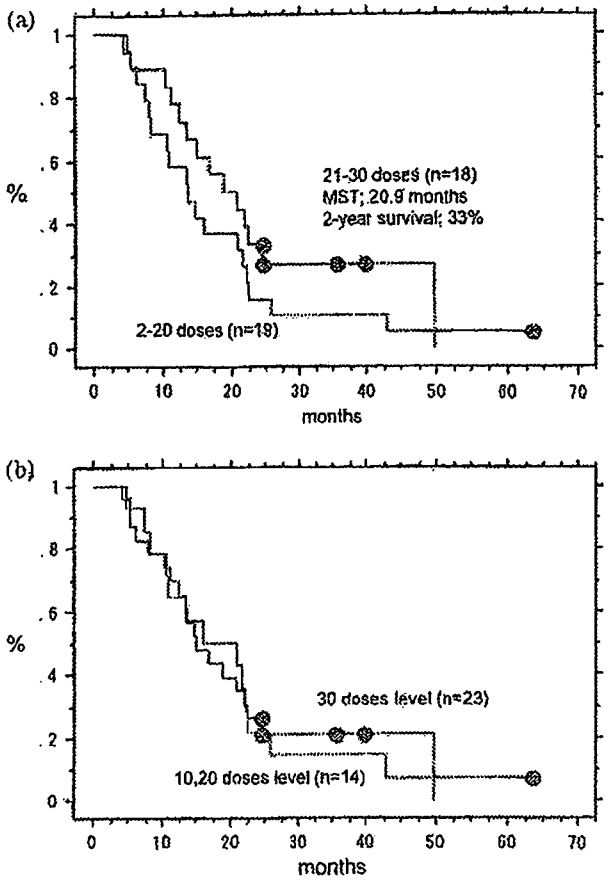

Fig. 4. (a, b) Overall survival rates according to the actual doses of PR-350. No significant difference between the two groups. (b) Overall survival rates according to the intended prescribed doses of PR-350. MST = median survival time.

The incidence of Grade 3 or more lymphopenia was 78%. However, only a few patients showed Grade 3 or more leucopenia or anemia. A major nonhematologic toxicity was radiation pneumonitis, and Grade 3 or more pneumonitis was noted in 6 patients (16%) including the 2 with treatment-related deaths. For 1 of the 2 patients with treatment-related deaths, the initial RT field exceeded one half of the involved lung, which violated the guidelines for RT fields. For the other patient with treatment-related death, extramural review revealed

Table 2. Hematologic toxicities after the second entry (full analysis set; $n = 37$)

Grade of toxicities	G1	G2	G3 or more
Leukocytes	12 (32%)	9 (24%)	2 (5%)
Lymphopenia	0 (0%)	6 (16%)	29 (78%)
Neutrophils	6 (16%)	9 (24%)	1 (3%)
Hemoglobin	2 (5%)	12 (32%)	3 (8%)
Platelets	11 (30%)	0 (0%)	1 (3%)
AST	9 (24%)	1 (3%)	1 (3%)
ALT	9 (24%)	3 (8%)	2 (5%)
Creatinine	1 (3%)	0 (0%)	0 (0%)

Table 3. Nonhematologic toxicities after the second entry (full analysis set; $n = 37$)

Grade of toxicities	G1	G2	G3 or more
Radiation pneumonitis	7 (19%)	5 (14%)	6* (16%)
Skin rash	5 (14%)	3 (8%)	3 (8%)
Peripheral neuropathy	9 (24%)	0 (0%)	0 (0%)
Radiation dermatitis	18 (49%)	4 (11%)	0 (0%)
Dysphagia/esophagitis	25 (68%)	6 (16%)	0 (0%)
Febrile neutropenia	0 (0%)	0 (0%)	1 (3%)
Edema	3 (8%)	1 (3%)	1 (3%)

* Two patients with treatment-related deaths were included.

apparent pulmonary fibrosis on his chest radiography before treatment, which was a violation of the eligibility criteria.

During induction CT, Grade 1 or 2 peripheral neuropathy was observed in 26 patients, and at the start of second entry 17 patients (46%) had only Grade 1 peripheral neuropathy. After the second entry, Grade 1 peripheral neuropathy was prolonged for 3 of the 17 patients. Newly developed peripheral neuropathy of Grade 1 was noted in 6 patients. In total, peripheral neuropathy of Grade 1 was noted in 9 patients (24%). Allergic skin rash of Grade 3 or less was observed in 11 patients (30%). Skin rash was seen out of RT field, and scored differently from radiation dermatitis. Notably, no Grade 3 or more esophageal toxicity was noted.

Pharmacokinetic study

Figure 5 shows changes in the serum concentration of PR-350 in the first and the last sessions. After both sessions, PR-350 was rapidly cleared by the kidney, and no accumulation was observed even after the 30th session. Similarly, no cumulative effect was demonstrated after the 10th and 20th sessions (data not shown).

DISCUSSION

In the Phase I portion of this trial, thoracic RT combined with 30 daily administrations of PR-350 at 2000 mg/m^2 after induction CT was well tolerated. As a single dose or five daily doses of PR-350 at 2000 mg/m^2 has been shown to be safe in previous clinical trials (18, 19), dose escalation

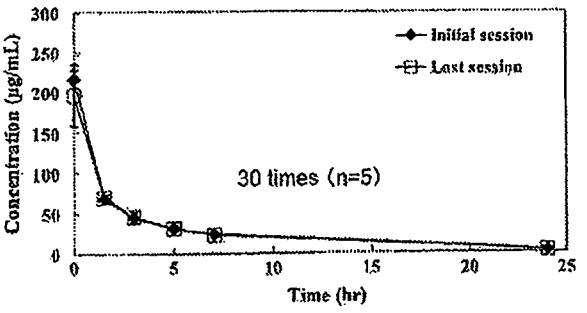

Fig. 5. Changes in serum concentration of PR-350 in the first and the last (30th) session. Means and standard errors are shown. PR-350 was rapidly cleared in both sessions, and no accumulation of PR-350 was observed in the 30th session.

was started from 10 doses of PR-350 in this study. As DLTs, radiation pneumonitis or skin rash of Grade 3 or more was noted in one third or less of 6 to 8 patients at each level, and so 30 daily administrations of PR-350 at 2000 mg/m^2 was determined as the recommended dosage in the Phase II portion of the trial.

A major hematologic toxicity was lymphopenia, although other hematologic toxicities were mild (Table 3). A major nonhematologic toxicity was radiation pneumonitis including two patients with TRD. Grade 3 or higher radiation pneumonitis was observed in 6 patients (16%). A similar rate of radiation pneumonitis is reported by a retrospective study at the National Cancer Center Hospital in Japan (20). In that analysis, severe radiation pneumonitis of Grade 3 or more was noted in 13% of 191 patients with lung cancer treated by CRT or RT alone between 1988 and 1998 (20). On the other hand, a less than 2% incidence of Grade 3 or higher pulmonary toxicity was reported for both sequential and concurrent CRT groups in a Japanese Phase III trial for locally advanced NSCLC using the same eligibility criterion on RT fields (6). It is unclear why pulmonary toxicity in the trial was so low. However the low total RT dose of 56 Gy may have contributed to that.

Because 3D RT planning was not available, it was impossible to correlate toxicity parameters with dose–volume histogram (DVH) information in this study. Although it can not be excluded that PR-350 enhances the effects of radiation on normal lung tissues, we consider that the relatively high incidence of radiation pneumonitis is attributable to our former two-dimensional RT technique. Extramural review of RT films revealed that two TRDs might have been attributable to a violation of protocol guidelines for RT fields or a violation of eligibility criteria on pulmonary disease. To evaluate the effect of PR-350 on radiation pneumonitis, an additional Phase II trial with a three-dimensional RT method may be required.

Neither Grade 3 or more esophageal toxicity, nor Grade 2 or more peripheral neuropathy, was noted. In the PK study, no accumulative effect was observed even after the 30th dose (Fig. 5). The major limitation of 2-nitroimidazoles including misonidazole and ethanidazole is neuropathy (10–12, 21, 22). For head-and-neck cancer, randomized clinical trials comparing RT plus ethanidazole and RT alone have been reported (21, 22). In these trials, ethanidazole at 2000 mg/m^2 given three times weekly for 17 doses was combined with RT, and peripheral neuropathy of Grade 1 to 3 was noted in 24% to 28% of patients. In the present trial, PR-350 at 2000 mg/m^2 was given five times weekly for 10 to 30 doses, and only peripheral neuropathy of Grade 1 was noted in 24% of patients. Thus, PR-350 is apparently less neurotoxic than ethanidazole.

