results, the combination of irinotecan and cisplatin given every 4 weeks is one of the standard treatments for advanced NSCLC in Japan. In that study, there were considerable delays in treatment with or dose omissions of irinotecan, mostly on day 15, because of leukopenia and/or diarrhea, and the dose intensity of irinotecan was only 30 mg/m^2/wk (range, 12–46) in contrast to the planned dose intensity of 45 mg/m^2/wk.[8] Therefore, we conducted this phase II study of irinotecan and cisplatin scheduled every 3 weeks to evaluate response rate, safety and dose intensity as a measure of feasibility in patients with advanced NSCLC.

PATIENTS AND METHODS

Eligibility Criteria

Patients with histologically or cytologically proven diagnosis of NSCLC were eligible for this study. Other eligibility criteria included the following: stage IIIB with malignant pleural or pericardial effusion or contralateral hilar node metastasis that precluded curative radiotherapy or stage IV; measurable disease; no prior therapy including chemotherapy, radiotherapy or surgery to the primary tumor; age ranging from 20 to 74 years; a life expectancy ≥12 weeks; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; an adequate baseline organ function defined

From the *Aichi Cancer Center Aichi Hospital, Okazaki, Japan; †Osaka City University Hospital, Osaka, Japan; ‡Kinki University Hospital, Osakasayama, Japan; §Hyogo Medical Center for Adults, Akashi, Japan; ¶Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Habikino, Japan; ‖Kumamoto Regional Medical Center, Kumamoto, Japan; and **Kinki-chuo Chest Medical Center, Sakai, Japan.

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Reprints: Hiroshi Saito, MD, Department of Respiratory Medicine, Aichi Cancer Center Aichi Hospital, 18 Kuriyado Kake-machi, Okazaki Aichi 444-0011, Japan. E-mail: hsaito@sun-inet.or.jp.

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as leukocyte count from 4000 to 12,000/mm^3, platelet count ≥ 100,000/mm^3, hemoglobin ≥9.5 g/dL, aspartate aminotransferase and alanine aminotransferase ≤100 IU/L, total bilirubin ≤1.5 mg/dL, serum creatinine ≤ the institutional upper limit of normal or 24-hour creatinine clearance ≥60 mL/min, and PaO_2 at rest ≥60 mm Hg. Patients were ineligible if they had the following criteria: superior vena caval syndrome; history of serious drug allergy; massive pleural or pericardial effusion or ascites that required drainage; active infection; persistent diarrhea (watery stool); paralytic ileus; interstitial pneumonia or pulmonary fibrosis; symptomatic brain metastasis; other concurrent active malignancy; uncontrolled diabetes mellitus; pregnancy or lactation, other concomitant serious medical conditions. The study protocol was approved by each institutional review board for clinical use. All patients gave written informed consent before enrollment.

Study Evaluations

Pretreatment baseline evaluation included a complete medical history and physical examination, complete blood cell count (CBC), blood chemistry studies, chest radiography, computed tomography (CT) of the chest, CT or ultrasound study of the abdomen, CT or magnetic resonance imaging of the brain, bone scintigraphy and electrocardiography. Complete blood cell count and blood chemistry studies were repeated weekly.

Treatment Schedule

Patients were treated intravenously with irinotecan 60 mg/m^2 on days 1 and 8 and cisplatin 60 mg/m^2 on day 1. Irinotecan was reconstituted in 250 mL of normal saline or 5% dextrose in water and infused over 60 minutes. Cisplatin was administered over 60 minutes with adequate hydration, usually ≥2500 mL infusion. Diuretics and antiemetics were given at the discretion of each treating physician. Therapy was repeated every 3 weeks for at least 4 cycles unless there was evidence of disease progression, unacceptable toxicity or withdrawal of consent.

Dose Modification

Dose modifications were made in response to any myelosuppression and nonhematologic toxicity that occurred. If a leukocyte count of less than 3000/mm^3 or a platelet count of less than 100,000/mm^3 was determined or if the patient had fever (≥38.0°C) or grade ≥1 diarrhea, or other grade ≥3 toxicity on days 8 through 15, irinotecan was withheld. Irinotecan was decreased by 10 mg/m^2 in the subsequent cycle if a leukocyte nadir count of less than 1000/mm^3 or a platelet nadir count less than 50,000/mm^3 or grade ≥2 diarrhea, or other grade ≥3 nonhematologic toxicity (excluding electrolytes imbalance, nausea, appetite loss, fatigue, and hair loss) was observed during the previous course of treatment. Cisplatin was decreased by 10 mg/m^2 in the subsequent cycle if grade ≥2 creatinine or other grade ≥3 nonhematologic toxicity (excluding electrolyte imbalance, nausea, appetite loss, fatigue, and hair loss) was observed during the previous course of treatment.

Evaluation

The Response Evaluation Criteria in Solid Tumors (RECIST) were used for response assessment.[9] Toxicity was evaluated according to National Cancer Institute-Common Toxicity Criteria (version 2.0). An independent review was conducted to validate the eligibility of the patients, staging, response, and toxicity.

Statistical Analysis

The primary end point of this study was the estimate of the response rate. We assumed that the response rate was 45% from a prior trial reported by Negoro et al[8] and the distance from the point estimate to the 95% confidence interval (CI) was 20%. Thus, 24 evaluable patients were required. If 11 out of 24 evaluable patients have response, the response rate is 46% with the exact 95% CI of 26% to 67%. Durations of response and survival were measured from the first day of the treatment, and the overall survival curve and progression-free survival curve were calculated by the method of Kaplan and Meier.[10]

RESULTS

Patient Characteristics

Between January and June 2003, 28 patients were entered in this study. Baseline characteristics of the evaluable patients were listed in Table 1. Twenty patients (74%) had stage IV disease and 11 patients (41%) had ECOG performance status of 0. Adenocarcinoma was the dominant histology (74%).

Treatment Administration

Patients received a median of 4 treatment cycles (range, 1–6 cycles). Seven patients received only 1 cycle of treatment because of adverse events (4 patients) and progressive disease (3 patients). A total of 92 cycles were given. Irinotecan administration on day 8 was withheld in 9 cycles (10%)

TABLE 1. Patients Characteristics

No. patients	27
Age (years)	
Median	63
Range	38–72
Gender (% of patients)	
Male	19 (70)
Female	8 (30)
Performance status (ECOG) (% of patients)	
0	11 (41)
1	16 (59)
Stage (% of patients)	
IIIB	7 (26)
IV	20 (74)
Histology (% of patients)	
Adenocarcinoma	20 (74)
Squamous cell carcinoma	7 (26)

ECOG, Eastern Cooperative Oncology Group.

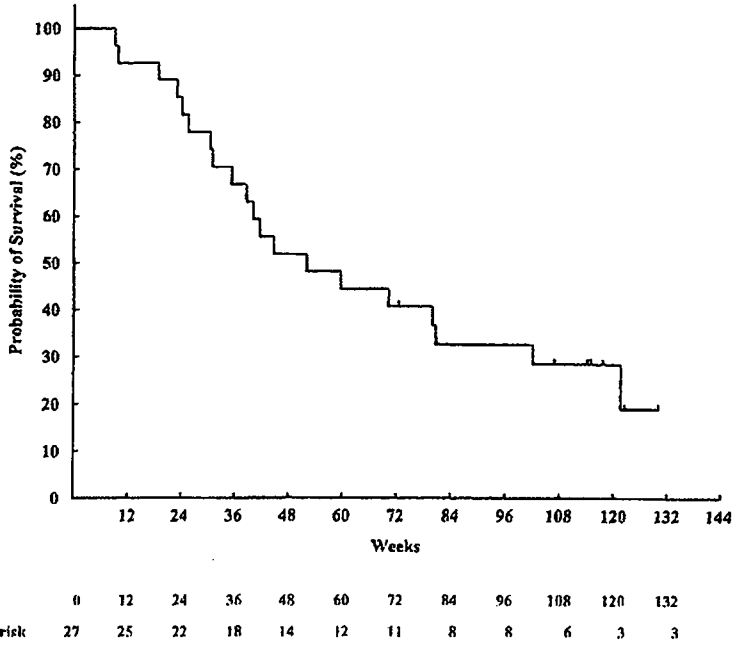

FIGURE 1. Kaplan-Meier survival curve of 27 evaluable patients with advanced nonsmall cell lung cancer.

and dose reduction was made in 41 cycles (45%). The dose of cisplatin was reduced in 18 cycles (20%). The dose-intensity of irinotecan was 34 mg/m^2/wk (85% of the planned dose) and cisplatin 19 mg/m^2/wk (95% of the planned dose).

Response and Survival

Three of 7 patients (43%) with stage IIIB disease achieved partial response while 5 of 20 patients (25%) with stage IV disease showed partial response, with an overall response rate of 30% (95% CI, 14–50%). The response rate for adenocarcinoma and squamous cell carcinoma were 20% and 57%, respectively. Thirteen patients showed stable disease and 6 had progressive disease. No complete response was seen. The median duration of response was 16 weeks (range, 10–26 weeks). The median survival time for all patients was 52 weeks and a 1-year and 2-year survival rate was 48% (95% CI, 29–67%) and 29% (95% CI, 11–46%), respectively (Fig. 1).

