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 $\geq$ 20 years; adequate bone marrow function (leukocyte count $\geq$ 4,000/μL, absolute neutrophil count [ANC] $\geq$ 2,000/μL, platelet count $\geq$ 100,000/μL, and hemoglobin $\geq$ 9.0 g/dL) and hepatic function (AST and ALT $\leq$ 100 U/L, or $\leq$ 200 U/L in the presence of liver metastases; bilirubin level $\leq$ 1.5 mg/dL); ECG findings within the normal range, and a left ventricular ejection fraction $\geq$ 50%; arterial oxygen partial pressure $\geq$ 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 $\geq$ 1,500/μL, his or her platelet count had to be $\geq$ 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 $\times$ 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 $\geq$ 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	1	22	10	11	52	.88
Refractory	16	1	7	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

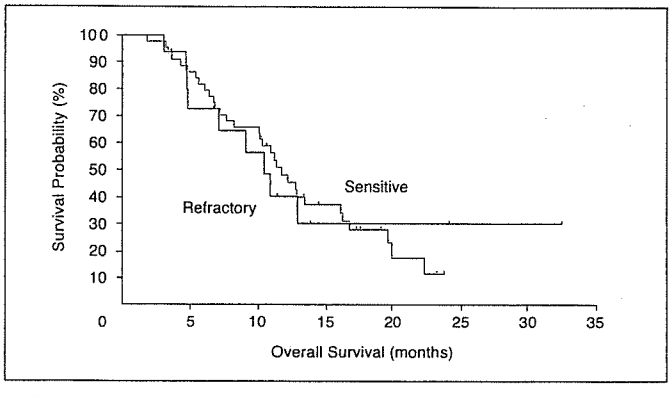

Fig 1. Median survival times in all patients with refractory or relapsed small-cell lung cancer were 10.3 months in the refractory group (n = 16) and 11.6 months in the sensitive group (n = 44), respectively ($P = .974$; log-rank test). The 1-year actuarial survival rate in patients with refractory disease 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	2	3	4	≥ Grade 3 No.	%
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	22	8	8	1	9	15.0
Asthenia	24	11	6	3	9	15.0
Hyponatremia	21	0	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	40	4	1	0	1	1.7
Elevated AST	20	0	1	0	1	1.7
Vomiting	7	3	0	1	1	1.7
Diarrhea	8	2	1	0	1	1.7
Constipation	3	1	1	0	1	1.7
Cognitive disturbance	0	0	1	0	1	1.7
Memory impairment	0	0	0	1	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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Phase I/II study of amrubicin, a novel 9-aminoanthracycline, in patients with advanced non-small-cell lung cancer

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Key words: amrubicin, advanced non-small-cell lung cancer, anthracycline, chemotherapy

Summary

Purpose: Amrubicin is a novel, totally synthetic 9-aminoanthracycline. The present phase I/II study was performed to define its maximum-tolerated dose (MTD), efficacy and toxicity in the treatment of previously untreated patients with advanced non-small-cell lung cancer (NSCLC). *Patients and Methods*: Chemonaive patients were required to have cytologically or histologically proven measurable NSCLC, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, and adequate organ functions. Amrubicin was administered by daily intravenous injection for 3 consecutive days every 3 weeks. *Results*: In a phase I study, four patients were enrolled at dose level 1 (40 mg/m^2/day) and four at dose level 2 (45 mg/m^2/day). No dose limiting toxicity (DLT), which was defined as toxicity consisting of grade 4 neutropenia and leukopenia lasting four days or more, and grade 3 or 4 toxicity other than neutropenia, leukopenia, anorexia, nausea/vomiting, and alopecia, was observed at these dose levels. Subsequently, at dose level 3 (50 mg/m^2/day), 3 of 5 patients experienced DLTs (leukopenia, neutropenia, thrombocytopenia, or gastrointestinal complications). The MTD and recommended dose (RD) were determined to be 50 mg/m^2/day and 45 mg/m^2/day, respectively. Three partial responses (PRs) were achieved in 13 patients (response rate, 23.1%) in a phase I study. In a phase II study, 15 patients were assessable for efficacy and toxicity at the RD, and four PRs were obtained (response rate, 26.7%). The major toxicities were leukopenia and neutropenia, while non-hematologic toxicities were mild. The overall response rate in the combined patient population of the phase I/II study was 25.0% (7 PRs in 28 patients), with a 95% confidence interval of 10.7% to 44.9%. *Conclusion*: Amrubicin exerted promising antitumor activity with acceptable toxicity.

Introduction

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, and is similar to doxorubicin in chemical structure, as shown in Figure 1 [1]. Amrubicin showed more potent antitumor activity than doxorubin on several human tumor xenografts implanted in nude mice [2]. Its toxic profile was qualitatively similar to that of doxorubicin in terms of acute toxicities [3], but amrubicin rarely caused delayed-type toxicity as observed with doxorubicin, especially cardiotoxicity [4, 5]. In an early phase II study of single-dose intravenous injection of 120 mg/m^2 every 3 weeks, amrubicin exhibited promising antitumor activity on non-small-cell lung cancer (NSCLC) with a response rate of 25% (95% confidence interval, 8.7% to 49.1%) [6].

A major characteristic of amrubicin that is closely associated with the efficacy and toxicity is that it is converted to an active metabolite, amrubicinol, via reduction of its C-13 ketone group to a hydroxy group. The *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 [7]. The *in vivo* antitumor activity of amrubicin was closely related to the tumor concentration of amrubicinol [8]. In addition, the experimental data have shown that amrubicin yields greater efficacy in daily treatment for 5 consecutive days than in a single treatment, due to accumulation of greater amounts of amrubicinol in tumor tissues [9].

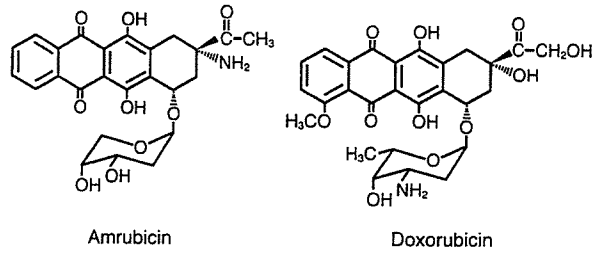

Figure 1. Chemical structures of amrubicin and doxorubicin

These data suggest that amrubicin may exert more potent effect against NSCLC in the divided treatment schedule than in the single-dose treatment schedule.