The overall response rate in the RT field was 76% (28/37). For patients who received 21 to 30 doses of PR-350, the overall response rate was as high as 89%. The MST and 2-year survival rate for FAS were 15.9 months and 24%, respectively. This result is well in the range of values for sequential CRT for locally advanced NSCLC (3, 6, 7). In the FAS, patients treated with suboptimal doses of PR-350 (10 or 20 doses) were included in the Phase I portion. Although the analysis according to the intended prescribed doses of PR-350 did not show the difference in survival rate (Fig. 4b), the MST and 2-year survival rate for 18 patients actually receiving 21 to 30 doses of PR-350 were 20.9 months and 33%, respectively (Fig. 4a). These values are well compatible with those for concurrent CRT (6, 7). This Phase II result is promising because a survival rate similar to that for concurrent CRT was obtained by daily administration of PR-350 with an incidence of acute toxicities as low as that for sequential CRT.

At present, concurrent CRT is the standard treatment for locally advanced NSCLC. However, acute toxicities are inevitably more common during concurrent CRT (4–7). So, concurrent CRT is not recommended for elderly patients or patients with a poor performance status. The low incidence of hematologic toxicities and radiation esophagitis in this study has special significance for these patients. The results of this Phase I/II study support the hypothesis that adding PR-350 to sequential CRT may decrease the rate of local recurrence without a significant increase in toxicity. Similarly, a promising clinical result obtained by adding a radiosensitizer, efaproxiral, to sequential CRT has been reported (23). Therefore, the present strategy of sequential CRT combined with PR-350 is a promising approach for locally advanced NSCLC, and a randomized study should be pursued. Furthermore, PR-350 may also be an ideal candidate for incorporation into concurrent CRT, as it could potentially increase the efficacy of concurrent CRT without increasing the toxicities.

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PHASE II STUDIES

Phase II study of amrubicin in previously untreated patients with extensive-disease small cell lung cancer: West Japan Thoracic Oncology Group (WJTOG) study

Takashi Yana · Shunichi Negoro · Minoru Takada · Soichiro Yokota · Yoshiki Takada · Takahiko Sugiura · Hidehiko Yamamoto · Toshiyuki Sawa · Masaaki Kawahara · Nobuyuki Katakami · Yutaka Ariyoshi · Masahiro Fukuoka

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Summary *Purpose:* To evaluate the efficacy and safety of amrubicin, (+)-(7*S*, 9*S*)-9-acetyl-9-amino-7-[(2-deoxy-β-D-*erythro*-pentopyranosyl)oxy]-7,8,9,10-tetrahydro-6,11-dihydroxy-5,12-naphthacenedione hydrochloride, in previously untreated patients with extensive-disease small cell lung cancer (SCLC).

Patients and methods: A total of 35 previously untreated patients with extensive-disease SCLC were entered into the study. Amrubicin was given by daily intravenous infusion at 45 mg/m^2/day for 3 consecutive days, every 3 weeks. Unless there was tumor regression of 25% or greater after the first cycle, or 50% or greater after the second cycle, treatment was switched to salvage chemotherapy in combination with etoposide (100 mg/m^2, days 1, 2, and 3) and cisplatin (80 mg/m^2, day 1).

Results: Of the 35 patients entered, 33 were eligible and assessable for efficacy and toxicity. Of the 33 patients, 3 (9.1%) had a complete response (95% confidence interval [CI], 1.9–24.3%) and 22 had a partial response, for an overall response rate of 75.8% (95% CI, 57.7–88.9%). Median survival time was 11.7 months (95% CI, 9.9–15.3 months), and 1-year and 2-year survival rates were 48.5% and 20.2%, respectively. The most common toxicity was hematologic. Non-hematologic toxicity of grade 3 or 4 was only seen in 3 patients with anorexia (9.1%) and 1 patient with alopecia (3.0%). Salvage chemotherapy was administered to only 6 patients.

T. Yana · M. Takada
Department of Internal Medicine, Osaka Prefectural Habikino Hospital, Habikino

S. Negoro
Department of Clinical Oncology, Osaka City General Hospital, Osaka

S. Yokota
Department of Internal Medicine, National Toneyama Hospital for Chest Diseases, Toyonaka

Y. Takada
Department of Radiology, Hyogo Medical Center for Adults, Akashi

T. Sugiura
Department of Internal Medicine, Aichi Cancer Center Hospital, Nagoya

H. Yamamoto
Department of Internal Medicine, Aso Iizuka Hospital, Iizuka

T. Sawa
Division of Respiratory Medicine, Gifu Municipal Hospital, Gifu

M. Kawahara
Department of Internal Medicine, National Kinki Central Hospital for Chest Disease, Sakai

N. Katakami
Division of Pulmonary Medicine, Kobe City General Hospital, Kobe

Y. Ariyoshi
Department of Internal Medicine, Prefectural Aichi Hospital, Okazaki

M. Fukuoka
Department of Medical Oncology, Kinki University School of Medicine, Osakasayama, Japan

T. Yana (✉)
Division of Respiratory Medicine, KKR Otemae Hospital, 1-5-34, Otemae, Chuo-ku, Osaka 540-0008, Japan
e-mail: t-yana@otemae.gr.jp

Conclusion: Amrubicin was active for extensive-disease SCLC with acceptable toxicity. Further studies in combination with other agents for SCLC are warranted.

Keywords Amrubicin · Small cell lung cancer · Anthracycline · Previously untreated patients · Phase II study

Introduction

Small cell lung cancer (SCLC) is a major cause of cancer deaths and accounts for 15 to 20% of all lung cancers [1]. Although this cancer is initially highly responsive to chemotherapy, the vast majority of patients will ultimately relapse and die of recurrent disease within 2 years [2]. Recently, combination chemotherapy with irinotecan and cisplatin for extensive-disease SCLC produced more survival benefit than etoposide and cisplatin, the worldwide standard regimen since 1981 [3, 4]. Median survival time and 2-year survival rate of the standard regimen is 12.8 months and 19.5%, respectively. Clearly, new and more effective agents against SCLC are needed.

Amrubicin is a totally synthetic 9-aminoanthracycline, (+)-(7*S*, 9*S*)-9-acetyl-9-amino-7-[(2-deoxy-β-D-*erythro*-pentopyranosyl)oxy]-7, 8, 9, 10-tetrahydro-6, 11-dihydroxy-5,12-naphthacenedione hydrochloride, with a chemical structure similar to that of doxorubicin (Fig. 1) [5]. Amrubicin showed more potent antitumor activity than doxorubicin in several human tumor xenografts implanted in nude mice [6]. Acute toxicity of amrubicin is qualitatively similar to that of doxorubicin [7], however, amrubicin shows almost no delayed toxicity (e.g. cardiotoxicity) [8, 9].

Amrubicin is converted to an active metabolite, amrubicinol, by reduction of its C-13 ketone group to a hydroxy group. *In vitro* cytotoxic activity of amrubicinol was almost equipotent to that of doxorubicin and 20 to 220 times more potent than that of its parent compound, amrubicin [10]. Amrubicinol is considered to be closely associated with the efficacy and toxicity of amrubicin [11].

Despite their similarity in chemical structure, amrubicin has a different mode of action to doxorubicin [12]. Amrubicin and its active metabolite, amrubicinol, are inhibitors of DNA topoisomerase II. Amrubicin and amrubicinol exert cytotoxic effects by stabilizing topoisomerase II-mediated cleavable complexes, while doxorubicin does not inhibit this step of the catalytic cycle of topoisomerase II at concentrations for which it demonstrates cytotoxicity. Doxorubicin is a potent DNA intercalator, and its cytotoxicity is thought to be mainly due to this. Amrubicin and amrubicinol are about one-tenth weaker DNA intercalators than doxorubicin. Therefore, they are similar to etoposide in terms of inhibition of topoisomerase II by stabilizing the cleavable complexes, although etoposide does not show any DNA intercalating activity.

In a phase I–II study in patients with non-small cell lung cancer, amrubicin was administered as a 5-min intravenous infusion for 3 consecutive days [13]. The maximum tolerated dose (MTD) was 50 mg/m^2/day and the dose-limiting toxicities were leukopenia, neutropenia, thrombocytopenia, and gastrointestinal complications. The recommended dose for the phase II study was 45 mg/m^2/day for 3 consecutive days every 3 weeks.

Based on these experimental data and preliminary clinical reports indicating that amrubicin may be active against lung cancer, the West Japan Thoracic Oncology Group (WJTOG) evaluated it for use in SCLC. The WJTOG conducted a phase II study in previously untreated extensive-disease SCLC patients as a first-line therapy. Salvage chemotherapy with etoposide and cisplatin and an early cessation rule were set in place as precautionary measures.