Toxicity

The major adverse events were shown in Table 2. Hematologic toxicity was the principal toxicity of this regimen. Grade 4 neutropenia and anemia was observed in 8 patients (30%) and 1 patient (4%), respectively. There was no grade 4 leukopenia. Thrombocytopenia was predominantly mild (grade 1–2) and only 1 patient had grade 3 toxicity. Nonhematologic toxicities mainly consisted of diarrhea, nausea and vomiting, and anorexia. Grade 3 diarrhea was observed in 6 patients (22%) but no patient had grade 4 diarrhea. Grade 3 infection was observed in 4 patients (15%) and 1 patient had febrile neutropenia. There were no treatment-related deaths.

TABLE 2. Major Toxicities by Patient and Cycle

	Grade 3/4	
	Patients (%), n = 27	Cycles (%), n = 92
Neutropenia	8/8 (59)	27/8 (38)
Leukopenia	8/0 (30)	10/0 (11)
Anemia	5/1 (22)	7/1 (9)
Thrombocytopenia	1/0 (4)	1/0 (1)
Diarrhea	6/0 (22)	9/0 (10)
Nausea	8/0 (30)	9/0 (10)
Vomiting	2/0 (7)	2/0 (2)
Infection	4/0 (15)	4/0 (4)
Anorexia	9/0 (33)	13/0 (14)

DISCUSSION

In this phase II study, we have explored the potential advantages of 3-week schedule of irinotecan and cisplatin in patients with advanced NSCLC and have achieved a 30% response rate. In the chemotherapy of advanced lung cancer, irinotecan is usually given weekly on days 1, 8, and 15 in a combination with cisplatin and the treatment cycle is repeated every 4 weeks. Masuda et al reported a 48% response rate in 4-week scheduled therapy for irinotecan and cisplatin in a phase II study.[7] Based on this result, 2 randomized phase III studies have been conducted in Japan. Negoro et al[8] compared a combination of irinotecan and cisplatin with a combination of cisplatin and vindesine and irinotecan alone while Niho et al[11] compared a combination of irinotecan and cisplatin with a combination of cisplatin and vindesine. The response rates of irinotecan and cisplatin were 44% and 29%,

respectively. Despite the difference of the response rates between the 2 phase III studies, the median survival times (50 versus 45 weeks) and the 1-year survival rates (47 versus 43%) were comparable between the 2 studies. These 2 studies have revealed that a combination therapy with irinotecan and cisplatin given every 4 weeks produced comparable survival to a combination of cisplatin and vindesine in patients with advanced NSCLC.[8,11] Furthermore, Negoro et al reported that in the subgroup analysis, the combination of irinotecan and cisplatin was superior to the combination of cisplatin and vindesine in survival prolongation in patients with stage IV disease.[8] The response rate of 30% in our study is between those of the 2 phase III studies evaluating 4-week scheduled therapy for irinotecan and cisplatin. This, plus the median survival time of 52 weeks and the 1-year survival of 48% in our study are encouraging.

Two groups evaluated 3-week scheduled therapy for irinotecan and cisplatin in patients with advanced NSCLC in the phase II studies.[12,13] Takeda et al administered irinotecan (75 mg/m^2) and cisplatin with antilate-diarrheal program and reported the response rate of 63%.[12] Han et al evaluated 2 sequences of 3-week scheduled therapy for irinotecan (80 mg/m^2) and cisplatin without any antidiarrheal measures and reported the overall response rate of 47%.[13] These studies including our own suggest that 3-week cycle of irinotecan and cisplatin is effective in patients with advanced NSCLC. Recently, another randomized phase III study conducted in Japan has compared the 4-week scheduled therapy for irinotecan and cisplatin as the control arm with 3 platinum-based doublets with new agents (carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine).[14] This study has shown that 4-week scheduled therapy for irinotecan and cisplatin was comparable to other platinum doublet therapy with new agents in terms of response rate and survival with different toxic profiles. Further evaluation will be necessary to clarify whether 3-week scheduled therapy for irinotecan and cisplatin is superior in terms of survival and toxicity to 4-week scheduled therapy as well as other platinum doublet therapy with new agents in the treatment of advanced NSCLC.

Neutropenia was the most prominent toxicity in this study and grade 4 neutropenia was observed in 8 patients (30%). This incidence was lower than in other studies evaluating the 4-week scheduled therapy for irinotecan and cisplatin, in which the incidence of grade 4 neutropenia was 37% to 38%.[7,8] The incidence of grade 4 neutropenia in the 4-week scheduled therapy for irinotecan and cisplatin was lower than in the platinum-based doublet in a combination with a new agent such as paclitaxel, gemcitabine, vinorelbine, and docetaxel.[15–18] In 3-week scheduled therapy, the incidence of grade 4 neutropenia is further reduced. Leukopenia was usually less severe than neutropenia. In our study, grade 3 leukopenia was observed in 30% of the patients and there was no grade 4 leukopenia observed. Anemia and thrombocytopenia were relatively mild with this regimen. Diarrhea was the most troublesome nonhematologic toxicity in irinotecan-containing regimens.[5,19] We observed grade 3 diarrhea in 22% of our patients and no patient experienced grade 4 diarrhea. Antilate-diarrheal program may be beneficial to further reduce moderate to severe diarrhea.[12]

Another aim of this study was to evaluate dose-intensity as a measure of the feasibility of a 3-week schedule of irinotecan and cisplatin. In the previous phase III study, the dose intensity of irinotecan was only 30 mg/m^2/wk (67% of the planned dose).[8] We planned to administer irinotecan at a dose of 60 mg/m^2 on days 1 and 8, giving the planned dose-intensity of irinotecan of 40 mg/m^2/wk. The actual dose-intensity of irinotecan administered was 34 mg/m^2/wk (85% of the planned dose). In contrast, the actual dose intensities of irinotecan in the studies of Takeda et al and Han et al were 48.5 mg/m^2/wk and 44 mg/m^2/wk, respectively.[12,13] One explanation for this difference is that we reduced the dose of irinotecan based on the toxicity in the previous cycle while they did not reduce the dose of irinotecan based on the toxicity in the previous cycle. Despite this difference, these data suggest that 3-week cycle of irinotecan and cisplatin is better tolerated than the 4-week scheduling of irinotecan and cisplatin with greater irinotecan dose-intensity.

In summary, this study suggests that therapy with a 3-week cycle of irinotecan and cisplatin is effective and feasible in the treatment of advanced NSCLC. Further evaluation of the combination of irinotecan and cisplatin, at the doses and schedule used in this study, is warranted in advanced NSCLC.

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ORIGINAL REPORT

Phase II Trial of Amrubicin for Treatment of Refractory or Relapsed Small-Cell Lung Cancer: Thoracic Oncology Research Group Study 0301

Sayaka Onoda, Noriyuki Masuda, Takashi Seto, Kenji Eguchi, Yuichi Takiguchi, Hiroshi Isobe, Hiroaki Okamoto, Takashi Ogura, Akira Yokoyama, Nobuhiko Seki, Yoshiko Asaka-Amano, Masao Harada, Akihiro Tagawa, Hiroshi Kunikane, Masanori Yokoba, Kazutsugu Uematsu, Takayuki Kuriyama, Yumi Kuroiwa, and Koshiro Watanabe

From the Department of Respiratory Medicine, Kitasato University School of Medicine, Sagamihara, Kanagawa; Department of Respirology, Tokai University School of Medicine, Isehara; Department of Respirology, Graduate School of Medicine, Chiba University, Chiba; Department of Pulmonary Disease, National Hospital Hokkaido Cancer Center, Sapporo; Department of Respirology, Yokohama Municipal Citizen's Hospital; Department of Respiratory Medicine, Kanagawa Cardiovascular & Respiratory Center, Yokohama; and Department of Internal Medicine, Niigata Cancer Center Hospital, Niigata, Japan.

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Address reprint requests to Noriyuki Masuda, MD, PhD, Department of Respiratory Medicine, Kitasato University School of Medicine, 1-15-1 Kitasato, Sagamihara, Kanagawa 228-0022, Japan; e-mail: masuda@med.kitasato-u.ac.jp.

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ABSTRACT

Purpose
This multicenter, phase II study was conducted to evaluate the activity of amrubicin, a topoisomerase II inhibitor, against refractory or relapsed small-cell lung cancer (SCLC).

Patients and Methods
SCLC patients with measurable disease who had been treated previously with at least one platinum-based chemotherapy regimen and had an Eastern Cooperative Oncology Group performance status of 0 to 2 were eligible. Two groups of patients were selected: patients who experienced first-line treatment failure less than 60 days from treatment discontinuation (refractory group), and patients who responded to first-line treatment and experienced disease progression ≥ 60 days after treatment discontinuation (sensitive group). Amrubicin was administered as a 5-minute daily intravenous injection at a dose of 40 mg/m^2 for 3 consecutive days, every 3 weeks.