In addition, it has been reported that epirubicin, the same anthracycline derivative as amrubicin, could be administered at higher doses in 3-day consecutive treatment every 3 weeks than in single-dose treatment every 3 weeks, and consequently the high dosage of epirubicin in the former treatment schedule resulted in a higher response rate, compared with standard dosages of epirubicin in the latter treatment schedule, in previously untreated patients with advanced NSCLC [10].

In the present phase I/II study, therefore, daily treatment for 3 consecutive days every 3 weeks was chosen as the divided treatment schedule, and the efficacy and safety of amrubicin were evaluated in previously untreated patients with advanced NSCLC.

Patients and methods

Patient eligibility

This study involved patients with histologically or cytologically confirmed unresectable NSCLC in stages IIIA, IIIB, and IV. Eligibility criteria included no prior treatment, measurable lesions, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, an estimated life expectancy of at least 2 months, and age less than 75 years. Adequate organ function was required and defined as: white blood cell (WBC) count $\geq$4,000/μL, platelet count $\geq$100,000/μL, hemoglobin level $\geq$10 g/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq$ 2 times the upper limit of normal, serum creatinine level $\leq$ normal limit, and electrocardiography (ECG) within normal limits.

The following patients were excluded: those with symptomatic brain metastasis or bone metastasis accompanying pain, those with plural fluid retention requiring treatment like drainage, those with continuous long term treatment with non-steroidal anti-inflammatory agents, glucocorticoids, or morphine derivatives, those with 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. All eligible patients were required to provide signed informed consent prior to entering this study. The individual investigational review board at each institution approved the treatment protocol.

Drug administration

Amrubicin (Sumitomo Pharmaceuticals Co., Ltd, Osaka, Japan) was supplied as a freeze-dried powder in vials containing 20 mg each, reconstituted in 20 mL of physiological saline or 5% glucose solution, and administered intravenously over 5 minutes on 3 consecutive days every 3 weeks. At least 2 cycles were instituted, except in case of disease progression, unacceptable toxicity or patient refusal.

Dose levels

The phase I study was started at a dosage of 40 mg/m^2/day to determine the dose limiting toxicity (DLT), maximum-tolerated dose (MTD) and recommended dose (RD) of amrubicin given on 3 consecutive days (120 mg/m^2/course). The starting dosage was set at the same dosage per cycle as that used in the early phase II study for NSCLC in which amrubicin was given once every 3 weeks [6], because experimentally, amrubicin could be administered at a higher total dosage in the divided treatment schedule than in the single treatment schedule [10].

The dosage of amrubicin was escalated by 5 mg/m^2/day (15 mg/m^2/course). At least four patients were entered at each dose level until the MTD was reached. The dose escalations were determined based on the tolerability observed during the first 3 weeks of treatment as follows. The dose at which none or one patient experienced a DLT was escalated, and the MTD was the dose at which at least two patients developed a DLT, i.e., the dose at which at least 2/4, 2/5 or 2/6 patients experienced a DLT. Dosages were not escalated for individual patients.

The following phase II study was performed at the RD estimated in the phase I study.

Definition of DLT, MTD, and RD

DLT was defined as toxicity consisting of grade 4 neutropenia and leukopenia lasting four days or more, and grade 3 or 4 toxicity other than neutropenia, leukopenia, anorexia, nausea/vomiting, and alopecia. MTD was defined as the dose level at which at least one-third of patients experienced a DLT. The RD was chosen as the dose one-level lower than the MTD.

Adjustment of dosage and schedule modification

The treatment was repeated if the WBC count recovered to $\geq$3,000/μL and the platelet count recovered to $\geq$100,000/μL. In incomplete recovery, the treatment was delayed until the WBC count recovered to $\geq$3,000/μL and the platelet count recovered to $\geq$100,000/μL. If the WBC count and platelet count did not recover within 5 weeks after administration of amrubicin, the trial was discontinued. If the WBC nadir was $<$1,000/μL for $\leq$3 days, or $\geq$1,000/μL and the platelet nadir was $\geq$50,000/μL, the treatment was conducted at the same dosage as the previous course. If the WBC nadir was $<$1,000/μL for $\geq$ 4 days and/or the platelet nadir was $<$50,000/μL, the dosage was reduced by 5 mg/m^2/day from the dosage of the previous course.

Treatment evaluation

Before treatment, all patients underwent medical history review, physical examination, hematology and serum biochemistry tests, urinalysis, ECG, and baseline tumor measurements (e.g. chest radiography, computed tomography (CT) scan, bone scintigraphy, abdominal CT, brain CT). All measurable and assessable lesions were evaluated within 2 weeks before start of treatment.

Complete and differential blood cell counts, platelet counts, and hematocrit values were obtained two times a week as a rule, and biochemical data [AST, ALT, alkaline phosphatase, LDH, total bilirubin, BUN, creatinine, serum bilirubin, albumin, total protein, and electrolytes (Na, K, Cl, and Ca)], and urinalysis findings (protein, glucose, urobilinogen, and occult blood), were recorded weekly. ECG was performed every treatment cycle.

Subjective symptoms and objective signs were checked daily for 5 consecutive days from the start of treatment in each cycle, and thereafter ad libitum.

Response and toxicity evaluation

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 [11], which is almost equal to the World Health Organization criteria [12]. A complete response (CR) was defined as the disappearance of all lesions. A partial response (PR) was defined as a reduction by 50% or more in the size of lesions measurable in two dimensions, objective improvement in any evaluable lesions, and no new lesions. CR and PR required response durations of at least four weeks. No change (NC) was defined as lesions unchanged (a reduction of $<$25% or an increase of $<$25% in the size of lesions) for at least four weeks. Progressive disease (PD) was defined as failure, with an increase of $\geq$25% in the size of lesions and appearance of new lesions. The Kaplan-Meier product-limit method was used to estimate the survival time.

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 [11], which is almost equal to the World Health Organization criteria [12]. For toxicity items that were not included on the record form, only their presence or absence was recorded, without grading.

Results

Patient characteristics

Thirteen patients were entered in the phase I study, and subsequently 17 patients in the phase II study, between November 1992 and September 1994. Of the 13 patients entered in the phase I study, 4 were treated at dose level 1 (40 mg/m^2/day $\times$ 3), 4 at level 2 (45 mg/m^2/day $\times$ 3), and 5 at level 3 (50 mg/m^2/day $\times$ 3); all were assessable for efficacy and safety.