Patients and methods

Eligibility criteria

Eligibility criteria included histologically or cytologically proven small cell lung cancer with extensive-disease defined as distant metastasis and/or disease involving the

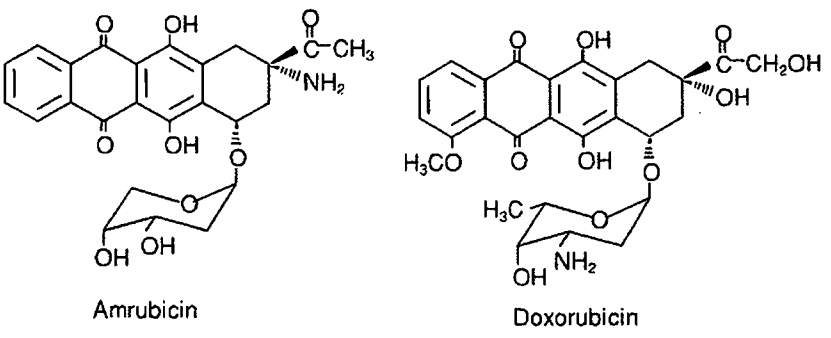

Fig. 1 Chemical structures of amrubicin and doxorubicin

contralateral hilar lymph nodes; no prior treatment; life expectancy of at least 2 months; the Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; at least one bidimensionally measurable lesion; age less than 80; adequate organ function, such as white blood cell (WBC) count of 4000×10^6/L or greater, hemoglobin level 10 g/dL or greater, platelet count 100×10^9/L or greater, AST and ALT less than 100 IU/L, bilirubin level 1.5 mg/dL or less, creatinine concentration 1.2 mg/dL or less, electrocardiogram (ECG) findings within normal range, and left ventricular ejection fraction (LVEF) of echocardiogram 60% or greater. All patients gave written informed consent. Ineligibility criteria were: brain or bone metastases requiring radiation; continuous long-term treatment with non-steroidal anti-inflammatory drugs and glucocorticoids; pulmonary fibrosis; serious complications and other active malignancy; or pregnant or nursing subjects.

This study was approved by the institutional review boards at each participating center.

Study design

Amrubicin (Sumitomo Pharmaceuticals Co., Ltd, Osaka, Japan) was dissolved in 20 mL normal saline and administered once intravenously as a 5-min infusion at a dose of 45 mg/m^2/day on days 1 to 3, every 3 weeks.

Before treatment, all patients underwent a medical history, physical examination, hematology and serum biochemistry tests, urinalysis, ECG, LVEF, and baseline tumor measurements (chest radiography, CT scans, bone scintigraphy, and other measurements as appropriate). All measurable and assessable lesions were evaluated within 2 weeks before treatment. ECG and LVEF were undertaken within 1 month before treatment.

Complete and differential blood cell counts, platelet counts, hematocrit analysis, biochemical analysis including AST, ALT, alkaline phosphatase, LDH, total bilirubin, BUN, creatinine, serum bilirubin, albumin, total protein, and electrolyte levels (Na, K, Cl, and Ca), and urinalysis (including protein, glucose, urobilinogen, and occult blood) were performed weekly as a rule. When severe myelosuppression was observed, complete and differential blood cell counts plus platelet counts were performed 2 times or more per week. ECG was undertaken every treatment cycle and LVEF every other cycle. Chest radiography and CT scans were carried out every cycle as a rule.

Subjective and objective symptoms were observed and recorded as appropriate.

Dose modifications were made according to WBC and platelet counts. If the WBC count nadir was lower than $1{,}000 \times 10^6$/L for 4 days or longer and/or the platelet count nadir was lower than 50×10^9/L, a dose reduction of 5 mg was stipulated in the subsequent treatment course. Treatment was postponed until the WBC and platelet counts recovered to $\geq 3{,}000 \times 10^6$/L and $\geq 100 \times 10^9$/L, respectively.

In patients who demonstrated tumor regression of 25% or greater after the first course of chemotherapy, amrubicin treatment was continued. After the second course, patients had to have achieved tumor regression of 50% or greater to continue to receive the drug up to a maximum of 6 courses. Treatment of combination chemotherapy with etoposide (100 mg/m^2 on days 1, 2, and 3) and cisplatin (80 mg/m^2 on day 1) was recommended for patients who failed to fulfill any of the above criteria.

Evaluation of response and toxicity

Response was assessed according to the "Criteria for the evaluation of the clinical effects of solid cancer chemotherapy" of the Japan Society for Cancer Therapy [14], which are virtually identical to those of the World Health Organization [15]. A complete response (CR) was defined as disappearance of all lesions for a minimum of 4 weeks. A partial response (PR) was defined as a 50% or greater decrease in the sum of the products of the diameters of measurable lesions for a minimum period of 4 weeks and no new lesions. No change (NC) was defined as a decrease in the tumor mass of less than 25% or any increase of less than 25%. Progressive disease (PD) was defined as an increase in the size of any measurable lesion by 25% or greater or the appearance of new lesions.

Toxicity grading was recorded based on the side effect record form in the "Criteria for the evaluation of the clinical effects of solid cancer chemotherapy" of the Japan Society for Cancer Therapy [14].

Statistical analyses

The estimated sample size was 30 to guarantee that the lower limits of 95% confidence interval would be at least 20% at 40% of expected response rate. An early cessation rule was in place to terminate the study if at least 4 responses had not been seen among 15 patients evaluated. Median overall survival was estimated using the product-limit (Kaplan-Meier) method [16].

Results

Patient characteristics

Of 35 patients entered into this study between May 1995 and January 1997, 33 patients were eligible and assessable for efficacy and toxicity. There were 2 ineligible patients because of serious complications before treatment (cardiac

Table 1 Patient characteristics

Patient characteristics	No. of patients (N = 33)	%
Age (years)		
Median	66	
Range	42–78	
Sex		
Male	29	87.9
Female	4	12.1
Performance status (ECOG)		
0	5	15.2
1	26	78.8
2	2	6.1
Stage		
IIIB	1	3.0
IV	32	97.0
Prior therapy		
No	33	100

ECOG: Eastern Cooperative Oncology Group.

failure and aggravation of hepatitis, respectively), and they did not receive amrubicin. Characteristics of the 33 eligible patients are shown in Table 1. Of the 33 patients, 13 (39%) were 70 years of age or older, 88% were male, and 94% had an ECOG performance status of 0 or 1.

Efficacy

Response to amrubicin is shown in Table 2. The early cessation rule was not imposed to terminate the study, as 10 responses were seen after 15 patients were enrolled. Of 33 patients, 3 achieved a complete response, giving a CR rate of 9.1% (95% CI, 1.9–24.3%), and 22 a partial response, for an overall response rate of 75.8% (95% CI, 57.7–88.9%). Of 7 patients, 6 experiencing no change under amrubicin treatment were switched to salvage chemotherapy. Of these, 2 had partial responses and the others had no change.

The overall survival curve is shown in Fig. 2. Median survival time was 11.7 months (95% CI, 9.9–15.3 months), and 1-year and 2-year survival rates were 48.5% (95% CI, 31.4–65.5%) and 20.2% (95% CI, 6.4–34.4%), respectively.

Toxicity

The major observed toxicity was hematologic, as shown in Table 3. All patients experienced leukopenia and neutropenia. Grade 3 or 4 leukopenia occurred in 51.5% of patients and grade 3 or 4 neutropenia in 84.8%. Anemia and thrombocytopenia were observed in 78.8% and 39.4% of patients, respectively, both with a frequency of grade 3 or 4 of 21.2%. Despite the severe hematologic toxicity of amrubicin, there was no febrile neutropenia or treatment-related death during the entire treatment of 33 patients. Granulocyte colony-stimulating factor (G-CSF) was used in 55 (40%) of a total of 136 cycles, in 13 patients (39%). Most hematologic toxicity in this trial was well-controlled without dose reduction: 88% of the total treatment cycles were delivered at the planned dosage of amrubicin, 45 mg/m^2/day.

Non-hematologic toxicities observed in more than 10% of patients were anorexia (54.5%), nausea and vomiting

Table 2 Response to amrubicin

No. of assessable patients	Response (No. of patients)				CR rate, % (95% CI)	Response rate, % (95% CI)
	CR	PR	NC	PD		
33	3	22	7	1	9.1 (1.9–24.3)	75.8 (57.7–88.9)

CR: complete response; PR: partial response; NC: no change; PD: progressive disease; 95% CI: 95% confidence interval.