Results
Between June 2003 and December 2004, 60 patients (16 refractory and 44 sensitive) were enrolled. The median number of treatment cycles was four (range, one to eight). Grade 3 or 4 hematologic toxicities comprised neutropenia (83%), thrombocytopenia (20%), and anemia (33%). Febrile neutropenia was observed in three patients (5%). Nonhematologic toxicities were mild. No treatment-related death was observed. The overall response rates were 50% (95% CI, 25% to 75%) in the refractory group, and 52% (95% CI, 37% to 68%) in the sensitive group. The progression-free survival, overall survival, and 1-year survival in the refractory group and the sensitive group were 2.6 and 4.2 months, 10.3 and 11.6 months, and 40% and 46%, respectively.

Conclusion
Amrubicin exhibits significant activity against SCLC, with predictable and manageable toxicities; this agent deserves to be studied more extensively in additional trials.

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INTRODUCTION

Approximately 15% of all patients with lung cancer are diagnosed with small-cell lung cancer (SCLC). Unlike other types of lung cancer, SCLC is sensitive to chemotherapy or radiation therapy.[1] Nonetheless, after experiencing an apparently successful induction therapy, most patients experience relapse within 2 years because of the emergence of drug-resistant cancer cells during the induction therapy or the existence of such cells before chemotherapy. Therefore, long-term survival is quite uncommon, with less than 25% of patients with limited-stage, and 1% to 2% of patients with extensive-stage disease remaining alive at 5 years.[2-4] Furthermore, the results of second-line chemotherapy against SCLC are disappointing, with relatively low response rates, brief remissions, and a short survival time.[1,5] In particular, little progress has been made in the re-treatment of patients who experienced progression during first-line therapy or who failed to achieve a progression-free survival of more than 60 to 90 days. As a result, to control SCLC more efficiently, new drugs that are effective for patients who have failed to respond to standard treatment, and who may have multidrug-resistant tumors, are urgently needed.

Amrubicin, a totally synthetic 9-aminoanthracycline, is converted to an active metabolite, amrubicinol, through the reduction of its C-13 ketone group to a hydroxy group.[6] Despite the similarity of its chemical structure to that of a representative anthracycline, doxorubicin, the mode of action of amrubicin differs from that of doxorubicin.[7] Amrubicin and amrubicinol are inhibitors of DNA topoisomerase II, which exert cytotoxic effects by stabilizing a topoisomerase II-mediated cleavable complex, and are approximately 1/10 weaker than doxorubicin as a DNA intercalator. The in vitro cytotoxic activity of amrubicinol was 18 to 220 times more potent than that of its parent compound, amrubicin.[8] In preclinical studies, amrubicin showed a more potent antitumor activity than doxorubicin in several human tumor xenografts implanted in nude mice,[9] and caused almost no cardiotoxicity.[9,10] The response rates to amrubicin at a dose of 45 mg/m^2 on days 1 to 3 in chemotherapy-naive patients with stage III or IV non-SCLC and extensive-stage SCLC were 25% and 79% on an intent-to-treat analysis, respectively.[11,12] The major grade 3 or 4 toxicities were neutropenia (72.1%), leukopenia (52.5%), anemia (23.0%), thrombocytopenia (14.8%), anorexia (4.9%), and nausea/vomiting (4.9%) in a phase II trial.[13]

The high activity of amrubicin as a single agent in untreated patients with extensive disease (ED) SCLC led us to carry out this phase II trial, which was designed to determine the antitumor activity and toxicity of amrubicin in previously treated patients with SCLC.

PATIENTS AND METHODS

Patient Selection

Before participation in the present study, each patient was examined to ensure he or she met the following criteria: histologic or cytologic proof of SCLC; recurrent or refractory disease after one or two previous chemotherapy regimens (at least one platinum-containing regimen); measurable disease; no chemotherapy or chest radiotherapy within 4 weeks before entry (measurable disease outside the radiation field); life expectancy of at least 8 weeks; performance status of 2 or better according to the Eastern Cooperative Oncology Group scale; age ≥ 20 years; adequate bone marrow function (leukocyte count ≥ 4,000/μL, absolute neutrophil count [ANC] ≥ 2,000/μL, platelet count ≥ 100,000/μL, and hemoglobin ≥ 9.0 g/dL) and hepatic function (AST and ALT ≤ 100 U/L, or ≤ 200 U/L in the presence of liver metastases; bilirubin level ≤ 1.5 mg/dL); ECG findings within the normal range, and a left ventricular ejection fraction ≥ 50%; arterial oxygen partial pressure ≥ 60 torr; and the written informed consent of the patient. Patients were ineligible if they had serious infectious diseases or other severe complications (heart disease, pulmonary fibrosis/interstitial pneumonia, or uncontrollable diabetes); had massive pleural or pericardial effusion, or ascitic fluid; had symptomatic brain metastases; had active concurrent malignancies; were lactating or pregnant women or hoped to become pregnant; had a history of a drug allergy; or had other medical problems severe enough to prevent compliance with the protocol. Prior amrubicin chemotherapy was not allowed. Trial document approval was obtained in advance from the ethics committee or institutional review board of each hospital.

Treatment Schedule

Amrubicin was dissolved in 20 mL of normal saline, and administered intravenously as a 5-minute infusion at a dose of 40 mg/m^2/d on days 1 to 3 every 3 weeks. Patients with evidence of disease progression or who experienced intolerable toxicity, such as grade 2 or worse pneumonitis, were removed from the study. Before the next course could be started, the patient's ANC had to be ≥ 1,500/μL, his or her platelet count had to be ≥ 100,000/μL, and any nonhematologic toxicities should have been downgraded to at least grade 1. If more than 6 weeks passed from the time of the last treatment before these criteria were satisfied, the patient was removed from the study.

Granulocyte colony-stimulating factor (G-CSF) was permitted as a therapeutic intervention but was not mandatory as a prophylactic agent against neutropenia for hematologic toxicity.

Subsequent doses were modified based on hematologic and nonhematologic toxicities. If the leukocyte count was less than 1,000/μL for 4 days or longer, the ANC was less than 500/μL for 4 days or longer, the platelet count nadir was less than 20 × 10^3/μL, or grade 3 or worse nonhematologic toxicity was observed, the dose of amrubicin was reduced to 35 mg/m^2/d. The dose of amrubicin also was reduced to 35 mg/m^2/d in patients who developed grade 3 febrile neutropenia.

Evaluation

Patients were evaluated to determine the stage of disease at the time of disease progression or at the time of relapse by taking a complete medical history and performing a physical examination, chest radiograph, computed tomography of the chest and abdomen, and other staging procedures as indicated, including computed tomography of the head and a bone scintiscan. Limited disease (LD) was defined as that confined to one hemithorax, including bilateral mediastinal and bilateral supraclavicular nodes: any involvement beyond these confines was defined as ED. Primary refractory disease (refractory group) was defined as relapse during the first-line chemotherapy regimen or less than 60 days after completing the initial chemotherapy regimen, and sensitive disease (sensitive group) was defined as relapse ≥ 60 days after completion of the first-line chemotherapy. Before the first course, each patient was assessed using a CBC, including a differential count and a platelet count, and serum chemistry tests for renal and hepatic functions as well as electrolytes. The CBC and biochemistry tests were repeated at least once a week after this initial evaluation, whereas the other investigations were repeated at least every 6 weeks to evaluate the target lesions.

Adverse events were recorded and graded using the National Cancer Institute Common Toxicity Criteria, Version 2.0 grading system. After completing the chemotherapy regimen, each patient was restaged using all of the tests used during the initial work-up. The tumor response was classified in accordance with the Response Evaluation Criteria in Solid Tumors.[14] The duration of the response was defined as the number of days from the documentation of the response to the detection of disease progression. The eligibility, evaluability, and response of each patient were assessed by extramural reviewers. The duration of survival, determined as the number of days between the enrollment of protocol therapy and death, was censored at the time last known alive for patients who had not died.

Statistical Methods

Kaplan-Meier survival estimates were used to summarize the time-to-event variables.[15] These included time to response, response duration, progression-free survival, and survival. Time-to-event outcomes were compared using the log-rank test. Other statistical analyses were performed using the χ^2 test or Fisher's exact test, and $P < .05$ was considered to indicate statistical significance. The primary end point was the response rate, which determined the sample size. We chose a 40% response rate as a desirable target level and a 20% response rate as uninteresting in the sensitive group, with a power in excess of 80% and less than 2.5% type I error. For the refractory group, the sample size was planned using an adequate power to demonstrate that the overall response rate was greater than 5%. If the true overall response rate were assumed to be 25%, a sample size of 16 assessable patients would have a power of 80% based on a 5% α level (one-sided test) and an exact binomial distribution.

RESULTS

Between June 2003 and December 2004, 60 patients were enrolled onto this multicenter trial. Sixteen and 44 patients in the refractory and sensitive groups were eligible for the study, and assessable for toxicity, response, and survival. The characteristics of the 60 patients

treated during this trial are listed in Table 1. Fourteen patients were women and 46 were men, and their median age was 67 years (range, 52 to 79 years). Eleven patients (18%) exhibited LD and 49 patients (82%) exhibited ED at the time of enrollment onto this study. All 60 patients had been pretreated using some form of topoisomerase inhibitor–based chemotherapeutic regimens: 24 patients had received prior topoisomerase I inhibitor (irinotecan or topotecan)–containing chemotherapy, 20 had had prior etoposide-containing chemotherapy, and 16 had received both topoisomerase I and II regimens (Table 2). Nineteen of these patients had received thoracic irradiation after or simultaneously with chemotherapy.