In the phase II study, 15 of 17 patients were assessable for efficacy and safety; 2 of them were ineligible because one had suffered from serious complications of pneumonitis and arrhythmia, a deviation against the inclusion criteria in the protocol, and another had been treated without registration prior to the study.

The characteristics of the eligible patients are listed in Table 1.

Phase I study

Toxicity. Hematologic toxicity is shown in Table 2. Dose-related leukopenia and neutropenia were noted. At dose level 1 (40 mg/m^2), one patient experienced grade 4

Table 1. Characteristics of eligible patients

Characteristic	No. of patients	
	Phase I study	Phase II study
No. of patients entered	13	17
No. of eligible patients	13	15
Gender(Male/Female)	8/5	10/5
Median age, years (range)	69 (45–74)	65 (29–72)
ECOG performance status		
0/1/2	5/3/5	1/12/2
Histology		
Squamous cell carcinoma	5	6
Adenocarcinoma	7	8
Large cell carcinoma	1	1
Stage (IIIA/IIIB/IV)	2/1/10	1/3/11

Table 2. Hematologic toxicity of amrubicin in phase I study

	Grade of toxicity (No. of patients)											
	40 mg/m^2 ($n = 4$)				45 mg/m^2 ($n = 4$)				50 mg/m^2 ($n = 5$)			
Toxicity	1	2	3	4	1	2	3	4	1	2	3	4
Hemoglobin, decrease	1	0	1	0	2	1	1	0	2	1	2	0
Leukopenia	1	1	1	1	1	0	3	0	0	0	3	2
Neutropenia	0	1	1	1	0	1	0	3	0	0	0	5
Thrombocytopenia	1	0	0	0	0	1	1	0	3	0	1	1

Table 4. Efficacy of amrubicin in phase I study

	No. of patients						
Dose	Total	CR	PR	NC	PD	ORR (%)	95% CI (%)
40 mg/m^2	4	0	1	1	2	25.0	
45 mg/m^2	4	0	2	1	1	50.0	
50 mg/m^2	5	0	0	5	0	0.0	
Total	13	0	3	7	3	23.1	5.0–53.8

Abbreviation: CR, complete response; PR, partial response; NC, no change; PD, progressive disease; ORR, overall response rate (CR + PR); 95% CI, 95% confidence interval

neutropenia and leukopenia, which did not last for 4 days or longer. At dose level 2 (45 mg/m^2), three of four patients also experienced grade 4 neutropenia, lasted 4 days or longer in only one. At this dose level, no grade 4 leukopenia was observed. Dose-limiting leukopenia and neutropenia lasting for more than 4 days were seen in two and in all five patients at dose level 3 (50 mg/m^2), respectively. Grade 3 or 4 hemoglobin decrease and thrombocytopenia each occurred in two patients at the highest dose level. Three patients required blood transfusion or platelet transfusion or both.

As shown in Table 3, non-hematologic toxicities observed frequently in this study were anorexia, nausea/vomiting, fever, diarrhea and alopecia, but no grade 3 or 4 toxicity was seen at dose level 1 or 2. On the contrary, at dose level 3, grade 3 or 4 toxicity was noted in three of five patients; grade 3 nausea/vomiting and melaena and grade 4 hematemesis in one patient each. Because the grade 3 melaena and grade 4 hematemesis were noted in two patients who had received indomethacin or diclofenac sodium over 50 days, these episodes were considered to be associated with the long-term treatment of nonsteroidal anti-inflammatory agents. Therefore, the criteria for entry into the study were revised in the subsequent studies to exclude patients who had been treated with nonsteroidal anti-inflammatory agents for a long period. There was no toxicity to renal or cardiac function but a mild effect on hepatic function was observed. As uncommon toxicities, two episodes of grade 1 vitreous floaters occurred at 40 and 45 mg/m^2, and one episode of grade 1 eruption occurred at 50 mg/m^2.

Based on the above results, the MTD and RD of amrubicin in a 3-day consecutive administration were determined as 50 mg/m^2 (150 mg/m^2/course) and 45 mg/m^2 (135 mg/m^2/course), respectively. The DLTs were leukopenia, neutropenia, thrombocytopenia and digestive dysfunction including nausea/vomiting, melaena, and hematemesis.

Table 3. Non-hematologic toxicity of amrubicin in phase I study

	Grade of toxicity (No. of patients)											
	40 mg/m^2 ($n = 4$)				45 mg/m^2 ($n = 4$)				50 mg/m^2 ($n = 5$)			
Toxicity	1	2	3	4	1	2	3	4	1	2	3	4
Stomatitis	0	0	0	0	0	0	0	0	1	1	0	0
Anorexia	2	1	0	–[a]	1	0	0	–[a]	0	2	0	–[a]
Nausea/vomiting	2	0	0	–[a]	3	0	0	–[a]	1	1	1	–[a]
Diarrhea	3	0	0	0	1	0	0	0	1	0	0	0
Fever	1	0	0	0	0	1	0	0	1	4	0	0
Alopecia	1	0	0	–[a]	1	3	0	–[a]	2	3	0	–[a]
Melaena	0	0	0	0	0	0	0	0	0	0	1	0
Hematemesis	0	0	0	0	0	0	0	0	0	0	0	1
AST, increase	1	0	0	0	1	0	0	0	2	0	0	0
ALT, increase	1	0	0	0	1	0	0	0	2	0	0	0
ALP, increase	0	0	0	0	1	0	0	0	0	0	0	0
BUN, increase	0	0	0	0	0	0	0	0	1	0	0	0

Abbreviation: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urine nitrogen.
[a]No grading.

Efficacy. Antitumor response is shown in Table 4. One of four patients (25.0%) at dose level 1 (40 mg/m^2) and two of four patients (50.0%) at dose level 2 (45 mg/m^2) showed PR. At dose level 3 (50 mg/m^2), three patients discontinued treatment after the first cycle because of toxicity, and none of five patients responded. In total, three of the 13 patients had PR, an overall response rate of 23.1%. One of five patients with squamous cell carcinoma (20.0%) and two of seven with adenocarcinoma (28.6%) responded.