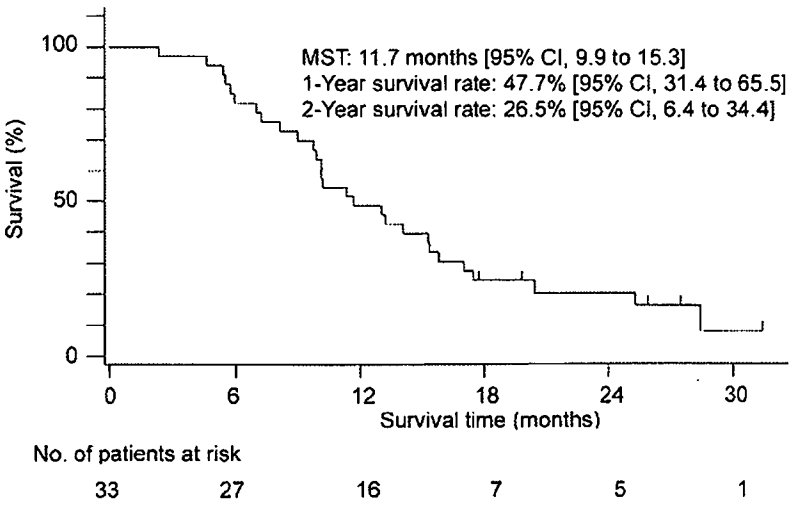

Fig. 2 Overall survival of patients with extensive-disease small cell lung cancer treated with amrubicin. MST: median survival time; 95% CI: 95% confidence interval

Table 3 Main treatment-related toxicity of amrubicin

Toxicity	No. of assessable patients	Toxicity grade others					
		1	2	3	4	≥ 1	≥ 3
		(No. of patients)				Frequency (%)	
Hematologic toxicity							
Anemia (hemoglobin)	33	12	7	6	1	78.8	21.2
Leukopenia	33	5	11	13	4	100	51.5
Neutropenia	33	1	4	14	14	100	84.8
Thrombocytopenia	33	3	3	1	6	39.4	21.2
Non-hematologic toxicity							
Stomatitis	33	2	1	0	0	9.1	0
Anorexia	33	12	3	3	–[a]	54.5	9.1
Nausea and vomiting	33	12	7	0	–[a]	57.6	0
Diarrhea	33	6	0	0	0	18.2	0
Fever	33	3	7	0	0	30.3	0
Phlebitis	33	1	1	0	0	6.1	0
Alopecia	33	11	8	1	–[a]	60.6	3.0
Total bilirubin elevation	33	1	1	0	0	6.1	0
AST elevation	33	5	0	0	0	15.2	0
ALT elevation	33	8	1	0	0	27.3	0
ALP elevation	33	1	0	0	0	3.0	0
BUN elevation	33	2	0	0	0	6.1	0
Others[b]	Headache, 1/33[c]; Rash, 1/33; Constipation, 1/33; Interstitial pneumonia, 1/33; Rhinorrhagia, 1/33; ECG abnormality, 3/32						

AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; BUN: blood urine nitrogen; ECG: electrocardiogram.

[a]Toxicity grade was not defined for these toxicities.

[b]Toxicities which were not graded.

[c]Proportion of number of reported patients to number of observed patients.

(57.6%), diarrhea (18.2%), fever (30.3%), alopecia (60.6%), AST increase (15.2%), and ALT increase (27.3%). Most of these were mild (≤grade 2), with only 3 patients (9.1%) experiencing grade 3 anorexia and 1 patient grade 3 alopecia (3.0%). A single patient developed interstitial pneumonia after the second cycle of treatment; however, it was reversibly recovered by steroid therapy and cessation of amrubicin treatment. ECG abnormality was observed in 3 patients (9.4%; supraventricular extrasystole, prolonged QT interval, and T wave flattening in 1 patient each), which did not need any treatment. No LVEF decrease was observed.

Discussion

Results of this phase II study demonstrate that amrubicin is an extremely active agent against extensive-disease SCLC. The complete response rate was 9.1% (95% CI, 1.9–24.3%), overall response rate 75.8% (95% CI, 57.7–88.9%), and median survival time 11.7 months (95% CI, 9.9–15.3 months). These results are comparable or even superior to those of the standard combination regimen of cisplatin and etoposide, used as the gold standard of extensive-disease SCLC therapy since 1981 and remaining unchanged over the last 2 decades [4].

SCLC is sensitive to cytotoxic anticancer agents. Of anticancer drugs developed before 1990, a number of agents with response rates of 20% or greater for SCLC were listed as active drugs [17]. Of these drugs, etoposide, cisplatin, carboplatin, doxorubicin, cyclophosphamide, and vincristine, are still currently used as important constituents of combination regimens in the treatment of SCLC. In addition, several drugs with significant activity for SCLC have been developed since 1990. Irinotecan showed a response rate of 33% to 47% even in previously treated patients who are generally less sensitive to chemotherapy [18, 19]. Recently a new combination regimen of irinotecan plus cisplatin was demonstrated to be significantly superior to standard regimen of etoposide plus cisplatin in median survival time (12.8 months vs. 9.4 months, $P = 0.002$) [3]. In addition, topotecan, paclitaxel, docetaxel, and gemcitabine are reported to have response rates of 26% to 41% for extensive-disease SCLC patients without previous treatment [20–24]. Compared to these agents, amrubicin demonstrated a much higher response rate (75.8%) in this study, indicating it is a promising novel agent with potential to overcome the therapeutic plateau of SCLC.

The major toxicity of amrubicin was hematologic. Grade 3 or 4 leukopenia was frequently observed in 51.5% of patients and grade 3 or 4 neutropenia in 84.8% of patients. Despite such severe hematologic toxicity, 88% of the total treatment cycles could be delivered without dose reduction and non-hematologic toxicities were mild. Although anorexia (54.5%) and nausea and vomiting (57.6%) were frequently observed, there were no episodes of grade 3 or 4 toxicity, except for 3 patients (9.1%) with grade 3 anorexia and 1 patient (3.0%) with grade 3 alopecia. A single patient developed interstitial pneumonia; however, this was reversible with steroid therapy. ECG abnormalities were observed in 3 patients, but they were each reviewed by a medical cardiologist and judged not to be clinically significant. No LVEF decrease was observed. Results show that the toxic profiles of amrubicin are acceptable and favorable in the treatment of extensive-disease SCLC, although due to its hematologic toxicity, in particular neutropenia, G-CSF support is needed.

In conclusion, amrubicin is a very active and promising agent with acceptable toxicity for patients with SCLC. Further studies are warranted in combination with other agents for this disease.

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PHASE II STUDIES

Phase II study of amrubicin, 9-amino-anthracycline, in patients with advanced non-small-cell lung cancer: a West Japan Thoracic Oncology Group (WJTOG) study

Koji Takeda · Nobuhide Takifuji · Shunichi Negoro · Kiyoyuki Furuse · Shinichiro Nakamura · Yoshiki Takada · Takanobu Hoso · Shinichi Hayasaka · Takashi Nakano · Jun Araki · Hiroshi Senba · Fumiyuki Iwami · Yasufumi Yamaji · Masahiro Fukuoka · Harumichi Ikegami

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Summary *Purpose:* We conducted a multicenter phase II study of amrubicin, a novel 9-aminoanthracycline, to evaluate its efficacy and safety in patients with non-small-cell lung cancer (NSCLC). *Patients and methods:* Entry requirements included cytologically or histologically proven measurable NSCLC, stage III or IV, no prior therapy, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and adequate organ function.