Response to Therapy and Survival

Among the 60 assessable patients, two patients (3%) achieved a complete response (CR) and 29 patients (48%) had a partial response (PR), for an overall response rate of 52% (95% CI, 38% to 65%; Table 2). Twelve patients had stable disease, and 17 had disease progression.

Table 1. Patient Characteristics

Characteristic	Sensitive Group	Refractory Group	Total
Total No. of patients	44	16	60
Sex			
Male	35	11	46
Female	9	5	14
Age, years			
Median	67	63	67
Range	52-79	52-76	52-79
Performance status (ECOG)			
0	23	5	28
1	20	8	28
2	1	3	4
Disease extent at relapse			
Limited disease	7	4	11
Extensive disease	37	12	49
Sites of metastases			
Adrenal gland	7	2	9
Lymph node	3	1	4
Lung	10	5	15
Bone	6	4	10
Brain	17	4	21
Liver	11	4	15
Skin	3	0	3
Other	5	0	5
Prior therapy			
Chemotherapy alone	28	12	40
Chemotherapy and chest irradiation	14	4	18
Chemotherapy and surgery	1	0	1
Chemotherapy, surgery, and irradiation	1	0	1
No. of prior chemotherapy regimens			
1	38	8	46
2	6	8	14
Response to prior chemotherapy			
CR	9	1	10
PR	35	8	43
SD or PD	0	7	7
Chemotherapy-free interval, days			
< 60	0	9	9
≥ 60	44	—	44

Abbreviations: ECOG, Eastern Cooperative Oncology Group; CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease.

Seven (44%) PRs and one (6%) CR were found among refractory patients, with an overall response rate of 50% (95% CI, 25% to 75%). Of eight refractory patients who responded to amrubicin, six had responded to the prior treatment, but had a relapse less than 60 days after completing initial chemotherapy, and two had a relapse during prior treatment. Of five refractory patients who had progressed after second-line treatment, one patient attained a PR to amrubicin treatment. Twenty-two (50%) PRs and one (2%) CR were attained in sensitive patients, with an overall response rate of 52% (95% CI, 37% to 68%). No significant difference in the overall response rate was seen when the patients were analyzed according to sex, performance status (0 to 1 *v* 2), response to initial chemotherapy, or disease extent (LD *v* ED). Of 40 patients pretreated with topoisomerase I inhibitor–containing regimens, 21 patients (53%) achieved a PR. It is noteworthy that 17 PRs (47%) and two CRs (6%) were attained in 36 patients who had had prior etoposide-containing chemotherapy. Responses were usually observed at a median of 32 days (range, 15 to 91 days) after the start of amrubicin treatment and occurred at all sites, including the brain (six of 21). The median time to progression was 2.6 months in the refractory patients, and 4.2 months in the sensitive patients.

Of the 60 patients, 19 patients (32%) were still alive as of April 26, 2006. The median survival time from the enrollment of the protocol treatment for all patients was 11.2 months (sensitive group, 11.6 months; refractory group, 10.3 months; Fig 1). The 1-year actuarial survival rate in patients with sensitive disease was 45.5%, compared with 40.3% in the patients with refractory disease. The 1-year survival rate for all patients was 44.1% (95% CI, 30.6% to 56.8%).

Toxicity and Treatment Received

Four patients were removed from the study after the first cycle of treatment because of progressive disease. Therefore, 56 patients received multiple courses of treatment in successive cycles. A total of 224 courses (58 refractory and 166 sensitive) were administered; all of these courses were included in the toxicity analysis (median cycles per patient, four; range, one to eight). Reduction of the amrubicin dose was required in 42 (18.8%) of cycles only in the sensitive group. Consequently, it was possible to deliver the full doses of amrubicin treatment in 80.4% of the entire 224 cycles. Thirty-eight (63%) of 60 patients could receive the planned four cycles. The major reasons for early discontinuation of treatment were disease progression (14 patients), acute pneumonia (two patients), and patient refusal (two patients). Most of the episodes of severe leukopenia and/or thrombocytopenia were observed during cycle 1; dose modifications were made in subsequent cycles.

The most frequent toxicity was myelosuppression, which affected leukocytes primarily: grade 3 or 4 neutropenia was seen in 28% and 55% of patients, respectively (Table 3). G-CSF was administered in 134 (60%) of the 224 cycles that were administered; 42 patients (70%) received G-CSF. However, only three episodes of fever were observed during the period of neutropenia. Thrombocytopenia was relatively infrequent throughout the study: grade 3 and 4 toxicity occurred in 20% and 0% of the patients, respectively. Grade 3 or 4 anemia was reported in 20 patients (33%). Nonhematologic toxicity was generally mild. The most frequent grade 3 or 4 nonhematologic toxicities included anorexia (15%), asthenia (15%), hyponatremia (8%), and nausea (5%). No cardiotoxicity, except for one transient atrial fibrillation, was observed during this trial.

Table 2. Response to Amrubicin Monotherapy

Characteristic	No. of Patients	CR	PR	SD	PD	Response Rate (%)	P
Overall	60	2	29	12	17	52	
Sex							
Male	46	0	23	10	13	50	.64
Female	14	2	6	2	4	57	
Performance status (ECOG)							
0-1	56	2	28	12	14	54	.35
2	4	0	1	0	3	25	
Disease extent							
Limited disease	11	2	2	3	4	36	.26
Extensive disease	49	0	27	9	13	55	
Sensitivity to prior CT							
Sensitive	44	2	21	10	11	52	.88
Refractory	16	0	8	2	6	50	
Prior treatment with topoisomerase inhibitor–based regimen							
Topo-I	24	0	12	5	7	50	.91
Topo-II	20	2	8	6	4	50	
Both	16	0	9	1	6	56	

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; Topo-I, topoisomerase I inhibitor–containing regimen; Topo-II, topoisomerase II inhibitor–containing regimen.
*95% CI, 38% to 65%.

No evidence of cumulative leukopenia, anemia, or asthenia toxicity was seen during subsequent courses at two dose levels. No treatment-related deaths occurred during this trial.

DISCUSSION

Treatment options for patients who experience relapse remain limited. Recently, a multicenter randomized trial demonstrated that single-agent topotecan was at least as efficacious as the three-drug combination of cyclophosphamide, doxorubicin, and vincristine for the treatment of patients with sensitive disease.[16] Topotecan showed a response rate of 24% *v* 18% for cyclophosphamide, doxorubicin, and vincristine ($P = .28$), with improved symptom control. The median survivals were superimposable between two treatments (25 *v* 24.7 weeks). The results of the phase III trial have made topotecan the only drug approved by the US Food and Drug Administration for the single-agent management of patients with relapsed SCLC.

Several reports on single-agent activity for newer chemotherapeutic agents, including topoisomerase I inhibitors,[17-21] taxanes,[22] gemcitabine,[23] and vinorelbine,[24,25] in the second-line setting have been made. However, few single agents are capable of producing a

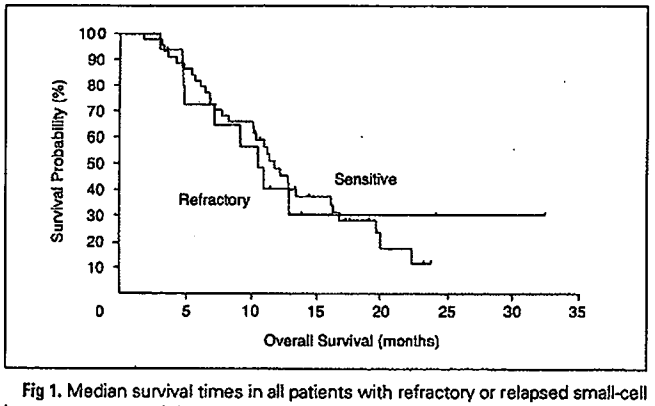

Fig 1. Median survival times in all patients with refractory or relapsed small-cell lung cancer were 10.3 months in the refractory group (n = 16) and 11.6 months in the sensitive group (n = 44), respectively ($P = .974$; log-rank test). The 1-year actuarial survival rate in patients with refractory disease was 40.3%, compared with 45.5% in the patients with sensitive relapse.