Phase II study

Efficacy. In the phase II study, amrubicin was administered daily for 3 consecutive days at 45 mg/m^2, which was the RD determined in the phase I study. The responses to amrubicin in patients with previously untreated NSCLC are shown in Table 5. Of 15 patients, four (26.7%) achieved PR. Of these responders, one patient (1/6, 16.7%) had a histology result indicating squamous cell carcinoma and three (3/8, 37.5%) had adenocarcinoma.

Table 5. Efficacy of amrubicin in phase II study

Histology	No. of patients					ORR (%)	95% CI (%)
	Total	CR	PR	NC	PD		
Adenocarcinoma	8	0	3	3	2	37.5	
Squamous cell	6	0	1	5	0	16.7	
Large cell	1	0	0	1	0	0.0	
Total	15	0	4	9	2	26.7	7.8–55.1

Abbreviation: CR, complete response; PR, partial response; NC, no change; PD, progressive disease; ORR, overall response rate (CR + PR); 95% CI, 95% confidence interval.

Table 6. Hematologic toxicity of amrubicin in phase II study

Toxicity	No. of pts.	Grade (No. of pts.)				≥ Grade 3	
		1	2	3	4	No. of pts.	%
Hemoglobin, decrease	15	4	3	3	1	4	26.7
Leukopenia	15	2	5	5	3	8	53.3
Neutropenia	15	0	4	3	8	11	73.3
Thrombocytopenia	15	0	1	3	1	4	26.7

Table 7. Non-hematologic toxicity in phase II study

Toxicity	No. of pts.	Grade (No. of pts.)				≥ Grade 3	
		1	2	3	4	No. of pts.	%
Stomatitis	15	3	0	0	0	0	0.0
Anorexia	15	8	3	0	—[a]	0	0.0
Nausea/vomiting	15	9	2	0	—[a]	0	0.0
Diarrhea	15	3	0	0	0	0	0.0
Fever	15	0	3	1	0	1	6.7
Phlebitis	15	2	0	0	0	0	0.0
Alopecia	15	4	5	0	—[a]	0	0.0
Peripheral neuropathy	15	0	1	0	0	0	0.0
ECG abnormalities	12	0	4	0	0	0	0.0
Arrhythmia	15	0	1	0	0	0	0.0
Palpitation	15	0	1	0	0	0	0.0
Pneumonia	15	0	1	0	0	0	0.0
AST, increase	15	3	0	0	0	0	0.0
ALT, increase	15	3	0	0	0	0	0.0
Total bilirubin	15	4	0	0	0	0	0.0
Proteinuria	15	1	0	0	0	0	0.0

Abbreviation: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urine nitrogen.
[a]No grading.

The two studies of phase I and II were combined, and the overall data were analyzed for response. Of 28 patients, seven achieved PR, accounting for an overall response rate of 25% (95% confidence interval, 10.7% to 44.9%). Median survival time was 9.1 months (95% confidence interval, 6.8 months to 12.1 months), and 1-year and 2-year survival rates were 35.7% (95% confidence interval, 18.0% to 53.5%) and 12.1% (0% to 24.6%), respectively.

Toxicity. Hematologic toxicity was common, as shown in Table 6. In particular, neutropenia and leukopenia developed in all patients, with grade 3 or 4 leukopenia at 53.3% and neutropenia at 73.3%. Hemoglobin decrease and thrombocytopenia were also frequently noted, but these were less severe, compared with leukopenia and neutropenia. Grade 3 or 4 hemoglobin decrease and thrombocytopenia were each observed in four patients (26.7%). Blood transfusion was required by two patients, and platelet transfusion by one.

Non-hematologic toxicity seen in the phase II study is summarized in Table 7. Stomatitis, anorexia, nausea/vomiting, diarrhea, fever and alopecia were commonly observed, but there were no grade 3 or 4 episodes except for one of grade 3 fever (6.7%). AST, ALT and total bilirubin levels, which were the referenced indices of hepatic function, were slightly increased, but no effect was seen on BUN or serum creatinine levels, the indices of renal function. There were four patients (33.3%) with abnormal ECG, showing nonspecific decreases in T-wave level without ST change. Other effects on cardiac function were palpitation and arrhythmia, occurring in one patient each. No patient had reactions such as abnormal visual system (i.e., myodesopsia), eruption, melaena, or hematemesis, all observed in the phase I study.

Discussion

The present study was performed as a 3-day consecutive administration every 3 weeks, on the basis of encouraging experimental findings that amrubicin exerted more potent antitumor activity on human tumor xenografts implanted in nude mice in the divided treatment schedule than in the single treatment schedule [9]. When given on 3 consecutive days every 3 weeks, amrubicin achieved an overall response rate of 25% (7PRs in 28 patients) in previously untreated patients with advanced NSCLC. It has been reported that amrubicin also demonstrated an overall response rate of 25% (5 PRs in 20 patients) in an early phase II study which was conducted in chemotherapy-naöve patients by single-dose intravenous injection of 120 mg/m^2 every 3 weeks [6]. The data, therefore, indicate that there was no difference in the response rate between two clinical studies conducted under different treatment schedules, but the scales were too small to evaluate which of the two treatment schedules is superior; single-dose treatment or 3-day consecutive treatment, because only 20 or 28 patients were enrolled into each study. Subsequent, larger scale clinical studies are needed for confirmation.

Currently, NSCLC is treated with newer agents such as taxanes, gemcitabine, vinorelbine, and irinotecan, in combination with cisplatin and carboplatin, and these agents have single-agent reproducible response rates of more than 20% for NSCLC [13, 14]. Amrubicin showed response rates of more than 20% in two clinical studies conducted independently and under differing treatment schedules, as described above. These reproducible results strongly suggest that amrubicin is an anticancer agent with promising single-agent activity on NSCLC, comparable to the newer agents for NSCLC in efficacy, and further clinical trials are warranted to evaluate it. In addition, amrubicin is different from other newer agents in mode of action [15], in that it is an potent inhibitor of topoisomerase II, so that amrubicin is expected to play an important role in combination therapy, differently from other agents.

The major toxicity of amrubicin was hematologic, and especially neutropenia and leukopenia were remarkable. In the phase II study, 53.3% and 73.3% of patients experienced grade 3 and 4 leukopenia and neutropenia, respectively. On the other hand, non-hematologic toxicity such as anorexia, nausea and vomiting, diarrhea, fever, and alopecia was frequently observed, but relatively mild; grade 3 or 4 episodes were not seen other than in one patient (6.7%) who experienced grade 3 fever.

