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.

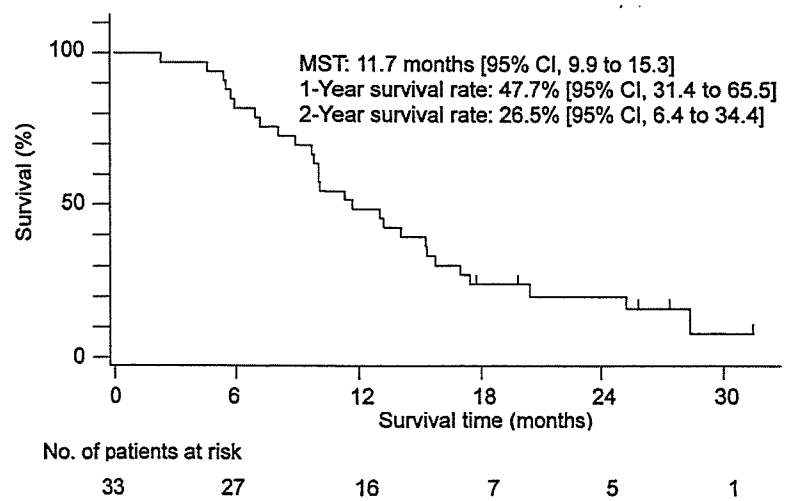

Fig. 2 Overall survival of patients with extensive-disease small cell lung cancer treated with amrubicin. MST: median survival time; 95% CI: 95% confidence interval

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 I–II study of amrubicin and cisplatin in previously untreated patients with extensive-stage small-cell lung cancer

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Background: Amrubicin, a totally synthetic 9-amino-anthracycline, demonstrated excellent single-agent activity for extensive-stage small-cell lung cancer (ED-SCLC). The aims of this trial were to determine the maximum-tolerated doses (MTD) of combination therapy with amrubicin and cisplatin, and to assess the efficacy and safety at their recommended doses (RD).

Patients and methods: Eligibility criteria were patients having histologically or cytologically proven measurable ED-SCLC, no previous systemic therapy, an Eastern Cooperative Oncology Group performance status of 0–2 and adequate organ function. Amrubicin was administered on days 1–3 and cisplatin on day 1, every 3 weeks.

Results: Four patients were enrolled at dose level 1 (amrubicin 40 mg/m^2/day and cisplatin 60 mg/m^2) and three patients at level 2 (amrubicin 45 mg/m^2/day and cisplatin 60 mg/m^2). Consequently, the MTD and RD were determined to be at level 2 and level 1, respectively. The response rate at the RD was 87.8% (36/41). The median survival time (MST) was 13.6 months and the 1-year survival rate was 56.1%. Grade 3/4 neutropenia and leukopenia occurred in 95.1% and 65.9% of patients, respectively.

Conclusions: The combination of amrubicin and cisplatin has demonstrated an impressive response rate and MST in patients with previously untreated ED-SCLC.

Key words: anthracycline, cisplatin, phase I–II, small-cell lung cancer

Introduction

Small-cell lung cancer (SCLC) is one of the most chemosensitive solid tumors, and the outcome of SCLC patients is slowly but surely improving. Combination chemotherapy consisting of cisplatin plus etoposide and concurrent twice-daily thoracic radiotherapy has yielded a 26% 5-year survival rate in limited-stage (LD) patients [1]. Despite the high response rate to combination chemotherapy, however, local and distant failure is very common, especially in extensive-stage (ED) patients. Moreover, resistance to chemotherapeutic agents develops easily after failure of initial treatment. Thus, long-term survivors are still very rare among patients with ED-SCLC. To improve the outcome of SCLC patients, several strategies, such as high-dose chemotherapy, dose-intensive chemotherapy, alternating chemotherapy and introduction of new drugs, have been investigated [2–6]. However, only the introduction of new agents has improved the outcome of SCLC patients. Combination chemotherapy with etoposide plus cisplatin or etoposide plus cisplatin alternating cyclophosphamide, doxorubicin and vincristine had been mainly used for SCLC in North America. Recently, a Japanese trial [Japan Clinical Oncology Group (JCOG) 9511] demonstrated the superiority of the combination of irinotecan and cisplatin for ED-SCLC patients over the combination of etoposide and cisplatin [6]. The development of more active chemotherapy, and especially the introduction of effective new drugs, is therefore essential to improve the survival of SCLC patients.