K. Takeda (✉) · N. Takifuji
Department of Clinical Oncology, Osaka City General Hospital, 2-13-22, Miyakojimahondohri, Miyakojima-ku, Osaka 5340021, Japan
e-mail: kkk-take@ga2.so-net.ne.jp

S. Negoro
Department of Thoracic Oncology, Hyogo Medical Center for Adults, Akashi, Japan

K. Furuse
Department of Internal Medicine, National Kinki Central Hospital for Chest Diseases, Sakai, Japan

S. Nakamura · H. Ikegami
Department of Pulmonary Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

Y. Takada
Department of Radiolgy, Hyogo Medical Center for Adults, Akashi, Japan

T. Hoso
Department of Respiratory Medicine, Wakayama Rosai Hospital, Wakayama, Japan

S. Hayasaka
Department of Respiratory Medicine, Kumamoto-Chuo Hospital, Kumamoto, Japan

T. Nakano
Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan

J. Araki
Department of Internal Medicine, Sasebo City General Hospital, Sasebo, Japan

H. Senba
Division of Respiratory Diseases, Kumamoto Regional Medical Center, Kumamoto, Japan

F. Iwami
Division of Respiratory Medicine, National Minamikyushu Hospital, Kajiki, Japan

Y. Yamaji
Department of Respiratory Medicine, Mitoyo General Hospital, Toyohama, Japan

M. Fukuoka
Department of Medical Oncology, Kinki University School of Medicine, Osakasayama, Japan

Amrubicin was given by daily intravenous injection at 45 mg/m^2/day for three consecutive days, repeated at 3 week intervals. Each patient received at least three treatment cycles. *Results:* Sixty-two patients were enrolled in this study. Of the 62 registered patients, 60 were eligible and assessable for efficacy, and 59 for toxicity. Overall response rate was 18.3% (95% confidence interval [CI], 9.5 to 30.4%) and median survival time was 8.2 months (95% CI, 6.7 to 10.4 months). Major toxicity was myelosuppression, with incidences of grade 3 or 4 toxicity of 78.0% for neutropenia, 54.2% for leukopenia, 30.5% for anemia, and 28.8% for thrombocytopenia. Non-hematological toxicities with a greater than 50% incidence were anorexia (69.5%), nausea/vomiting (55.9%), and alopecia (75.9%), but were relatively mild, with grade 3 toxicities observed in only one patient each (1.7%). *Conclusion:* Amrubicin was an active, well-tolerated agent in the treatment of NSCLC.

Keywords Amrubicin · Anthracycline · Non-small-cell lung cancer · Phase II study

Introduction

Non-small-cell lung cancer (NSCLC) is already a leading cause of cancer-related deaths worldwide, with an incidence which is increasing. Current therapeutic options are unsatisfactory, however, and development of novel, more effective antitumor agents has been sought.

Amrubicin is a novel, totally synthetic 9-aminoanthracycline, (+)-(7S,9S)-9-acetyl-9-amino-7-[(2-deoxy-β-D-*erythro*-pentopyranosyl)oxy]-7,8,9,10-tetrahydro-6,11-dihydroxy-5,12-naphthacenedione hydrochloride, with a similar structure to doxorubicin (Fig. 1) [1].

An important characteristic of amrubicin is that it is a prodrug which is converted to the active metabolite, amrubicinol, via reduction of its C-13 ketone group to a hydroxy group by carbonyl reductase [2]. *In vitro* studies have shown that the cytotoxic activity of amrubicinol is 20 to 220 times more potent than that of its parent compound, amrubicin, and has closely similar potency to doxorubicin [3]. The efficacy and toxicity of amrubicin is therefore largely dependent on the tissue distribution of amrubicinol. Among results to date, amrubicin showed more potent antitumor activity than doxorubicin in several human tumor xenografts implanted in nude mice [4], and antitumor activity was closely reflective of the tumor concentration of amrubicinol [5]. The acute toxicity profile of this agent is qualitatively comparable to that of doxorubicin [6], but it has rarely been shown to cause the delayed-type toxicity observed with doxorubicin, particularly cardiotoxicity [7, 8], nor did it exacerbate doxorubicin-induced myocardial toxicity in dogs [8]. Amrubicin and amrubicinol are weak DNA intercalaters and potent inhibitors of topoisomerase II [9].

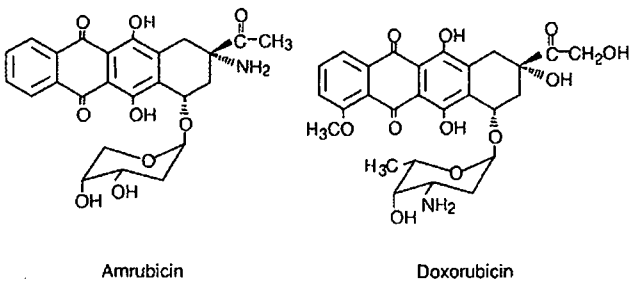

Fig. 1 Chemical structures of amrubicin and doxorubicin

Clinically, amrubicin showed substantial activity against NSCLC in an early phase II study of single intravenous injection of 120 mg/m^2 every 3 weeks, with a partial response (PR) rate in 5 of 20 previously untreated patients (25%; 95% CI, 8.7 to 49.1%) [10]. An additional phase I–II study for NSCLC was conducted by daily intravenous administration for three consecutive days [11], on the basis of experimental findings that amrubicin showed better efficacy in a divided treatment schedule than in a single injection [12]. The maximum tolerated dose was set at 50 mg/m^2/day and the recommended dose for the phase II study was 45 mg/m^2/day. Overall response rate in the phase I–II study was 25.0% (95% CI, 10.7 to 44.9%), with seven PRs in 28 previously untreated patients. These reproducible response rates of more than 20% in two clinical studies suggest that amrubicin may be a promising agent in the treatment of NSCLC, in contrast to doxorubicin which shows only marginal activity against NSCLC [13].

Here, we conducted one of two phase II studies with an identical protocol and monitoring to assess the efficacy and safety of amrubicin by daily intravenous administration for three consecutive days in previously untreated patients with advanced NSCLC.

Patients and methods

Eligibility

This study investigated patients with histologically or cytologically confirmed unresectable NSCLC in stages IIIA, IIIB, and IV. Eligibility criteria included no prior treatment, measurable lesions, an ECOG performance status of 0 to 2, an estimated life expectancy of at least 2 months, and age less than 75 years. Adequate organ function was also required, with a WBC count ≥4,000/μL, platelet count ≥100,000/μL, hemoglobin level ≥10 g/dL, AST and ALT< 100 U/L, total bilirubin level ≤1.5 mg/dL, serum creatinine level ≤1.2 mg/dL, ECG within normal limits, and left ventricular ejection fraction (LVEF, echocardiogram) ≥60%.

Exclusion criteria included symptomatic brain metastasis, bone metastasis requiring radiation treatment, accumulation of plural fluid requiring treatment like drainage, continuous long-term treatment with non-steroidal anti-inflammatory agents, glucocorticoids, or morphine derivatives, serious complications or other active cancer, and those judged by the investigators to be inappropriate for the study. Patients who were pregnant, breast-feeding, or taking inadequate contraceptive precautions were also ineligible. Further, the protocol was amended during the course of the study to exclude patients with confirmed or suspected interstitial pneumonitis owing to the exacerbation of asymptomatic interstitial pneumonitis, identified by chest X-ray or computed tomographic (CT) scan before treatment, in three patients in an identical study, of whom two died [14]. The study protocol was approved by the institutional review board at each hospital, and written informed consent was obtained from all patients prior to participation.

Treatment

Amrubicin (Sumitomo Pharmaceuticals Co., Ltd, Osaka, Japan) was supplied as a freeze-dried powder in vials containing 20 mg each. It was reconstituted in 20 mL of physiological saline or 5% glucose solution and given by intravenous infusion at 45 mg/m^2/day over 5 min on three consecutive days, with the cycle repeated every 3 weeks. A minimum of three cycles was undertaken except in the occurrence of disease progression, unacceptable toxicity or patient noncompliance.

Before treatment, all patients underwent medical history review, physical examination, hematology and serum biochemistry tests, urinalysis, electrocardiography (ECG), echocardiogram for left ventricular ejection fraction (LVEF), and baseline tumor measurements (e.g. chest radiography, CT scans, bone scintigraphy). Measurable and assessable lesions were evaluated within 2 weeks of the start of treatment, and ECG and LVEF within 1 month.

Laboratory variables were measured weekly as a rule, including complete differential blood cell counts, platelet counts, hematocrit, blood biochemistry, and urinalysis. Complete differential blood cell and platelet counts were obtained at least twice weekly when myelosuppression was observed. The ECG was measured with every treatment cycle, and the LVEF test every second cycle. Chest radiography and CT scans were carried out every cycle as a rule.

Subjective symptoms and objective signs were observed and recorded as required

Adjustment of dosage and schedule modification

Treatment was repeated when the WBC count recovered to ≥3,000/μL and the platelet count recovered to ≥100,000/μL. Treatment was delayed when recovery was incomplete until these values were reached, and withdrawn if they were not reached within 5 weeks. Dosage was maintained as in the previous course if the WBC nadir was <1,000/μL for ≤3 days, or ≥1,000/μL and the platelet nadir was ≥50,000/μL, and reduced by 5 mg/m^2/day from the previous dosage if the respective values were <1,000/μL for ≥4 days and/or <50,000/μL.