As noteworthy toxicity, grade 3 melaena and grade 4 hematemesis were noted in one patient each in the phase I study, although these episodes were not observed in the clinical trials using single-bolus treatment [6, 16]. These toxicities were considered to be associated with the long-term treatment of nonsteroidal anti-inflammatory agents, because these two patients had received indomethacin or diclofenac sodium for more than 50 days. The criteria for entry into the study was therefore revised to exclude patients who had been treated with nonsteroidal anti-inflammatory agents for a long period, and thereafter such episodes have not been experienced. As uncommon toxicity, two episodes of grade 1 myodesopsia and one episode of grade 1 eruption occurred in a phase I study, but these episodes were not observed in the subsequent phase II study.

In a phase II study, 4 patients (33.3%) experienced ECG abnormality, showing nonspecific decreases in T-wave level without ST change. Other effects on cardiac function were palpitation and arrhythmia, which occurred in one patient each. All these effects seemed to be different from cardiomyopathy caused by cumulative doses of doxorubicin, but these data show that amrubicin might affect cardiac function in a different manner from doxorubicin. Therefore, careful observation might be needed concerning the effects of amrubicin on cardiac function in subsequent clinical studies.

Appendix

Amrubicin has showed reproducible response rates of 18.3% (11/60) and 27.9% (17/61) in two subsequent phase II studies when used as single agents in previously untreated patients with advanced NSCLC. Amrubicin, therefore, is considered to be comparable to newer agents such as paclitaxel, docetaxel, gemcitabine, vinorelbine, and irinotecan in efficacy for NSCLC. The clinical study of amrubicin in combination with other agents, in particular cisplatin, is currently planned.

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Combination chemotherapy of gemcitabine and vinorelbine for patients in stage IIIB–IV non-small cell lung cancer: a phase II study of the West Japan Thoracic Oncology Group (WJTOG) 9908

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Summary *Objectives:* Vinorelbine (V) and gemcitabine (G) are two active single agents used in the treatment of non-small cell lung cancer (NSCLC). A multicenter clinical trial (West Japan Thoracic Oncology Group (WJTOG) 9908) was conducted to evaluate the efficacy and toxicity of V and G in patients (pts) with advanced NSCLC. *Methods:* Eligibility criteria: no previous chemotherapy; performance status (PS) 0 or 1; age <75 years old. V, 25 mg/m^2, was given as a 2–3 min IV infusion, followed by a 30 min IV infusion of G, 1000 mg/m^2, on days 1 and 8 of each 21-day cycle. *Results:* From April 2000 to September 2000, 52 pts were enrolled in the study. Two pts were ineligible. Baseline characteristics: median age 60, males 30 (60%), Eastern Cooperative Oncology Group (ECOG) PS 0/1 = 21/29 (58%), stage IIIB/IV = 12/38 (76%), adenocarcinoma = 35 (70%). The median number of cycles administered was 2. Fifty pts were evaluable for response. The response rate was 18% by the Response Evaluation Criteria in Solid Tumors (RECIST) (no complete response (CR), 9 partial response (PR), 25 stable disease, 12 progressive disease, 4 not evaluable). Grade III/IV toxicities were as follows: neutropenia grade III/IV = 66%, anemia grade III/IV = 16%, thrombocytopenia grade III/IV = 2%, nausea grade III/IV = 10%, vomiting grade III/IV = 0%, documented infection grade III/IV = 10%, skin rash grade III/IV = 2%, and hepatic grade III/IV = 8%. There were no treatment-related deaths. The median time to progression was 4.1 months. The overall median survival time (MST) was 13.9 months (range, 2.4 to >16.2 months) with a median follow-up time of 13.9 months. The MST for stage IIIB and stage IV was >14.5 and 12.7 months, respectively. The overall estimated 1-year survival rate was 55.4%. *Conclusions:* This regimen has modest activity and is very well tolerated, with an encouraging 1-year survival rate.

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1. Introduction

Non-small cell lung cancer (NSCLC) represents about 80% of cases of lung cancer. The prognosis of patients (pts) with this cancer is poor, since less than a third of patients present with resectable disease at the time of diagnosis, and two-thirds of them are inoperable and are potential candidates for systemic chemotherapy. Four meta-analyses of trials comparing the use of chemotherapy with best supportive care concluded that chemotherapy could prolong survival time by a modest but statistically significant amount of time and should be offered to patients with good performance status (PS) [1–4]. Cisplatin-based combination therapy is currently considered to be the most active treatment for advanced NSCLC. However, cisplatin has a low therapeutic ratio, with significant toxicities including severe nausea and vomiting, general malaise, renal toxicity requiring adequate hydration, and ototoxicity.

Recently, several new drugs such as CPT-11, docetaxel, paclitaxel, gemcitabine (G), and vinorelbine (V) have also demonstrated a promising antitumor activity against NSCLC, with documented response ranging from 13 to 27% [5]. Among these agents, gemcitabine is a new nucleotide antimetabolite of deoxycytidine resembling cytarabine that has demonstrated activity both as a single agent and in combination with cisplatin [6–9]. The objective response rate obtained with combination chemotherapy ranges from 32 to 54% in chemotherapy-naïve patients with advanced NSCLC.

Vinorelbine, a semisynthetic vinca alkaloid, has also demonstrated activity for first-line treatment of patients with advanced NSCLC, with a response rate of between 20 and 25% and a median survival of 33 weeks [10]. A prospective randomized trial was also conducted to compare vinorelbine and cisplatin with vindesine and cisplatin, or vinorelbine alone to evaluate whether one of these regimens provided a survival advantage over the others [11]. Vinorelbine-cisplatin yielded a longer survival duration and a higher response rate than did vindesine-cisplatin or vinorelbine alone. Furthermore, vinorelbine was studied in a randomized Italian phase III trial in which vinorelbine, combined with best supportive care, was compared with best supportive therapy (BST) alone [12]. Vinorelbine was given 30 mg/m^2 on days 1 and 8 every 3 weeks for six cycles. A 20% response rate was seen in the vinorelbine arm, and a median survival difference of 27 weeks versus 21 weeks favored the vinorelbine arm.