Amrubicin (SM-5887) is a totally synthetic anthracycline and a potent topoisomerase II inhibitor [7–14]. It has antitumor activity, and is more potent than doxorubicin against various mouse experimental tumors and human tumor

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xenografts. Amrubicin and its 13-hydroxy metabolite, amrubicinol, inhibit purified human DNA topoisomerase II [11]. Amrubicinol is 10–100 times more cytotoxic than amrubicin [9]. The potent therapeutic activity of amrubicin is caused by the selective distribution of its highly active metabolite, amrubicinol, in tumors [9]. In an experimental animal model, amrubicin did not exhibit any chronic cardiotoxicity potential, and no deleterious effects on doxorubicin-induced cardiotoxicity in dogs was observed [14]. In a phase II study of amrubicin using a schedule of 45 mg/m^2 on days 1–3 every 3 weeks, in 33 previously untreated ED-SCLC patients, an overall response rate of 76% and a complete response (CR) rate of 9% were reported [15]. Moreover, median survival time (MST) was 11.7 months in the single-agent phase II study of amrubicin. Amrubicin is one of the most active new agents for SCLC. Thus, we conducted a phase I/II study of amrubicin plus cisplatin for untreated ED-SCLC, because cisplatin is considered as one of the most important drugs in the treatment of SCLC. The aims of this trial were to determine the maximum-tolerated doses (MTD) of combination therapy of amrubicin with cisplatin, to assess the efficacy and safety for ED-SCLC at their recommended doses (RD), and to examine the pharmacokinetics of the drug combination.

Patients and methods

Patient selection

Patients with histologically and/or cytologically documented SCLC were eligible for this study. Each patient was required to meet the following criteria: extensive-stage disease [16]; no prior therapy for primary lesion; measurable lesion; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; expected survival time >2 months; age 20–74 years; adequate hematological function [white blood cell (WBC) count 4000–12 000/mm^3, neutrophils ≥2000/mm^3, platelets ≥100 000/mm^3, hemoglobin ≥10 g/dl]; adequate hepatic function [total bilirubin within 1.5× the upper limit of normal; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) within 2.5× the upper limit of normal]; adequate renal function (creatinine within the upper limit of normal); partial pressure of arterial oxygen 60 torr; no abnormality requiring treatment on electrocardiogram; left ventricle ejection fraction >60%; written informed consent. Patients with symptomatic brain metastasis, pleural effusion that required drainage, non-steroidal anti-inflammatory drug or glucocorticoid use for >50 days, pericarditis carcinomatous, active infection, varicella, superior vena cava syndrome, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), gastric and/or duodenal ulcer, severe heart disease, severe renal disease, active concomitant malignancy, symptomatic pneumonitis and/or pulmonary fibrosis and pregnant/nursing women were excluded. This study was approved by the Institutional Review Board at each hospital.

Patient evaluation

Pretreatment evaluation consisted of complete blood cell counts, differential, routine chemistry measurements, progastrin-releasing peptide (ProGRP), neuron-specific enolase, electrocardiogram, echocardiography, chest radiograph, chest and abdominal computed tomography (CT) scan, whole-brain magnetic resonance imaging (MRI) or CT scan, and isotope bone scan. Complete blood cell counts, differential and routine chemistry measurements were performed at least once a week during the chemotherapy.