Response and toxicity evaluation

Response was assessed in accordance with the "Criteria for the evaluation of the clinical effects of solid cancer chemotherapy" of the Japan Society for Cancer Therapy [15], which are virtually identical to those of the World Health Organization [16], namely with a complete response (CR) defined as the disappearance of all lesions for a minimum of 4 weeks; a partial response (PR) as a 50% or greater decrease in the sum of the products of the diameters of the measurable lesions for a minimum period of 4 weeks and no new lesions; no change (NC) as a decrease in the tumor mass of less than 50% or any increase of less than 25%; and progression disease (PD) as an increase in the size of any measurable lesion by 25% or the appearance of new lesions.

Toxicity was graded based on the side effect record form of the Japan Society for Cancer Therapy criteria [15]. Toxicity items not included on the record form were recorded as present or absent without grading.

Table 1 Patient characteristics

Patient characteristics	No. of patients	Percent
No. of enrolled patients	62	
No. of eligible patients	60	
Age, years		
Median	65.5	
Range	41–75	
Gender		
Male	37	61.7
Female	23	38.3
Performance status (ECOG scale)		
0	8	13.3
1	41	68.3
2	11	18.3
Histology		
Squamous cell carcinoma	24	40.0
Adenocarcinoma	29	48.3
Large cell carcinoma	7	11.7
Stage		
IIIA	5	8.3
IIIB	14	23.3
IV	41	68.3

ECOG Eastern Cooperative Oncology Group

Table 2 Response to amrubicin

	No. of patients	Response (No. of patients)					Response rate, % [95%CI]
		CR	PR	NC	PD	NE	
Eligible patients	60	0	11	30	16	3	18.3 [9.5–30.4]
Histology:							
Squamous cell carcinoma	24	0	6	9	7	2	25.0
Adenocarcinoma	29	0	5	17	6	1	17.2
Large cell carcinoma	7	0	0	4	3	0	0
Stage							
IIIA	5	0	2	3	0	0	40.0
IIIB	14	0	3	7	3	1	21.4
IV	41	0	6	20	13	2	14.6
Performance status (ECOG):							
0	8	0	2	4	2	0	25.0
1	41	0	8	22	10	1	19.5
2	11	0	1	4	4	2	9.1

Abbreviations: CR, complete response; PR, partial response; NC, no change; PD, progressive disease; NE, not evaluated; ECOG, Eastern Cooperative Oncology Group

Statistical analyses

Primary endpoint was response rate. In this study, the number of patients was estimated as 60 to guarantee at least 10% response rate with a probability of 95% at 20% of expected response rate. Secondary endpoints were overall survival and safety. The time frame for overall survival was defined as the time from treatment until onset of the event. Kaplan–Meier life table was constructed for patient survival, 1-year survival, 2-year survival and median survival time [17]. All analyses were done using SAS, version 8.2 (SAS Institute Inc., Cary, North Carolina).

Results

Patient characteristics

Of 62 patients registered between April 1995 and September 1997 through 14 participating institutions in Japan, 60 patients were eligible and assessable for efficacy and 59 were assessable for safety (Table 1). Two patients were ineligible due to the protocol deviation in the inclusion criteria, not NSCLC in one patient and receiving prior chemotherapy in a second patient. Another patient was not safety-assessable due to a withdrawal of informed consent soon after the completion of first cycle treatment. By stage, 41 patients had stage IV disease, 14 had stage IIIB, and 5 had stage IIIA. Histologically, 29 patients had adenocarcinoma, 24 squamous cell carcinoma, and only 7 large cell carcinoma. Most patients had a good performance status (PS) of 0 or 1, but 11 (18.3%) had PS of 2. No patient had received any prior treatment, including radiotherapy.

Response and survival

Response among the 60 eligible patients was 11 PRs, giving an overall response rate of 18.3% (95% CI, 9.5 to 30.4%) (Table 2). Responders were 6 (25.0%) of 24 patients with squamous cell carcinoma and 5 (17.2%) of 29 with adenocarcinoma.

Regarding the overall survival curve, median survival time was 8.2 months (95% CI, 6.7 to 10.4 months), and 1- and 2-year survival rates were 34.9% and 7.6%, respectively (Fig. 2).

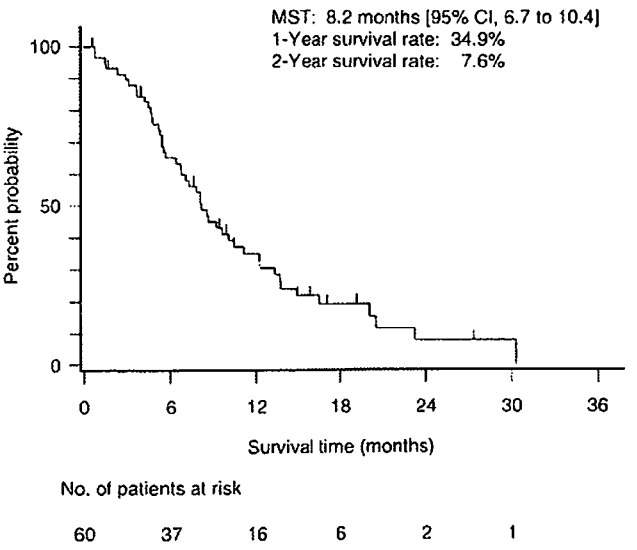

Fig. 2 Overall survival of patients with advanced non-small-cell lung cancer following treatment with amrubicin. Median survival time was 8.2 months (95% confidence interval, 6.7–10.4 months)

Table 3 Major treatment-related hematologic toxicity of amrubicin

Toxicity	No. of assessable patients	Toxicity grade					
		1	2	3	4	≥1	≥3
		(No. of patients)				Frequency (%)	
Anemia (hemoglobin)	59	16	17	16	2	86.4	30.5
Leukopenia	59	5	16	21	11	89.8	54.2
Neutropenia	59	0	7	12	34	89.8	78.0
Thrombocytopenia	59	12	3	9	8	54.2	28.8

Safety

Hematologic toxicities observed throughout the present clinical trial for which a causal relationship to amrubicin could not be denied are shown in Table 3. The most common was myelosuppression, particularly neutropenia, leukopenia and anemia (hemoglobin decrease) with frequencies of 89.8, 89.8 and 86.4%, respectively. Thrombocytopenia was somewhat lower frequent (54.2%). Among these, the incidence of grade 3 or 4 toxicity was 78.0% for neutropenia, 54.2% for leukopenia, 30.5% for anemia, and 28.8% for thrombocytopenia.

Although mild, non-hematologic toxicities included stomatitis, anorexia, nausea/vomiting, diarrhea, fever, alopecia, and AST/ALT elevation were each seen in more than 10% of the patients (Table 4). Grade 3/4 episodes were seen only for anorexia, nausea/vomiting, and alopecia with frequencies of each 1.7%. ECG abnormalities for which a relationship to amrubicin was unknown were seen in two patients, one with transient negative T and the second with ST depression, but were judged not to be clinically significant on review by a cardiologist. A decrease in LVEF for which a causal relation to amrubicin could not be denied was seen in two patients, one with a decrease from 73% at base line to 53% after three cycles of treatment and in the second from 69 to 52% after two cycles. LVEF values fluctuate readily under the influence of various factors, and these changes are not particularly abnormal. Moreover, no accompanying changes in ECG or symptoms were seen, and thus the medical significance was not clear. However, given that amrubicin is an anthracycline derivative, like doxorubicin, the cardiotoxicity of which is well known, treatment was discontinued as precaution.

Discussion

This present study indicates that amrubicin is an active agent in the treatment of patients with NSCLC. Overall response rate was 18.3% (95% CI, 9.5 to 30.4%) and median survival time was 8.2 months (95% CI, 6.7 to 10.4 months). In an identical study, which included 61 patients, amrubicin achieved overall response rate of 27.9%, with 1 CR and 16 PRs, and median survival was 9.8 months [14]. Thus, the overall response rate for amrubicin in these two studies with an identical protocol was 23.1% (95% CI, 16.0 to 31.7%).

Table 4 Major treatment-related non-hematologic toxicities of amrubicin

Toxicity	No. of assessable patients	Toxicity grade					
		1	2	3	4	≥1	≥3
		(No. of patients)				Frequency (%)	
Stomatitis	59	7	2	0	0	15.3	0
Anorexia	59	20	20	1	–[a]	69.5	1.7
Nausea and vomiting	59	21	11	1	–[a]	55.9	1.7
Diarrhea	59	9	0	0	0	15.3	0
Fever	59	8	7	0	–[a]	25.4	0
Phlebitis	59	2	0	0	0	3.4	0
Alopecia	58	27	16	1	–[a]	75.9	1.7
Total bilirubin elevation	58	4	0	0	0	6.9	0
AST elevation	59	10	1	0	0	18.6	0
ALT elevation	59	9	4	0	0	22.0	0
ALP elevation	59	3	1	0	0	6.8	0
BUN elevation	59	4	0	0	0	6.8	0
Others[b]	LVEF decrease, 2/42[c]; ECG abnormality, 2/54[c]						

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urine nitrogen; LVEF, left ventricular ejection fraction; ECG, electrocardiogram

[a] Toxicity grade not defined.