A recent randomized Eastern Cooperative Oncology Group (ECOG) study that included four new popular platinum-based regimens did not show any survival differences among the more than 1000 patients, and it also documented a disappointingly low response rate with the range of 15.3–21.3% [13]. There is no one new chemotherapy combination that can be said to be clearly superior at the moment. In view of the single-agent activity in NSCLC and the lack of overlapping toxicity of gemcitabine and vinorelbine as well as their different mechanism of action, a multicenter phase II trial was conducted to evaluate the tolerance and efficacy of their combination.

2. Patients and methods

2.1. Eligibility criteria

Eligibility criteria for study entry included histologically or cytologically confirmed stage IIIB or IV NSCLC; no prior chemotherapy; the presence of at least one unidimensional measurable disease; age 20–74 years; an Eastern Cooperative Oncology Group performance status of 0–1; adequate baseline organ function, defined as $4000/\mu l \leq WBC \leq 12{,}000/\mu l$, platelet $\geq 100{,}000/\mu l$, hemoglobin ≥ 9.5 g/dl, serum transaminase levels $\leq 2.5\times$ of the upper limit of normal, bilirubin $\leq 1.5\times$ of the upper limit of normal, creatinine < 1.5 mg/dl; $PaO_2 \geq 60$ mmHg; a life expectancy of at least 3 months; and written informed consent. The study was conducted according to the Helsinki Declaration and was approved by the ethics committees of participating centers. Prior palliative radiotherapy to symptomatic metastases was allowed, provided that these lesions were not monitored for response. Patients with recurrence after operation were allowed. Patients with the following criteria were excluded from the study: signs and symptoms of brain metastases; pleural effusion requiring chest tube drainage; apparent pericardial effusion; uncontrollable angina pectoris, diabetes mellitus, hypertension, congestive heart failure and active infection; myocardial infarction < 3 months before the date of diagnosis; interstitial pneumonitis diagnosed by plain chest X-ray; pregnant women. Patients in stage IIIB who were candidates for initial radiotherapy for a primary tumor were excluded from the study. Patients with other serious underlying medical conditions that would impair the ability of the patient to receive the protocol treatment were also ineligible for the study.

2.2. Treatment plan

The treatment consisted of vinorelbine, 25 mg/m^2 intravenous infusion in 20 ml of normal saline solution over 2–3 min, followed by gemcitabine 1000 mg/m^2 intravenous infusion in 100 ml of normal saline solution over 30 min on days 1 and 8 every 3 weeks. This dose schedule was taken according to the results from Gridelli et al. They reported the combination gemcitabine 1000 mg/m^2 plus vinorelbine 25 mg/m^2 had the less frequent and less severe toxicity with equal antitumor activity compared with other treatment schedules [14]. Dexamethasone and 5-hydroxytryptamine-3 receptor antagonists were given before chemotherapy as antiemetic prophylaxis. Treatment of day 8 was delayed until recovery (no longer than 1 week) if the WBC count fell <2000/μl and/or the platelet count was <70,000/μl and if nonhematologic toxicities were ≥grade 2 excluding those due to nausea/vomiting and alopecia. Otherwise, the patient was removed from the study.

The subsequent course of chemotherapy was begun on day 22 if the WBC count was >3000/μl, the platelet count was ≥100,000/μl, PS was 0–1, transaminases were ≤2.5× of the upper limit of normal, the serum bilirubin was ≤1.5× of the upper limit of normal, and the creatinine was <1.5 mg/dl. Two weeks delay of initiation of the subsequent course was allowed; otherwise, the patient was withdrawn from the study.

For dose adjustments in the subsequent cycle, vinorelbine and gemcitabine were reduced to 20 and 800 mg/m^2, respectively, when the patient suffered from grade 4 neutropenia lasting for more than 4 days, chemotherapy-induced neutropenic fever was higher than 38 °C, thrombocytopenia ≤20,000/μl, or nonhematologic toxicities ≥grade 3 excluding those due to nausea/vomiting and alopecia. Recombinant human granulocyte colony-stimulating factor was not used prophylactically. Patients with progressive disease at any time were withdrawn from the study; patients with stable disease received a minimum of two cycles, whereas patients with a complete response (CR) or partial response (PR) were treated until disease progression began. Radiation consolidation was planned for stage IIIB patients at the discretion of the treating physician.

2.3. Staging and follow-up procedures

Before entering the study, all patients underwent a physical examination, complete blood count, blood chemistry, urinalysis, chest X-ray, thoracic, abdominal, and brain CT scans, bone scan, ECG, pulmonary function tests, blood gas analysis, and other specific tests when indicated. Patients were monitored weekly throughout treatment by physical examination, recording of toxic effects, complete blood cell count with differential, and blood chemistry with repetition of all tests that were abnormal at baseline. Study drug-related toxicities were evaluated according to National Cancer Institute Common Toxicity Criteria (version 2).

2.4. Definition of response

Objective response of a tumor to an anticancer agent was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) [15]. A CR of target lesions was defined as the disappearance of all target lesions for a minimum of 4 weeks, during which no new lesion could appear. A PR was defined as at least a 30% decrease in the sum of the longest diameter of target lesions for a minimum of 4 weeks, during which no new lesion could appear. PD was defined as at least a 20% increase in the sum of the longest diameter of the target lesion or the appearance of one or more new lesions. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

A CR of nontarget lesions was defined as the disappearance of all nontarget lesions and normalization of tumor marker level. An incomplete response/stable disease was defined as the persistence of one or more nontarget lesion(s) and/or the maintenance of tumor marker level above the normal limits. PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions. An extramural review was conducted to validate the eligibility of the patients, staging, responses, and toxicities during regular meetings of the WJTOG.

2.5. Statistical methods

A Simon two-stage minimax phase II design was used to estimate sample size. It was estimated that the power of this study to detect a true response rate of 40% was 0.8 at the 5% level, requiring the accrual of 45 patients. Fifty-two patients had been accrued at the end of the study. Overall survival and progression-free survival were analyzed using the method of Kaplan and Meier. Survival was measured from the date of initial treatment to the date of death or last follow-up examination. Progression-free survival was measured from the date of documentation of first response to the date of first evidence of progressive disease.