Table 3. Worst Toxicity by 60 Patients During Amrubicin Monotherapy

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	≥ Grade 3 No.	≥ Grade 3 %
Neutropenia	1	7	17	33	50	83.3
Leukopenia	4	12	30	12	42	70.0
Hemoglobin	15	24	17	3	20	33.3
Thrombocytopenia	21	14	12	0	12	20.0
Anorexia	2	8	6	4	9	15.0
Asthenia	24	11	6	3	9	15.0
Hyponatremia	21	20	5	0	5	8.3
Nausea	18	5	3	0	3	5.0
Febrile neutropenia	0	0	3	0	3	5.0
Hypokalemia	13	0	2	0	2	3.3
Fever	10	5	2	0	2	3.3
Pneumonia	0	0	2	0	2	3.3
Hypoalbuminemia	20	4	1	0	1	1.7
Elevated AST	20	0	1	0	1	1.7
Vomiting	5	3	1	0	1	1.7
Diarrhea	8	2	1	0	1	1.7
Constipation	5	1	1	0	1	1.7
Cognitive disturbance	0	0	1	0	1	1.7
Memory impairment	0	0	1	0	1	1.7
Atrial fibrillation	0	0	1	0	1	1.7
Infection with neutropenia	0	0	1	0	1	1.7

high incidence of response among patients with early relapse or disease progression during treatment. Smit et al[26] reported the results of phase II trial for paclitaxel given as a 3-hour infusion at a dose of 175 mg/m^2 every 3 weeks in patients refractory to cyclophosphamide, doxorubicin, and etoposide. Although the response rate of 29% was at the upper level of activity for any single agent in this setting, two early deaths and two toxicity-related deaths occurred in the trial, and the median survival time was a disappointingly short 100 days.

This phase II study demonstrated that amrubicin monotherapy is active against refractory or relapsed SCLC, as shown by the overall response rate of 52% (95% CI, 38% to 65%) in 60 patients (Table 2). Although the activity of second-line treatments usually depends on tumor responsiveness to first-line treatment, we could not find any difference in response rates between the two groups (the response rate of 50% [95% CI, 25% to 75%] for refractory disease, and 52% [95% CI, 37% to 68%] for sensitive relapse). This high response rate in chemotherapy-resistant patients is encouraging given the fact that response rates of less than 10% are usually attained for single-agent chemotherapy in patients with this disease category.[27] Furthermore, a promising similar survival outcome was obtained in the two groups (10.3 *v* 11.6 months in refractory and sensitive group, respectively; Fig 1). These results suggest that amrubicin may be a useful new addition to treatment strategies for chemotherapy-resistant patients. Obviously, however, more SCLC patients with refractory disease treated with amrubicin will be needed to determine the true response rate in this population, given that the number of patients in this study is too small to draw any valid conclusion about the ultimate clinical activity of this regimen.

DNA topoisomerase I and II are functionally related and are believed to act in concert in a variety of genetic processes.[28] Preclinical studies have demonstrated that resistance to camptothecin, a topoisomerase I inhibitor, is often accompanied by the upregulation of topoisomerase II, causing hypersensitivity to agents that target topoisomerase II.[29] This enhanced sensitivity (collateral sensitivity) may explain, in part, the high response rate observed in our patients, given that most of the patients had been heavily pretreated during topoisomerase I inhibitor (irinotecan or topotecan)–containing regimens. Furthermore, objective responses were documented in 19 of 36 patients who had been treated with etoposide, a potent topoisomerase II inhibitor, which suggests that there is some degree of non–cross resistance between amrubicin and etoposide.

The toxicity profile noted in this trial was predictable from that described previously for the phase I and II trials[12,13,30]; myelosuppression was the major toxic effect. All adverse effects were manageable. Because grade 3 or 4 neutropenia occurred in 85% of patients with no prior chemotherapy who were treated using the Japanese Ministry of Labor, Health and Welfare–approved dose level of 45 mg/m^2 per day for 3 days in a previous phase II trial,[12] a reduced dose of 40 mg/m^2 per day for 3 days was chosen in this trial in view of the chemotherapeutic and radiotherapeutic pretreatment. The low incidence of severe and clinically relevant bone marrow toxicity in our trial may be due to the use of this lower dose of amrubicin (Table 3). The incidence of a decrease in the left ventricular ejection fraction attributable to amrubicin was null, and this effect was never the cause of treatment discontinuation. The incorporation of amrubicin instead of doxorubicin in anthracycline-containing regimens might decrease the incidence of cardiotoxicity, thereby improving the therapeutic index of doxorubicin-containing regimens in future trials.

In conclusion, amrubicin is an active agent for the treatment of refractory or relapsed SCLC. The overall response rate of 50% and the overall survival time of 10.3 months in patients with refractory disease are noteworthy. Given the greater activity of single-agent amrubicin, additional studies in previously treated patients with SCLC are warranted, especially for the patients who are refractory to previous therapy, either as a single agent or in combination with cytotoxic agents or target-based agents.

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The authors indicated no potential conflicts of interest.

Author Contributions

Conception and design: Noriyuki Masuda, Koshiro Watanabe
Provision of study materials or patients: Sayaka Onoda, Noriyuki Masuda, Takashi Seto, Kenji Eguchi, Yuichi Takiguchi, Hiroshi Isobe, Hiroaki Okamoto, Takashi Ogura, Akira Yokoyama, Nobuhiko Seki, Yoshiko Asaka-Amano, Masao Harada, Akihiro Tagawa, Hiroshi Kunikane, Masanori Yokoba, Kazutsugu Uematsu, Takayuki Kuriyama, Yumi Kuroiwa
Collection and assembly of data: Sayaka Onoda, Noriyuki Masuda, Takashi Seto, Kenji Eguchi, Yuichi Takiguchi, Hiroshi Isobe, Hiroaki Okamoto, Takashi Ogura, Akira Yokoyama, Nobuhiko Seki, Yoshiko Asaka-Amano, Masao Harada, Akihiro Tagawa, Hiroshi Kunikane, Masanori Yokoba, Kazutsugu Uematsu, Takayuki Kuriyama, Yumi Kuroiwa
Data analysis and interpretation: Sayaka Onoda, Noriyuki Masuda, Takashi Seto, Koshiro Watanabe
Manuscript writing: Noriyuki Masuda
Final approval of manuscript: Noriyuki Masuda, Koshiro Watanabe

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ORIGINAL REPORT

Phase II Study of Etoposide and Cisplatin With Concurrent Twice-Daily Thoracic Radiotherapy Followed by Irinotecan and Cisplatin in Patients With Limited-Disease Small-Cell Lung Cancer: West Japan Thoracic Oncology Group 9902

Hiroshi Saito, Yoshiki Takada, Yukito Ichinose, Kenji Eguchi, Shinzoh Kudoh, Kaoru Matsui, Kazuhiko Nakagawa, Minoru Takada, Shunichi Negoro, Kenji Tamura, Masahiko Ando, Takuhito Tada, and Masahiro Fukuoka

From the Department of Respiratory Medicine, Aichi Cancer Center Aichi Hospital, Okazaki, Aichi; Departments of Thoracic Oncology and Respiratory Medicine, Hyogo Medical Center for Adults, Akashi, Hyogo; Department of Thoracic Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka; Department of Internal Medicine, National Hospital Organization Shikoku Cancer Center, Matsuyama, Ehime, Department of Respiratory Medicine, Osaka City University Hospital, Department of Thoracic Malignancy, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Habikino, Department of Medical Oncology, Kinki University School of Medicine, Osakasayama, Department of Pulmonary Medicine, Rinku General Medical Center, Izumisano; Department of Radiology, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Habikino, Osaka; Department of Medical Oncology, Kinki University School of Medicine, Nara Hospital, Ikoma, Nara; and the Health Service, Kyoto University, Kyoto, Japan.

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Address reprint requests to Hiroshi Saito, MD, Department of Respiratory Medicine, Aichi Cancer Center Aichi Hospital, 18 Kuriyado Kake-machi, Okazaki Aichi 444-0011, Japan; e-mail: hsaito@sun-inet.or.jp.

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ABSTRACT

Purpose
We initially conducted a randomized phase II study to compare irinotecan and cisplatin (IP) versus irinotecan, cisplatin, and etoposide (IPE) after etoposide and cisplatin (EP) with concurrent twice-daily thoracic radiotherapy (TRT) in limited-disease small-cell lung cancer (LD-SCLC). We amended the protocol to evaluate IP after EP with concurrent twice-daily TRT in a single-arm phase II study because of an unacceptable toxicity in IPE.

Patients and Methods
Previously untreated patients with LD-SCLC were treated intravenously with etoposide 100 mg/m^2 on days 1 through 3 and cisplatin 80 mg/m^2 on day 1 with concurrent twice-daily TRT (1.5 Gy per fraction, a total dose of 45 Gy) beginning on day 2 followed by three cycles of irinotecan 60 mg/m^2 on days 1, 8, and 15 and cisplatin 60 mg/m^2 on day 1 of a 4-week cycle.

Results
Of the 51 patients enrolled, 49 patients were assessable for response and toxicity. The overall response rate and complete response rate were 88% and 41%, respectively. The median survival time for all patients was 23 months. The 2-year and 3-year survival rates were 49% and 29.7%, respectively. The median progression-free survival was 11.8 months. The major toxicities observed were neutropenia (grade 4, 84%), febrile neutropenia (grade 3, 31%), infection (grade 3 to 4, 33%), electrolytes imbalance (grade 3 to 4, 20%), and diarrhea (grade 3 to 4, 14%).

Conclusion
EP with concurrent twice-daily TRT followed by the consolidation of IP appears to be an active regimen which deserves further phase III testing in patients with LD-SCLC.