[b] Toxicities not graded.

[c] Ratio of number of reported patients to number of observed patients.

NSCLC is known to have poor sensitivity to chemotherapy [18–20], but the recent development of newer agents such as paclitaxel, docetaxel, gemcitabine, vinorelbine, and irinotecan has seen considerable improvements in therapeutic outcomes [21, 22], with response rates of more than 20% when used as single agents in previously untreated patients with advanced NSCLC. The present results indicate that amrubicin which is different from these newer agents in mode of action [9], namely the inhibition of topoisomerase II, is comparable to these newer agents in efficacy for NSCLC.

The major toxicity of amrubicin was hematologic, particularly neutropenia and leukopenia. In contrast, no febrile neutropenia was observed. Non-hematologic toxicity was relatively mild, with the only grade 3/4 episodes being seen for anorexia, nausea/vomiting, and alopecia with frequencies of each 1.7%. These safety results are supported by those from an identical study [14]. In that study, interstitial pneumonitis developed in three patients, of whom two died [14]. So the protocol was revised to exclude patients with confirmed or suspected interstitial pneumonitis. In the present study, interstitial pneumonitis was not seen.

Among cardiotoxicity, abnormalities in ECG and a decrease in LVEF were seen in two patients each. These changes were asymptomatic and did not overlap in the same patients. These findings suggest that unlike the case of cardiomyopathy caused by doxorubicin, the effect of amrubicin on cardiac function is neither serious nor definite. It is well known that doxorubicin experimentally and clinically causes cardiomyopathy which is cumulative toxicity caused by long-term treatment. In contrast, amrubicin on repeated administration did not cause cardiotoxicity or aggravate doxorubicin-induced cardiotoxicity in rabbits and dogs [7, 8]. Although cardiomyopathy has not been clinically observed to date, careful observation on the effects of amrubicin on the heart is required in further clinical studies, especially for patients on long-term treatment.

In conclusion, amrubicin showed promising activity against NSCLC in the present study. In a previous study, moreover, the combination of amrubicin and cisplatin demonstrated an impressive response rate and median survival time for extensive-stage SCLC (87.8% and 13.6 months, respectively) [23]. We are presently planning a phase II study of the combination of amrubicin and cisplatin for advanced NSCLC.

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Phase II Study of Paclitaxel and Irinotecan Chemotherapy in Patients With Advanced Nonsmall Cell Lung Cancer

Fumihiro Oshita, MD, Haruhiro Saito, MD, Kouzo Yamada, MD, and Kazumasa Noda, MD

Objectives: We conducted a phase II study of combination chemotherapy with paclitaxel (Pac) and irinotecan (CPT) to determine the qualitative and quantitative toxicities and efficacy of the combination against advanced nonsmall cell lung cancer (NSCLC).

Patients and Methods: Patients with stage IIIB or IV NSCLC were treated with CPT at 60 mg/m^2 and Pac at 160 mg/m^2 every 2 weeks.

Results: Between May 2002 and July 2004, 39 of registered 46 patients received 4 to 6 cycles of chemotherapy, and 7 patients discontinued treatment because of disease progression in 5 patients and grade 2 pneumonitis in 2 patients. Grade 3 anemia, leukopenia, neutropenia, and elevation of bilirubin occurred in 4.0%, 0.5%, 1.0%, and 0.5%, respectively. Twenty-one patients responded, and the overall response rate was 45.6%. The median survival time was 355 days and the 1-year survival rate was 47.8%.

Conclusion: Pac plus CPT was efficacious and safe in NSCLC.

Key Words: paclitaxel, irinotecan, nonsmall cell, lung cancer

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Current chemotherapy regimens for metastatic nonsmall cell lung cancer (NSCLC) are not particularly effective, and the disease cannot be cured even with the most effective chemotherapy. Current international guidelines recommend the use of platinum-based chemotherapy for patients with advanced NSCLC,[1] and the use of doublets including platinum plus a third-generation agent has been widely accepted for patients with a good performance status. A meta-analysis of the published literature clearly showed the superiority of platinum-containing regimens in terms of objective response rate, and this superiority was found throughout the subgroup analyses performed.[2] The study results also confirmed that platinum-based therapy is generally associated with higher toxicity, particularly nausea and vomiting, hematologic toxicity, and nephrotoxicity. Nevertheless, platinum-based regimens can be administered as safely as nonplatinum therapies when patients are selected correctly. However, this study did not include every combination of nonplatinum drugs, and it is necessary to examine every such new combination for efficacy and toxicity.

Combined analysis of two randomized phase III studies demonstrated that irinotecan (CPT) combined with cisplatin significantly improves survival compared with vindesine and cisplatin in patients with advanced NSCLC.[3] In Japan, CPT is considered a key drug against NSCLC. Preclinical studies that have evaluated combinations of a camptothecin with a taxane have yielded promising results, and several studies have demonstrated an additive or synergistic interaction between camptothecin and taxanes.[4] Our previous phase I study of a Pac and CPT combination showed that pneumonitis was the dose-limiting toxicity and led to a recommendation of Pac 160 mg/m^2 and CPT 60 mg/m^2 every 2 weeks for further study.[5] This study also demonstrated an objective response rate of 58.3% and a 1-year survival rate of 54.2%. Accordingly, we expected the combination of Pac and CPT to display high activity against NSCLC and designed a phase II study to determine the efficacy and toxicities.

PATIENTS AND METHODS

The Institutional Review Board of Kanagawa Cancer Center reviewed and approved this study prior to commencement.

Patients

Patients with histologically or cytologically confirmed NSCLC were registered. Eligibility criteria were: clinical stage IIIB or IV, an expected survival of at least 12 weeks, age <70 years, Eastern Cooperative Oncology Group PS score ≤1, leukocyte count ≥4000/μL, hemoglobin ≥10 g/dL, platelet count ≥100,000/μL, total serum bilirubin ≤1.5 mg/dL, aspartate aminotransferase and alanine aminotransferase ≤90 IU/L, and serum creatinine ≤1.5 mg/dL. Patients who had experienced postoperative recurrence were eligible for this study, but a 4 or more week rest period was required after surgery. Patients who had received chemotherapy or radiotherapy were excluded from this study. Written informed consent was obtained from every patient.

Chemotherapy

All patients without disease progression were treated every 2 weeks for a total of 4 courses of chemotherapy. CPT was administered at a dose of 60 mg/m^2 on day 1. Pac was administered at a dose of 160 mg/m^2 on day 1. Premedication

From the Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama, Japan.

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Reprints: Fumihiro Oshita, MD, Department of Thoracic Oncology, Kanagawa Cancer Center, Nakao 1-1-2, Asahi-ku, Yokohama 241-0815, Japan. E-mail: foshita@kcch.jp.

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consisting of 20 mg dexamethasone and 50 mg ranitidine was infused. A 50-mg oral dose of diphenhydramine was also administered. Prophylactic G-CSF, 50 $\mu g/m^2$ per day or 2 $\mu g/kg$ per day, was administered subcutaneously on days 6 to 10. Patients were given a 5-HT_3 antagonist intravenously. Subsequent courses of chemotherapy were started when patients satisfied the organ function criteria: leukocyte count $\geq 3000/\mu L$, neutrophil count $\geq 1500/\mu L$, platelet count $\geq 75{,}000/\mu L$, and less than grade 1 nonhematologic toxicities, except alopecia. Grade 3 nausea and vomiting did not preclude subsequent courses of chemotherapy. Chemotherapy was repeated for a maximum of 6 courses unless the disease progressed, but it was stopped if the tumor response was judged to be NC after 4 courses. Tumor response was evaluated according to RECIST criteria.[6] Toxicities were evaluated according to the NCI-CTC (version 2) criteria.[7]

Study Design

We chose a 50% response rate as a desirable target level and a 30% response rate as uninteresting. The study design had power in excess of 90% and less than 10% error; therefore, 22 assessable patients in the first step and 24 in the second step were required according to the optimal design of Simon.[8] We decided to stop the study if there were fewer than 8 responders in the first step. The regimen was defined as active if there were 18 or more responders out of the total of 46 patients. Overall survival was estimated by the method of Kaplan and Meier.