3. Results

From April 2000 until September 2000, 52 patients were recruited for the study from 19 centers of the West Japan Thoracic Oncology Group (WJTOG). Of these, two patients did not meet the eligibility criteria for efficacy analysis: one because of metastatic prostate cancer, and one who did not receive chemotherapy because of active pneumonia. Fifty patients fulfilling all eligibility criteria were treated on this study. Patient characteristics are listed in Table 1. There were 30 men and 20 women, with a median age of 60 years (range 28–74). Twenty-one patients had PS 0, and 29 had PS 1. Twelve patients had stage IIIB disease, and 38 patients had stage IV disease. Adenocarcinoma was the predominant histologic type. Two patients had previous therapy: one received gamma knife radiation for metastatic brain tumor, and the other received surgery for primary lung cancer. The median number of courses per patient was 2, with a range of 1–13 courses. Fifty patients were assessable for toxicity and fulfilled all criteria of assessment for response evaluation. Four patients received only one course of treatment. Of them, one patient developed a grade 3 allergic reaction after treatment on day 1. One patient withdrew his consent from the treatment because of grade 2 liver dysfunction. One patient had grade 3 skin eruption immediately after treatment of day 1, and the fourth patient had empyema on day 8. These four patients were not evaluable for response. Of the evaluable 46 patients, no patient achieved a CR, 9 achieved a PR, 25 had SD, and 12 had PD (Table 2). On an intent-to-treatment analysis, the objective response rate was 18% (9 of 50 patients; 95% CI = *8.6*–31.4%).

Table 1 Patient characteristics

	Number of patients
Patients enrolled	50
Sex	
Male	30
Female	20
Age	
Median	60
Range	28–74
Performance status	
0	21
1	29
Stage	
IIIB	12
IV	38
Histology	
Adenocarcinoma	35
Squamous cell carcinoma	12
Large cell carcinoma	3
Prior treatment	
Surgery	1
X knife for brain metastasis	1
None	48

Table 2 Response rate

	Number of patients	Percentage
Complete response	0	0
Partial response	9	18
Stable disease	25	50
Progressive disease	12	24
Not evaluable	4	8
Response rate		18[a]
Total	50	100

[a] 95% confidence interval: 8.6–31.4%.

3.1. Toxicity

Toxicity was evaluated in all eligible patients and in all courses. Myelosuppression was the only toxicity that resulted in dose reduction (Table 3). Grade 3/4 adverse events were as follows: leukopenia in 22 patients (44%), neutropenia in 33 patients (66%), anemia in 8 patients (16%), and thrombocytopenia in 1 patient (4%). There were seven patients who suffered from neutropenic fever. All these patients were successfully treated with broad-spectrum antibiotics. No thrombocytopenic episode was complicated by hemorrhage, and no patient required platelet transfusion.

Nonhematologic adverse events were generally mild and well tolerated. Liver enzyme derangement was observed in 38 patients, grade 1 or 2 in 34 patients (68%) and grade 3 in 4 patients (8%). All these patients were treated successfully with supportive measures. Nephrotoxicity was not a problem. Grade 3 nausea/vomiting was observed in five patients (10%). Diarrhea and alopecia were mild. Grade 1 local vasculitis along side injected vein due to vinorelbine was observed in two patients (4%). Moderate deterioration in PS (grade 3) was observed in eight patients (16%). Details on adverse effects are listed in Table 3.

Four patients discontinued treatment because of adverse events. One patient developed a serious

Table 3 Hematologic and nonhemologic toxicity

Toxicity	National Cancer Institute Common Toxicity Criteria			
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
WBC	6 (12)	16 (32)	19 (38)	3 (6)
Neutrophil	8 (16)	4 (8)	13 (26)	20 (40)
Hemoglobin	30 (60)	11 (22)	7 (14)	1 (2)
Platelet	24 (48)	3 (6)	1 (2)	0
GOT/GPT	18 (36)	16 (32)	4 (8)	0
Creatinine	2 (4)	0	0	0
Nausea	8 (16)	7 (14)	5 (10)	0
Vomiting	5 (10)	5 (10)	0	0
Delayed vomiting	1 (2)	0	0	0
Diarrhea	4 (8)	3 (6)	0	0
Alopecia	18 (36)	1 (2)	0	0
Fever	17 (34)	2 (4)	0	0
Infection	6 (12)	4 (8)	5 (10)	
Dyspnea	5 (10)	6 (12)	0	0
Skin eruption	0	3 (6)	1 (2)	0
Neuropathy	2 (4)	0	0	0
Vasculitis	2 (4)	0	0	0
Performance status	21 (42)	4 (8)	8 (16)	0

allergic reaction that was treated with antihistamines and corticosteroids. One patient developed grade 3 skin eruption that was successfully treated. One patient developed grade 2 transaminase elevation that was reversible. The fourth patient developed empyema after the first course of treatment and was successfully treated with chest tube drainage and appropriate antibiotics. There were no treatment-related deaths.

3.2. Second-line therapy

Of 12 patients in stage IIIB, 5 were treated with platinum-based chemotherapy after the gemcitabine–vinorelbine regimen. Three patients were treated with thoracic radiotherapy for symptom palliation. Three patients received only best supportive therapy. One patient received surgery of the primary tumor. Of thirty-eight patients in stage IV, 28 were treated with systemic chemotherapy; 17 received platinum plus taxen; 3 received further courses of gemcitabine plus vinorelbine; 4 received taxen alone; and 4 received platinum-based combination regimen without taxen. Eight patients received only best supportive therapy. Two patients were treated with thoracic radiotherapy.

3.3. Survival

The median time to progression of 34 patients was 4.1 months (range, 0.1 to ≥13.7 months). The overall median survival time (MST) was 13.9 months (range, 2.4 to ≥16.2 months) with a median follow-up time of 13.9 months (Fig. 1a). The

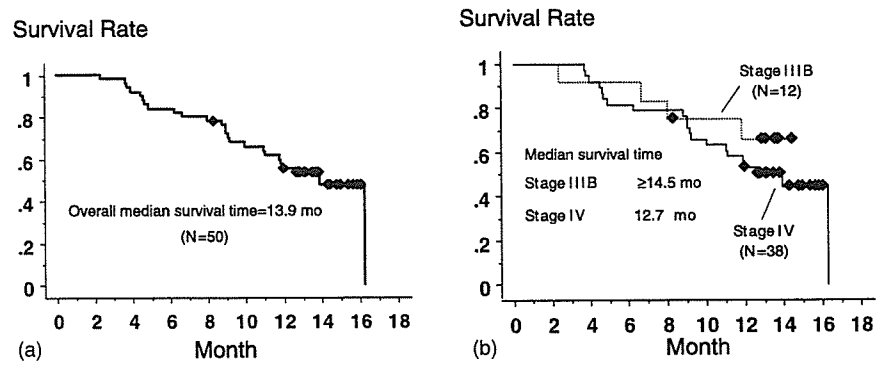

Fig. 1 (a) Overall survival time. (b) Survival time according to stage.

median survival time for stage IIIB was ≥14.5 months, and for stage IV, it was 12.7 months (Fig. 1b). The overall estimated 1-year survival rate was 55.4%. The estimated 1-year survival rate for stages IIIB and IV was 66 and 53%, respectively.