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INTRODUCTION

Small-cell lung cancer (SCLC), which accounts for approximately 15% of all lung cancer cases, is clinically categorized as the two stages, limited disease and extensive disease. Two meta-analyses have shown the combined modality of chemotherapy and thoracic radiotherapy (TRT) to improve the survival of patients with limited-disease (LD-) SCLC in comparison to chemotherapy alone.[1,2] The schedule, dose, and fractionation of TRT have previously been examined in patients with LD-SCLC in several randomized controlled studies.[3-7] On the basis of the results of these studies, etoposide and cisplatin (EP) with concurrent twice-daily TRT is currently a standard care for the treatment for LD-SCLC. However, the 5-year survival rate is less than 30%, and most patients experience a relapse of the primary tumor or distant metastasis.[3-6] To further improve the therapeutic efficacy, one approach is to develop a new chemoradiotherapy regimen incorporating with a novel active agent.

Irinotecan hydrochloride, a camptothecin derivative, is among the most active chemotherapeutic agents against SCLC with a response rate of 37% as a single agent.[8] A randomized phase III study revealed that irinotecan and cisplatin (IP) was superior to EP in patients with extensive-disease SCLC (ED-SCLC).[9] However, the role of IP in the treatment of LD-SCLC remains to be defined. To clarify the role of this combination regimen in LD-SCLC, we initially conducted a randomized phase II study to

compare two consolidation chemotherapy regimens, IP versus irinotecan, cisplatin and etoposide (IPE), after EP with concurrent twice-daily TRT in LD-SCLC.[10] However, EP with concurrent twice-daily TRT followed by IPE was not feasible because of unacceptable toxicity including grade 4 neutropenia (92%), grade 4 diarrhea (25%), grade 4 infection (25%) and one treatment-related death. We therefore amended the protocol to evaluate EP with concurrent twice-daily TRT followed by consolidation therapy with IP in a single-arm phase II study and herein report the results of this study.

PATIENTS AND METHODS

Eligibility Criteria

Patients with histologically or cytologically confirmed LD-SCLC (stage I disease was excluded) were eligible for this study. A limited stage was defined as disease confined to one hemithorax, the mediastinum, and the bilateral supraclavicular area. Cases with a small amount of pleural effusion and a negative cytology were included in the limited-stage group. Other eligibility criteria included the following: no prior chemotherapy or radiotherapy; measurable disease; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; age between 20 and 70 years; life expectancy of at least 3 months; adequate baseline organ function defined as leukocyte count ranging from 4,000 to 12,000/mm^3, hemoglobin concentration of at least 9.5 g/dL, platelet count at least 100,000/mm^3, AST and ALT 2.0× the upper limit of the normal range (ULN) or less, serum total bilirubin 1.5 mg/dL or less, serum creatinine ULN or less, 24-hour creatinine clearance of at least 60 mL/min, and Pao_2 at rest of at least 70 mmHg. The radiation portal should be equal or less than half of one lung.

The patients were ineligible if they had the following criteria: interstitial pneumonitis or pulmonary fibrosis; other respiratory diseases that precluded TRT; malignant pleural effusion or malignant pericardial effusion; active concomitant or a recent (< 3 years) history of any malignancy; uncontrolled angina pectoris, myocardial infarction less than 3 months before the enrollment or congestive heart failure; uncontrolled diabetes mellitus or hypertension; severe infection; intestinal paralysis or obstruction; pregnancy or lactation; or other serious concomitant medical conditions. The study protocol was approved by each institutional review board for clinical use. All patients gave their written informed consent before enrollment.

Study Evaluation

The pretreatment baseline evaluation included a complete medical history and physical examination, a CBC, blood chemistry studies, flexible bronchoscopy, electrocardiography, chest radiography, computed tomography of the chest, computed tomography or ultrasound study of the abdomen, computed tomography or magnetic resonance imaging of the brain, bone scintigraphy and bone marrow aspiration with or without biopsy. A CBC and blood chemistry studies were repeated every week. At the end of the study, all of these studies except for flexible bronchoscopy and bone marrow aspiration were repeated unless the patient had stable or progressive disease.

Treatment Schedule

The patients initially received induction chemoradiotherapy consisting of etoposide 100 mg/m^2 on day 1 through 3 and cisplatin 80 mg/m^2 on day 1 with concurrent twice-daily TRT. After the induction chemoradiotherapy, the patients received three cycles of consolidation chemotherapy consisting of irinotecan 60 mg/m^2 on days 1, 8, and 15 and cisplatin 60 mg/m^2 on days 1. Consolidation chemotherapy was repeated every 4 weeks for three cycles.

The first cycle of consolidation chemotherapy was begun 4 week after the initiation of induction chemoradiotherapy if the leukocyte count was at least 4,000/mm^3; the platelet count was at least 100,000/mm^3; AST and ALT 2.0× ULN or less; serum bilirubin 1.5 mg/dL or less; serum creatinine of ULN or less; the patient did not have fever (≥ 38°C), diarrhea within the past 24 hours, or intestinal paralysis or obstruction; and Pao_2 of at least 70 mmHg. The subsequent cycle of consolidation chemotherapy was repeated if the leukocyte count was at least 3,500/mm^3; the platelet count was at least 100,000/mm^3; AST and ALT 2.0× ULN or less; serum bilirubin 1.5 mg/dL or less; serum creatinine ULN or less; the patient did not have fever (≥ 38°C), diarrhea within the past 24 hours, or intestinal paralysis or obstruction. The use of granulocyte colony-stimulating factor (GCSF) was recommended after day 4. However, its administration was withheld on the day of administration of irinotecan.

TRT was performed with 6 MV or higher photons from a linear accelerator and began on day 2 of the induction chemoradiotherapy. Patients received 1.5 Gy per fraction twice daily with at least a 4-hour interval (preferably a 6-hour interval or more) between each fraction over a 3-week period (a total dose of 45 Gy). A radiation field included the primary tumor, the bilateral mediastinal and ipsilateral hilar lymph nodes with a margin of 1.5 to 2.0 cm. Radiation to the supraclavicular lymph nodes was administered only if they were involved. The inferior border extended 5 cm below the carina or to a level including ipsilateral hilar structures, whichever was lower. After initial irradiation with a dose of 30 Gy, off-cord (ie, the spinal cord was outside the field) oblique boost fields were used. The radiation field in the afternoon was not different from that in the morning. Computed tomography planning was not required and lung density corrections were not performed. Prophylactic cranial irradiation (PCI) was administered to the patients achieving complete response or good partial response with a total dose of 25 Gy in 10 fractions.

Dose Modification

Dose modification based on the toxicity of the induction chemoradiotherapy was not allowed at the time of the first administration of IP. In each cycle of IP, irinotecan on day 8 or 15 was withheld if a leukocyte count of less than 2,000/mm^3 or a platelet count of less than 50,000/mm^3 was determined, or if a patient had fever (≥ 38°C) or grade 2 or higher hepatotoxicity or any diarrhea within the last 24 hours or intestinal paralysis or obstruction. In the second and the third cycle of consolidation chemotherapy, the dose modification was made as follows. If a leukocyte nadir count of less than 1,000/mm^3 or a neutrophil nadir count of less than 500/mm^3 for 3 or more days or if febrile neutropenia developed or if a platelet nadir count of less than 25,000/mm^3 was observed or if grade 2 hepatotoxicity or diarrhea was observed, irinotecan was decreased by 10 mg/m^2 in the subsequent cycle, if grade 2 or lower renal toxicity was observed during the previous course of treatment, only cisplatin decreased by 25%, if grade 3 or higher nonhematologic toxicity (excluding nausea, vomiting, and hair loss) developed, then cisplatin decreased by 25% and irinotecan decreased by 10 mg/m^2 in the following cycle. The patients were removed from the study if the following toxicities were observed: grade 4 diarrhea; grade 3 or higher renal toxicity or creatinine of at least 2.0 mg/dL; grade 3 or higher hepatotoxicity; grade 2 or higher pulmonary toxicity or Pao_2 at rest less than 60 mmHg.

Evaluation

The Response Evaluation Criteria in Solid Tumors (RECIST) were used for the response assessment.[11] Toxicity was evaluated according to the National Cancer Institute–Common Toxicity Criteria (version 2.0). An extramural review was conducted to validate the eligibility of the patients, staging, and response.

Statistical Analysis

The primary end point of this study was the 2-year survival rate. We calculated the sample size based on Fleming's single-stage design of the phase II study.[12] We set a 2-year survival rate of 35% as a baseline survival rate and 20% as the high level of interest with a power of 0.9 at a one-sided significance level of .05, requiring an accrual of 53 eligible patients. The study was initially begun as a randomized phase II study to compare two consolidation arms, namely IP versus IPE after concurrent chemoradiotherapy. Because of the unacceptable toxicity in the triplet regimen, the study was modified to a single-arm phase II study to evaluate IP after EP with concurrent TRT and 11 patients in the IP arm were included in the analysis of this study.