Treatment schedule

At level 1, chemotherapy consisted of cisplatin 60 mg/m^2 on day 1 and amrubicin 40 mg/m^2 on days 1–3. Amrubicin was administered as an intravenous injection over 5 min and cisplatin was administered as a drip infusion over 60–120 min with adequate hydration. At level 2 the dose of amrubicin was increased to 45 mg/m^2 on days 1–3. Level 3 was planned with cisplatin 80 mg/m^2 on day 1 and amrubicin 45 mg/m^2 on days 1–3. The chemotherapy was repeated every 3 weeks for four to six courses. Intrapatient dose escalation was not allowed. Administration of granulocyte colony-stimulating factor (G-CSF) was permitted prophylactically for patients expected to experience grade 3 neutropenia during the first course. Prophylactic administration of G-CSF was only permitted at second or later courses.

The administrations of both cisplatin and amrubicin were postponed if patients met the following criteria: WBC <3000/mm^3; neutrophils <1500/mm^3; platelets <100 000/mm^3; AST and ALT >5× the upper limit of normal; total bilirubin >1.5× the upper limit of normal; creatinine >1.3× the upper limit of normal; ECOG PS 3 or 4; active infection; grade 2 or worse non-hematological toxicity, except for alopecia, anorexia, nausea, vomiting or fatigue.

The administrations of both cisplatin and amrubicin were withdrawn if patients met the following criteria: tumor regression <15% after first course or <30% after second course; WBC <3000/mm^3; neutrophils <1500/mm^3; platelets <100 000/mm^3; no recovery from grade 3 or 4 non-hematological toxicity at 6 weeks after the start of previous chemotherapy; abnormality of electrocardiogram requiring treatment for more than 6 weeks; left ventricle ejection fraction <48%; treatment delay of >4 weeks.

The dose of amrubicin was decreased 5 mg/m^2/day if patients met the following criteria: grade 4 leukopenia or neutropenia for ≥4 days; grade 3 neutropenia with fever; platelets <20 000/mm^3 during the previous course. The dose of cisplatin was decreased to 75% if creatinine increased to >1.5× the upper limit of normal during the previous course.

The dose-limiting toxicity (DLT) was defined as follows: grade 4 leukopenia or neutropenia for ≥4 days; grade 3 febrile neutropenia; platelets <20 000/mm^3; grade 3 or worse non-hematological toxicity except for nausea, vomiting, anorexia, fatigue, hyponatremia and infection. Initially, three patients were treated at each dose level. If DLT was not observed in any of the three patients, dose escalation was carried out. If DLT was observed in one of three patients, an additional three patients were entered at the same dose level. If DLT was observed in three or more of six patients, or two or three of the initial three patients, we considered that dose to be the MTD. If DLT was observed in one or two of six patients, dose escalation was also carried out. Dose escalation was determined based only on the data from the first course of chemotherapy.

Response and toxicity evaluation

Response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) and tumor markers were excluded from the criteria [17]. CR was defined as the complete disappearance of all clinically detectable tumors for at least 4 weeks and no new lesions. Partial response (PR) was defined as at least a 30% decrease in the sum of the longest diameters of target lesion, taking as reference the baseline sum longest diameter, the required non-progression in non-target lesions and no new lesions for at least 4 weeks. Stable disease (SD) included: regression of target lesions insufficient to meet the criteria for PR, a <20% increase in the sum of the longest diameter of target lesion, taking as reference the smallest sum longest diameters recorded since the treatment started, the required non-progression in non-target lesions and no new lesions for at least 6 weeks. Progressive disease (PD) indicated a >20% increase in the sum of the longest diameters of target lesion, taking as reference the smallest sum longest diameter recorded since the treatment started

and/or unequivocal progression of existing non-target lesions and/or appearance of new lesions. The evaluation of objective tumor response for all patients was performed by an external review committee.

Toxicity grading criteria of the National Cancer Institute Common Toxicity Criteria (version 2.0) was used for evaluation of toxicity.

Statistical analysis

This study was designed to reject response rates of 70% (P0) at a significance level of 0.05 (one-tailed) with a statistical power of 80% to assess the activity of the regimen as a 85% response rate (P1) at the recommended dose. The upper limit of rejection was 29 responses (CR + PR) among 37 evaluable patients. Overall survival was defined as the interval between the first administration of the drugs in this study and death or the last follow-up visit. Median overall survival was estimated using the Kaplan–Meier method [18].