4. Discussion

The 1-year survival for patients with advanced NSCLC has increased from as low as 10—40% over the last two decades when patients are treated with cisplatin-based combination chemotherapy. Meta-analysis of multiple trials comparing chemotherapy to best supportive care proved that the cisplatin-based therapy improved the survival of these patients, although the benefits were modest [1—4]. On average, the median survival of the cisplatin-treated patients improved by 10 weeks, and the 1-year survival rate improved by 10%. Despite these data, some medical oncologists remain skeptical and do not routinely treat advanced NSCLC with cisplatin-based chemotherapy. This reluctance can be explained partly by the inherent toxicity of the chemotherapy regimens and perceived negative effect on quality of life. Recently it has been shown that new chemotherapeutic agents such as CTP-11, docetaxel, paclitaxel, gemcitabine, and vinorelbine result in improvement in response rates with an increase in 1- and 2-year survivors [5]. In addition to their antitumor activity, these agents are less toxic than cisplatin in terms of nausea, vomiting, ototoxity, and general malaise, and their use does not require a large amount of fluid to prevent renal impairment.

The present report describes the phase II trial combining gemcitabine and vinorelbine in the treatment of chemo-naïve patients with advanced NSCLC. There are at least five phase II trials (results in full paper) in which gemcitabine and vinorelbine treatment has been given to chemo-naïve patients with advanced NSCLC. The observed response rate of 18% in our study was not better than that reported in other gemcitabine—vinorelbine regimens for advanced NSCLC, which have shown responses ranging from 25 to 72.5% [16—20]. It should be noted, however, that not only the dosage of gemcitabine and vinorelbine but also the timing of the drug administration was variable from study to study. The gemcitabine and vinorelbine dose intensity attained in the present study was 667 and 16.7 mg/m^2 per week, respectively. The projected gemcitabine and vinorelbine dose intensity in other studies was 600—830 and 15—20 mg/m^2 per week, respectively. Chen et al reported the highest response rate of 72.5% and median survival time of 11 months [18]. The treatment in their study consisted of vinorelbine 20 mg/m^2 and gemcitabine 800 mg/m^2 on days 1, 8, and 15 every 4 weeks. The higher response may be partly attributed to the larger number of stage IIIB patients (45%) included in their study compared to ours (stage IIIB, 24%). The other reason may be due to the difference of median number of treatment courses (three—six courses in other studies versus two courses in ours), since some patients achieved PR only after three courses of chemotherapy.

As far as MST is concerned, the MST of 13.9 months and the 1-year survival rate of 55.4% in our trial are superior to other established cisplatin-based regimens and are very encouraging in the context of advanced NSCLC [7—9,12,13]. This is particularly true for patients with stage IV, who had a MST of 12.7 months and a 1-year survival rate of 53%. The reported MST of other gemcitabine—vinorelbine regimens in phase II studies for advanced NSCLC ranged from 8 to 12.6 months and a 1-year survival rate of 30—48.1% [16,20]. There are at least three reasons why patients in our study had a good MST and a favorable 1-year survival rate. First of all, all our patients had an initial good PS, 0 or 1. The second reason is that only a limited number of patients (16%) deteriorated in their PS to grade 3 after chemotherapy, and most of the patients could receive platinum-based combination chemotherapy when they could not attain an objective response. Finally, 24% of patients received docetaxel as a second-line chemotherapy. Docetaxel has recently been demonstrated to be not only effective in first-line use but also to have considerable activity when used for second-line therapy [21,22].

Feliu et al. conducted a phase II study of a gemcitabine—vinorelbine regimen in NSCLC patients age 70 years or older or patients who cannot receive cisplatin [17]. Treatment comprised of vinorelbine, 25 mg/m^2 plus gemcitabine, 1000mg/m^2, both on days 1, 8, and 15 every 28 days. Forty-nine patients were included, 38 of whom were age 70 years or older and 11 of whom were less than 70 years old but who had some contraindication to receiving cisplatin. The overall response rate was 26%, and the 1-year survival rate was 33%. They concluded that the gemcitabine—vinorelbine combination was moderately active and well tolerated except in patients age 75 years or older. Recently two randomized studies comparing a gemcitabine—vinorelbine combination to single-agent gemcitabine or vinorelbine has been reported in an elderly population with NSCLC. An improved survival with gemcitabine plus

vinorelbine regimen over vinorelbine alone and improvement in some tumor-related symptoms was reported in one study [23]. However this was not confirmed by the other larger randomized phase III study, which demonstrated that single-agent therapy is at least as good as combination therapy in terms of survival [24]. Therefore, additional comparative studies comparing nonplatinum-containing doublets chemotherapy to single-agent chemotherapy are needed to determine the most appropriate chemotherapy regimen in terms of tolerability, quality of life, and cost-effectiveness, especially for elderly patients. However, these data as a whole demonstrated that nonplatinum doublets combination chemotherapy with gemcitabine and vinorelbine is active and well tolerated in the elderly patients.

The toxicity of the current regimen was modest and easily managed. Myelosuppression was the main adverse effect, with grade 3 or 4 neutropenia of 66%. However, neither treatment-related deaths nor serious infection occurred, and patients recovered rapidly from neutropenia. Grade 2 or 3 elevation of serum transaminase was noted in 40% of patients, with no significant morbidity. The majority of our patients did not have any nausea or vomiting, and few patients suffered from alopecia. Only two patients (4%) suffered from grade 1 neuropathy, and very few patients developed vasculitis. In general, toxicity induced by this nonplatinum-containing doublets regimen was well tolerated and less toxic than cisplatin-containing regimens.

In conclusion, the combination of gemcitabine and vinorelbine is active and well tolerated in the treatment of advanced NSCLC. The randomized comparison with platinum-containing regimens is deserved, with particular interest not only in clinical response but also in quality of life and toxicity profile.

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