The duration of survival was measured from the day of entry onto the study, and the overall survival curve and progression-free survival curve were calculated according to the method of Kaplan and Meier.[13]

Patients Characteristics

Between February 2000 and November 2002, 51 patients were enrolled onto this study. Table 1 lists the baseline characteristics of the patients. Two patients were considered to be ineligible because a secondary primary tumor was found after the administration of EP with concurrent TRT. Therefore, 49 patients were assessable for response and toxicity.

Treatment Administration

Seven patients were removed from the study after the administration of EP with concurrent TRT because of treatment delay due to toxicity (six patients) and patient rejection (one patient). Eight patients each discontinued the treatment after each cycle of IP. The major reasons for the discontinuation of IP included treatment delay due to toxicity (three patients), diarrhea (three patients), and ileus (three patients), patient rejection (two patients), and the doctor's judgment (two patients). Overall, 34 patients (69%) received at least two cycles of IP and 26 patients (53%) completed the entire treatment. Irinotecan was omitted in 35 (11%) of 306 cycles. The dose-intensity of irinotecan was 30.5 mg/m^2/wk (68% of the planned dose) and cisplatin 11.6 mg/m^2/wk (77% of the planned dose) in the consolidation chemotherapy.

Response and Survival

On an intention-to-treat basis, the overall response rates and the complete response rates were 88% (95% CI, 78.6% to 96.9%) and 41%, respectively. After a median follow-up of 29.9 months, the median survival time for all patients was 23 months (Fig 1). The 2-year and 3-year survival rates were 49% and 29.7%, respectively. The median progression-free survival was 11.8 months (Fig 2).

Toxicity

Tables 2 and 3 show the major toxicities. Grade 4 neutropenia was observed in 80% of the patients and 10 (20%) patients had febrile neutropenia in concurrent chemoradiotherapy, whereas grade 4 neutropenia was observed in 40% of the patients and seven patients (17%) had febrile neutropenia in consolidation chemotherapy. In contrast, anemia and thrombocytopenia were relatively mild. One patient had grade 4 esophagitis in concurrent chemoradiotherapy. In the consolidation chemotherapy, grade 3 or 4 diarrhea was observed in six patients (14%) and grade 3 or 4 infection was observed in seven patients (17%). Two patients had grade 3 or 4 radiation pneumonitis. Grade 4 adhesive ileus developed in a patient who had a history of abdominal surgery and ileus. The major toxicities observed through the entire course of the treatment were neutropenia (grade 4, 84%), febrile neutropenia (grade 3, 31%), infection (grade 3 to 4, 33%), electrolytes imbalance (grade 3 to 4, 20%) and diarrhea (grade 3 to 4, 14%). There was one treatment-related death caused by radiation pneumonitis.

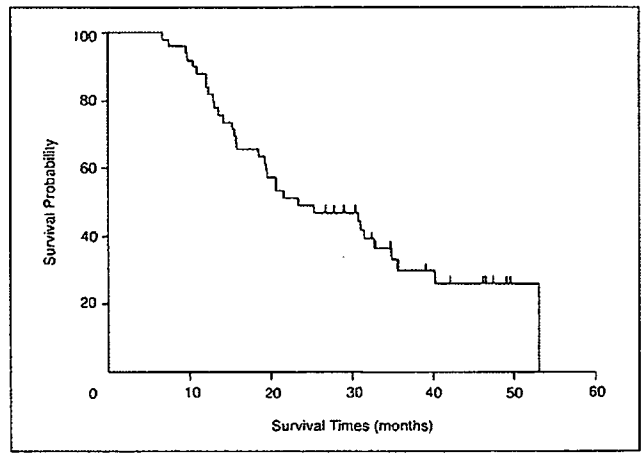

Fig 1. Kaplan-Meier survival curve of 49 eligible patients with limited-disease small-cell lung cancer. The median survival time was 23 months, and the 2-year and 3-year survival rates were 49% and 29.7%, respectively.

Patterns of Relapse

Table 4 lists first sites of relapse. Of 12 patients (24%) with local relapse (defined as relapse within the radiation portal), only one had a relapse solely at locoregional sites and 11 at both local and distant site including three with brain metastasis. Of 27 patients (55%) with distant relapse only, 13 had brain metastasis. Overall, 16 patients (33%) showed brain metastasis as the initial site of relapse, and eight of them had received PCI.

Table 1. Patient Characteristics (N = 51)

Characteristic	No.	%
Age, years		
Median	62	
Range	45-70	
Sex		
Male	42	82
Female	9	18
ECOG performance status		
0	22	43
1	28	55
2	1	2
Stage		
II	2	4
IIIA	35	69
IIIB	14	27

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

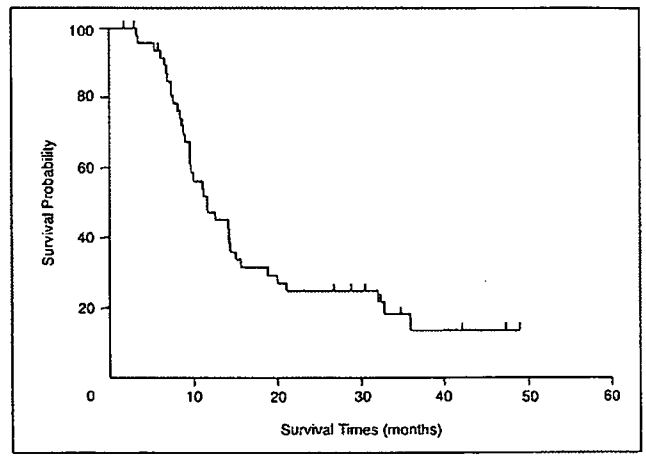

Fig 2. Kaplan-Meier progression-free survival curve of 49 eligible patients with limited-disease small-cell lung cancer. The median progression-free survival time was 11.8 months.

Table 2. Major Toxicities During Concurrent Chemoradiotherapy (n = 49)

Toxicity	Grade 3		Grade 4	
	No.	%	No.	%
Hematologic				
Leukopenia	27	55	19	39
Neutropenia	8	16	39	80
Anemia	2	4	1	2
Thrombocytopenia	10	20	0	0
Febrile neutropenia	10	20	0	0
Nonhematologic				
Nausea/vomiting	7	14	0	0
Diarrhea	0	0	0	0
Constipation	0	0	0	0
Infection	9	18	0	0
Mucositis	0	0	0	0
Esophagitis	0	0	1	2
Dyspnea	1	2	0	0
Pneumonitis	0	0	0	0
Hepatic	0	0	0	0
Electrolytes	2	4	2	4

In this phase II study, we evaluated the consolidation of IP after EP with concurrent twice-daily TRT and thus achieved an overall response rate of 88%, a 2-year-survival rate of 49% and a 3-year-survival rate of 29.7%. Although the number of assessable patients was slightly smaller than the planned sample size, this study confirmed 24 2-year survivors, and the power calculation showed a 97% probability to correctly reject inactive treatment, thus yielding only a 35% or less 2-year-survival rate. These results are comparable to those in phase III studies evaluating EP with concurrent twice-daily TRT.[3-6] Jeremic et al[7] reported a better survival outcome by using daily carboplatin and etoposide with concurrent twice-daily TRT followed by EP. However, this result has rarely been confirmed by other groups. The Japanese Clinical Oncology Group (JCOG) conducted a pilot study to evaluate the feasibility of IP after EP with concurrent TRT (JCOG9903).[14] The doses and schedule of cisplatin, etoposide, and irinotecan and dose, fractionation and schedule of TRT were similar to ours. They reported that this regimen was feasible with a response rate of 97%, a 2-year survival rate of 41% and a 3-year survival rate of 38%, which are similar to those in our study. Although a phase III study conducted in Japan showed the superiority of IP over EP in ED-SCLC,[9] another phase III study conducted in North America failed to confirm the superiority of IP over EP.[15] A randomized phase III study to compare IP versus EP after EP with concurrent TRT is currently ongoing in patients with LD-SCLC in Japan.

Table 3. Major Toxicities During Consolidation Chemotherapy (n = 42)

Toxicity	Grade 3		Grade 4	
	No.	%	No.	%
Hematologic				
Leukopenia	27	64	8	19
Neutropenia	18	43	17	40
Anemia	17	40	5	12
Thrombocytopenia	8	19	0	0
Febrile neutropenia	7	17	0	0
Nonhematologic				
Nausea/vomiting	9	21	0	0
Diarrhea	5	12	1	2
Constipation	3	7	2	5
Ileus	2	5	1	2
Infection	9	21	1	2
Mucositis	0	0	0	0
Esophagitis	0	0	0	0
Dyspnea	2	5	0	0
Pneumonitis	1	2	1	2
Hepatic	1	2	0	0
Electrolytes	4	10	1	2

Table 4. Site of First Failure (n = 49)

Site	No. of Patients	%
Progression free	10	20
Locoregional	1	2
Locoregional and distant	11	22
Distant	27	55
Brain only	8	16
Brain and others	5	10
Others	14	29

Although a potential approach is to substitute irinotecan for etoposide in the combination of EP with concurrent TRT, we did not combine IP concurrently with TRT because two phase I studies demonstrated that combining IP with concurrent TRT was not feasible when the full dose of irinotecan was administered on days 1, 8, and 15.[16,17] On the basis of these results, we administered IP as consolidation therapy after EP with concurrent twice-daily TRT. After this article was initially submitted, Langer et al[18] reported phase I study of once every 3 weeks scheduling of IP with concurrent twice-daily TRT (45 Gy) or once-daily TRT (70 Gy) in patients with LD-SCLC, thus concluding that IP with concurrent twice-daily TRT was safe and feasible. A further evaluation of this regimen is thus warranted.