Table 1. Characteristics of treated patients

	Phase I	Phase II	Total
Number of patients	7	37	44
Gender			
Male	5	31	36
Female	2	6	8
Age (years)			
Median	65	64	64.5
Range	54–73	50–74	50–74
ECOG PS			
0	0	5	5
1	7	32	39
2	0	0	0
Stage			
IIIB	0	2	2
IV	7	35	42
Prior therapy			
Yes	0	1	1
No	7	36	43
Serum ALP			
Normal	7	29	36
Elevated	0	7	7
Serum LDH			
Normal	3	14	17
Elevated	4	23	27
Na			
Normal	6	35	41
Decreased	1	2	3
Number of metastases			
0	0	2	2
1	4	27	31
2	3	6	9
3	0	1	1
4 or more	0	1	1

In one patient, serum ALP level could not be measured.
ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ALP, alkaline phosphatase.

Pharmacokinetic analysis

Pharmocokinetic analysis was performed in patients entering the phase I section of this study. One milliliter of the blood was taken from the patients before administration of amrubicin, and at 0 min, 15 min, 1, 2, 3, 4, 8 and 24 h after administration on days 1 and 3 in the first course of chemotherapy. Concentrations of amrubicin and its active metabolite, amrubicinol, in plasma and red blood cells were measured as reported elsewhere [9].

Results

Patient characteristics

Between April 2001 and December 2002, 45 patients with ED-SCLC were enrolled and 44 were treated in this study (Table 1). One patient did not receive the protocol treatment because atrial fibrillation was observed just before administration on day 1 of the first course. All treated patients were assessed for response, survival and toxicity. The median age of the treated patients was 64.5 years (range 50–74). There were 36 males and eight females. Five patients had an ECOG PS 0 and 39 patients had PS 1. Only one patient received surgery for brain metastasis as a prior therapy.

MTD and DLT in the phase I study

Four patients were enrolled at dose level 1 (amrubicin 40 mg/m^2 on days 1–3 and cisplatin 60 mg/m^2 on day 1) and three patients at level 2 (amrubicin 45 mg/m^2 on days 1–3 and cisplatin 60 mg/m^2 on day 1). Toxicities in the phase I study are listed in Table 2. No DLT were observed during the first course of level 1. At level 2, grade 4 neutropenia for ≥4 days and febrile neutropenia occurred in one patient, and febrile neutropenia and grade 3 constipation occurred in another patient. Consequently, the MTD and RD were determined to be level 2 and level 1, respectively.

Pharmacokinetics of amrubicin and its active metabolite, amrubicinol

Pharmacokinetic parameters of amrubicin in plasma were almost identical on days 1 and 3 at the two dose levels (Table 3). No clear dose relationship in the area under the concentration–time curve (AUC) of amrubicin in the plasma was observed. The AUC of amrubicinol in red blood cells tended to increase on day 3 at both doses (Table 4). No clear dose relationship in the AUC of amrubicinol in red blood cells was observed. Combination with cisplatin did not alter the pharmacokinetics of amrubicin and amrubicinol (data not shown).

Treatment received in patients treated at the RD

Forty-one patients were treated at the RD: amrubicin 40 mg/m^2 on days 1–3 and cisplatin 60 mg/m^2 on day 1. Of 41 patients, 32 (78%) patients received more than three