RESULTS

Between May 2002 and July 2004, 46 patients were registered in the phase II study (Table 1). A total of 22 patients were registered for assessment of response in the first stage. Nine of 22 patients in the first stage responded and 24 patients were registered in the second stage. A total of 198 cycles was administered to 46 patients. Thirty-nine patients received 4 to 6 cycles of chemotherapy, except for 7 patients who discontinued treatment in the first or second cycles because of disease progression in 5 patients and grade 2 pneumonitis with pulmonary infiltration in 2 patients. Adverse effects and events are summarized in Table 2. Grade 3 anemia, leukopenia, neutropenia, and elevation of bilirubin occurred in 4.0%, 0.5%, 1.0%, and 0.5%, respectively. There were no grade 4 toxicities.

Twenty-one of 46 patients achieved partial response, 18 no change, 6 progressive disease, and 1 not evaluated, and the overall response rate was 45.6% in phase II study. The median duration of partial response was 154 days (range, 76–380 days). The median survival time was 355 days and the 1-year survival rate was 47.8% (Table 3). The outcome in 70 patients including those from the phase I study (5) demonstrated that 1 patient achieved complete response, 34 PR, and the overall response rate was 50.0%. The median survival time was 361 days and the 1-year survival rate was 50.0%.

TABLE 1. Patient Characteristics

Characteristic	Value
Total	46
Age (years)	
Median	61
Range	43–69
Gender (no. patients)	
Male	29
Female	17
Performance status (ECOG) (no. patients)	
0	12
1	34
Clinical stage (no. patients)	
IIIB	6
IV	34
Postoperative recurrence	6
Histology (no. patients)	
Adenocarcinoma	36
Others	10
No. metastatic organs (no. patients)	
1	27
≥2	13
Brain metastasis (no. patients)	8

TABLE 2. Adverse Effects and Events

	NCI-CTC Grade (No. Cycles)					
Toxicity	0	1	2	3	4	% ≥Grade 3
Hemoglobin	29	137	24	8	0	4.0
Leukocyte	162	23	12	1	0	0.5
Neutrophil	167	19	10	2	0	1.0
Platelets	188	10	0	0	0	—
Bilirubin	165	22	10	1	0	0.5
Creatinine	192	6	0	0	0	—
SGOT	146	51	1	0	0	—
SGPT	135	55	8	0	0	—
Infection	194	3	1	0	0	—
Nausea/vomiting	143	51	4	0	0	—
Diarrhea	165	31	2	0	0	—
Myalgia	97	76	25	0	0	—
Arthralgia	110	64	24	0	0	—
Neuropathy	107	76	15	0	0	—
Fever	183	14	1	0	0	—
Allergic reaction	195	3	0	0	0	—
Alopecia	95	79	24	0	0	—
Pneumonitis	196	0	2	0	0	—
Hypotension	193	5	0	0	0	—
Arrhythmia	194	4	0	0	0	—

NCI-CTC, National Cancer Institute-Common Toxicity Criteria (version 2).

DISCUSSION

The objective response rate of 50.0% and 1-year survival rate of 50.0% with our nonplatinum Pac and CPT regimen in 70 patients in phase I and phase II studies are somewhat better than in a large phase III trial of 4 platinum-based chemotherapy regimens, which showed response rates of 17% to 22% and 1-year survival rates of 31% to 34%.[9] The

TABLE 3. Therapeutic Outcome in Phase II Study

Response	No. Patients
Complete response	0
Partial response	21
No change	18
Progressive disease	6
Not evaluated	1
Response rate (%)	45.6
Median survival time (days)	355
% of 1-year survivor	47.8

antitumor activity of the Pac and CPT combination is thought to be attributable to a synergistic action between these drugs. A possible mechanism of the synergy is a drug-drug interaction, such as that shown in a pharmacokinetic study that demonstrated elevation of the AUC of CPT and SN-38 by Pac infusion.[10] Although we acknowledge the possibility that Pac and CPT might affect each other's pharmacokinetics, increasing their activity against NSCLC, we also considered that another possible mechanism for this high activity of the Pac and CPT combination might be related to influx and efflux in the cell system. The combination of Pac and SN-38 down-regulates the level of multidrug resistance-associated protein, which may be an efflux pump for cisplatin, in ovarian cancer cell lines, suggesting that this combination will overcome drug resistance.[11]

The combination of Pac and CPT also appears useful in that little toxicity was observed in this study. No patients experienced grade 4 toxicities. All patients, except the 5 patients who developed disease progression during treatment and the 2 patients who experienced grade 2 pneumonitis with pulmonary infiltration, were able to receive 4 to 6 cycles of this therapy. The pneumonitis was thought to be attributable to a booster effect of an allergic reaction when 180 mg/m^2 or higher of Pac was combined with CPT in the phase I study, but no patients experienced pneumonitis during cycles 2 to 6 of chemotherapy in this phase II study. Therefore, pneumonitis was seen at a frequency similar to that in other combination chemotherapies. Neutropenia was mild because of the prophylactic use of G-CSF in this study. We used G-CSF when monocytopenia less than 150/μL appeared in the phase I study,[5] and most patients received G-CSF for 5 days starting on days 5, 6, or 7. Consequently, G-CSF was given routinely for 5 days from day 5 to day 9 in every cycle in the present study. This less toxic regimen may be helpful in the treatment of high-risk patients, such as the elderly or those with poor performance status or moderately severe complications.

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ORIGINAL ARTICLE

Phase II study of weekly chemotherapy with paclitaxel and gemcitabine as second-line treatment for advanced non-small cell lung cancer after treatment with platinum-based chemotherapy

Kiyoshi Mori · Yukari Kamiyama · Tetsuro Kondo · Yasuhiko Kano · Tetsuro Kodama

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Abstract
Purpose We evaluated the tolerability and activity of the combination of weekly paclitaxel (PTX) and gemcitabine (GEM) in second-line treatment of advanced non-small cell lung cancer (NSCLC) after treatment with platinum-based chemotherapy.
Patients and methods PTX (100 mg/m^2) and GEM (1,000 mg/m^2) were administered to patients with previous treated NSCLC on days 1 and 8 every 3 weeks.
Results A total of 40 patients (performance status 0/1/2, 7/27/6 pts) were enrolled. The response rate was 32.5% (95% confidence interval: 18.0–47.0%). The median survival time was 41.7 weeks (95% confidence interval: 28.5–54.7 weeks). The median time to disease progression was 19 weeks. Hematological toxicities (grade 3 or 4) observed included neutropenia in 60%, anemia in 15%, and thrombocytopenia in 12.5% of patients. Non-hematological toxicities were mild, with the exception of grade 3 diarrhea, pneumonitis, and rash in one patient each. There were no deaths due to toxicity.
Conclusion The combination of weekly PTX and GEM is a feasible, well-tolerated, and active means of second-line treatment of advanced NSCLC.

Keywords Non-small cell lung cancer · Second-line chemotherapy · Weekly chemotherapy · Gemcitabine · Paclitaxel

K. Mori (✉) · Y. Kamiyama · T. Kondo · Y. Kano · T. Kodama
Department of Thoracic Diseases, Tochigi Cancer Center, 4-9-13, Yonan, Utsunomiya, Tochigi 320-0834, Japan
e-mail: kmori@tcc.pref.tochigi.jp

Y. Kamiyama
e-mail: ykamiyam@tcc.pref.tochigi.jp

T. Kondo
e-mail: tkondo@tcc.pref.tochigi.jp

Y. Kano
e-mail: ykano@tcc.pref.tochigi.jp

T. Kodama
e-mail: tkodama@tcc.pref.tochigi.jp

Introduction

The clinical usefulness of second-line chemotherapy has been established for cases of advanced non-small cell lung cancer (NSCLC) in which tumor has recurred or exhibits resistance to treatment after first-line chemotherapy. The effectiveness of docetaxel, pemetrexed, and elrotinib for second-line chemotherapy for NSCLC has been demonstrated in phase III clinical studies [13, 23, 24]. Furthermore, paclitaxel (PTX) and gemcitabine (GEM) have been shown to be effective against NSCLC resistant to platinum preparations [5, 16, 20]. There appears to be partial non-cross-resistance between these drugs and platinum preparations.

In previous attempts at second-line chemotherapy for NSCLC, the response rate was 0–38% for patients treated with PTX alone at intervals of 3 weeks [12, 21, 25] and 8–37.5% for patients treated with low-dose weekly PTX therapy [5, 16, 26, 28]. On the other hand, the rate of response to uncombined GEM therapy was 6–21% [7, 11, 17, 20, 22].

In combined PTX and GEM therapy, the two drugs exhibit interactions with each other but no overlap or synergism of adverse reactions. When this combined