One group evaluated IP administered as an induction followed by EP with concurrent twice-daily TRT.[19] Their results are comparable to those of our study and EP with concurrent twice-daily TRT.[3-6] However, this regimen was highly myelotoxic (grade 4 neutropenia, 91%) with febrile neutropenia in 60% of the patients. Furthermore, early TRT is an important issue to obtain the improved outcome in LD-SCLC. Recent meta-analyses revealed that when platinum-based chemotherapy was concurrent with TRT in LD-SCLC, an improved survival was associated with early TRT.[20-22] Another group evaluated the addition of paclitaxel to EP with concurrent TRT.[23] Although their results are comparable to those of our study and EP with concurrent twice-daily TRT,[3-6] they concluded that the triplet regimen would not further improve the survival outcome in patients with LD-SCLC.

Esophagitis is a toxicity of a particular concern in concurrent chemoradiotherapy. We observed grade 3 or 4 esophagitis in one patient (2%), whereas the JCOG9903 trial reported it in 7% of the patients. These figures contrast with those in the studies evaluating etoposide and a platinum with concurrent twice-daily TRT (9% to 32%).[3-7] The substitution of irinotecan for etoposide may reduce the incidence of grade 3 or 4 esophagitis. Furthermore, a lower incidence of esophagitis has been noted in a Japanese trial.[4] A possible explanation for this includes differences in the

chemotherapy interval (once every 4 weeks *v* once every 3 weeks) and in ethnic background. Neutropenia was the most prominent toxicity in this study and its incidence is higher than that in the Turrisi et al study.[3] However, no toxic death resulting from neutropenia was observed. Diarrhea was the most troublesome nonhematologic toxicity of irinotecan and one of the major causes for treatment discontinuation in this study.

Brain metastasis as an initial site of relapse was observed in 33% of our patients. The JCOG9903 trial reported brain metastasis in 37% of their patients. These rates were higher than those in the studies evaluating etoposide and a platinum with concurrent twice-daily TRT.[4,7] The rate of local recurrence solely was observed in only one patient and none in the JCOG9903 trial. This contrasts with the higher rate of distant failure either with or without local failure in these two studies (77% and 67%, respectively). These increased rates of distant failure including brain metastasis may be partly explained by insufficient administration of IP as consolidation.

A limitation of this study is the treatment feasibility. In this study, 53% of the patients completed the entire treatment and 69% received two or more cycles of IP. The respective values were 58% and 73% in the JCOG9903 trial.[14] In contrast, Takada et al reported that 86% of the patients completed the treatment in EP with concurrent twice-daily TRT.[4] Although the optimal duration of consolidation chemotherapy remains unclear, we consider that at least two cycles of IP is clinically meaningful in view of encouraging survival outcomes in these phase II studies. Whether the relatively low completion rate of IP causes increased distant metastasis and detrimentally affects the outcome will be addressed by the ongoing phase III study. To improve the feasibility, certain supportive measures including the prophylactic GCSF and/or antidiarrheal measures[24] and different dose scheduling (eg, 3-weekly scheduling of IP) should be considered in future studies.

In conclusion, EP with concurrent twice-daily TRT followed by the consolidation of IP appears to be active in patients with LD-SCLC, thus supporting the conduct of the currently ongoing phase III study to compare EP with concurrent twice-daily TRT followed by the consolidation of either EP or IP.

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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

The authors indicated no potential conflicts of interest.

Author Contributions

Conception and design: Hiroshi Saito, Shunichi Negoro, Masahiro Fukuoka
Administrative support: Masahiro Fukuoka
Provision of study materials or patients: Hiroshi Saito, Yoshiki Takada, Yukito Ichinose, Kenji Eguchi, Shinzoh Kudoh, Kaoru Matsui, Kazuhiko Nakagawa, Minoru Takada, Shunichi Negoro, Kenji Tamura, Takuhito Tada, Masahiro Fukuoka
Collection and assembly of data: Kazuhiko Nakagawa, Kenji Tamura
Data analysis and interpretation: Hiroshi Saito, Kazuhiko Nakagawa, Kenji Tamura, Masahiko Ando
Manuscript writing: Hiroshi Saito, Masahiko Ando, Takuhito Tada
Final approval of manuscript: Hiroshi Saito, Yoshiki Takada, Yukito Ichinose, Kenji Eguchi, Shinzoh Kudoh, Kaoru Matsui, Kazuhiko Nakagawa, Minoru Takada, Shunichi Negoro, Kenji Tamura, Masahiko Ando, Takuhito Tada, Masahiro Fukuoka

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Phase II Study of Weekly Paclitaxel for Relapsed and Refractory Small Cell Lung Cancer

NOBUYUKI YAMAMOTO[1,2], JUNJI TSURUTANI[1], NARUO YOSHIMURA[3], GYO ASAI[1,2], AZUSA MORIYAMA[1], KAZUHIKO NAKAGAWA[1], SHINZO KUDOH[3], MINORU TAKADA[4], YOSHIAKI MINATO[5] and MASAHIRO FUKUOKA[1]

[1]*Kinki University School of Medicine, Department of Medical Oncology;*
[2]*Shizuoka Cancer Center, Division of Thoracic Oncology;*
[3]*Osaka City University School of Medicine, First Department of Internal Medicine;*
[4]*Rinku General Medical Center, Respiratory Division;*
[5]*National Kinki Central Hospital for Chest Diseases, Department of Internal Medicine, Japan*

Abstract. *The purpose of this study was to evaluate the efficacy and toxicity of single-agent paclitaxel given weekly to patients with relapsed and refractory small cell lung cancer (SCLC). Patients were treated with 80 mg/m^2 paclitaxel administered weekly for 1 h for 6 weeks in an 8-week cycle. Twenty-two patients were enrolled, 21 of whom were eligible. The patient characteristics included: 20 males, 1 female; median age 66 years (range 48 - 75); performance status 0/1 in 19 and 2 in 5 patients. Grade 3/4 leukopenia and neutropenia occurred in 47.5% and 64%, respectively. Other grade 3/4 toxicities included infection, skin rash, neuropathy and pulmonary toxicity. There were 5 partial responses in 3 out of the 11 sensitive cases and 2 out of the 10 refractory cases, respectively. Paclitaxel, administered as a weekly infusion at a dose of 80 mg/m^2, was effective in treating relapsed and refractory SCLC.*

More than 95% of patients with small cell lung cancer (SCLC), who are initially treated with paclitaxel 80 mg/m^2, present a relapse and their response to a second-line therapy is poor. The responses obtained are usually brief, and the median survival is generally less than 4 months (1). Nevertheless, second-line chemotherapy may provide a significant palliation of symptoms and does result in a prolongation of survival in many patients.

The activity of paclitaxel as a single agent has been investigated in both previously-untreated and -treated SCLC patients. Two phase II trials were conducted to investigate its efficacy as a first-line treatment for SCLC. In a trial conducted by the Eastern Cooperative Oncology Group (ECOG), Ettinger *et al.* administered 250 mg/m^2 paclitaxel as a 24-h infusion to 36 patients (2), among whom 11 partial responses were observed. Kirschling *et al.* obtained a similar response rate, 41%, in a group of 37 patients on an identical paclitaxel dose-schedule (3). The results of a phase II study in previously treated patients were reported by Smit *et al.* (4). All 24 patients in that trial developed progressive disease within 3 months of receiving at least one previous chemotherapy regimen. Seven patients (29%) had a partial response to 175 mg/m^2 paclitaxel as a 3-h infusion. These data show that paclitaxel exhibits single-agent efficacy in SCLC comparable to that of the best agents. The results of Smit *et al.'s* study in patients with refractory SCLC are particularly impressive, since most response rates reported with single-agent or combination regimens in this population have been less than 15%. However, life-threatening toxicity occurred in 4 of these patients, 2 of whom experienced hematological toxicity.

Recent reports of the activity and tolerability of weekly doses of paclitaxel have generated a great deal of clinical interest. Weekly paclitaxel therapy has generally been quite well tolerated, causing minimal toxicity and no apparent cumulative myelosuppression. Substantial evidence from clinical trials indicates that weekly paclitaxel is effective and generally well tolerated as both a first- and second-line treatment for advanced NSCLC. A phase I/II trial by Koumakis *et al.* in a second-line setting tested weekly paclitaxel infused for the first 6 weeks of each 8-week cycle, and demonstrated that a paclitaxel dose escalation from 60 mg/m^2 to 90 mg/m^2 was tolerated (5).

Correspondence to: Nobuyuki Yamamoto, MD, Thoracic Oncology Division, Shizuoka Cancer Center Hospital, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan. Tel: +81-(0)55-989-5222, Fax: +81-(0)55-989-5634, e-mail: n.yamamoto@scchr.jp

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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.