Table 2. Toxicities during the first course in the phase I study

	Level 1 ($n=4$)					Level 2 ($n=3$)				
Amrubicin	40 mg/m^2 days 1–3					45 mg/m^2 days 1–3				
Cisplatin	60 mg/m^2 day 1					60 mg/m^2 day 1				
	Grade (NCI CTC)					Grade (NCI CTC)				
	0	1	2	3	4	0	1	2	3	4
Leukopenia	0	1	1	2	0	0	0	1	1	1
Neutropenia	0	0	0	2	2	0	0	0	0	3
Febrile neutropenia	4	–	–	0	0	1	–	–	2	0
Hemoglobin	1	1	2	0	0	2	1	0	0	0
Thrombocytopenia	1	2	0	1	0	0	2	0	1	0
Stomatitis	3	0	1	0	0	3	0	0	0	0
Nausea	1	1	2	0	–	1	1	0	1	–
Constipation	3	0	1	0	0	1	0	1	1	0
Hyponatremia	2	1	0	0	1	1	2	0	0	0
Hypocalcemia	3	0	1	0	0	3	0	0	0	0

Dose limiting toxicity at level 2: febrile neutropenia, two patients; grade 4 neutropenia ≥4 days, one patient; grade 3 constipation, one patient.
NCI CTC, National Cancer Institute Common Toxicity Criteria.

Table 3. Pharmacokinetics of amrubicin in plasma

Dose	n	Day	$T_{1/2\alpha}$ (h)	$T_{1/2\beta}$ (h)	V_d (l)	CL (l/h)	$AUC_{0-24\,h}$ (ng h/ml)
40 mg/m^2	4	1	0.11 ± 0.04	2.29 ± 0.31	46.6 ± 11.0	13.6 ± 1.8	2995 ± 434
	4	3	0.08 ± 0.01	2.89 ± 0.34	50.0 ± 10.6	11.6 ± 1.9	3511 ± 514
45 mg/m^2	3	1	0.13 ± 0.05	2.39 ± 0.34	56.3 ± 10.6	14.9 ± 1.8	3052 ± 402
	3	3	0.09 ± 0.03	2.27 ± 0.18	51.9 ± 3.7	14.2 ± 2.3	3217 ± 479

$T_{1/2\alpha}$, half-life at distribution phase; $T_{1/2\beta}$, half-life at elimination phase; V_d, volume of distribution; CL, clearance; AUC, area under the concentration–time curve.

courses of chemotherapy, and 10 (31%) of these 32 patients needed dose reduction of amrubicin at the fourth course (Table 5). Of 41 patients, 22 (54%) patients completed four courses of chemotherapy without dose modification. The main cause of dose reduction was myelosuppression, especially leukopenia and neutropenia.

Objective tumor response and overall survival

The objective tumor responses are given in Table 6. Four CRs and 32 PRs occurred, for an objective response rate of 87.8% [95% confidence interval (CI) 73.8% to 95.9%] in 41 patients treated at the RD. The objective response rate for all 44 patients was 88.6% (95% CI 75.4% to 96.2%). The overall survival times of the 41 patients treated at the RD are shown in Figure 1. The MST of the 41 patients was 13.6 months (95% CI 11.1–16.6), with a median follow-up time for eight censored patients of 16.4 months (95% CI 14.2–18.8). The 1- and 2-year survival rates were 56.1% and 17.6%, respectively. The MST of all 44 patients was 13.8 months (95% CI 11.1–16.6). The 1- and 2-year survival rates of all 44 patients were 56.8% and 21.4%, respectively.

Table 4. Pharmacokinetics of amrubicinol in red blood cells

Dose	n	Day	$T_{1/2}$ (h)	$AUC_{0-24\,h}$ (ng·h/ml)
40 mg/m^2	4	1	21.0 ± 3.1	1412 ± 314
	4	3	20.7 ± 4.8	2159 ± 622
45 mg/m^2	3	1	19.6 ± 6.1	1098 ± 277
	3	3	18.1 ± 5.7	2027 ± 332

$T_{1/2}$, elimination half-life; AUC, area under the concentration–time curve.

Table 5. Treatment received in patients treated at the recommended dose

Cycle	n	Amrubicin (mg/m^2)			Cisplatin (mg/m^2)	
		40	35	30	60	45
1	41	41			41	
2	36	30	6		36	
3	33	26	5	2	33	
4	32	22	8	2	32	
5	18	9	5	4	18	
6	13	6	3	4	12	1

Table 6. Response rates

	n	CR	PR	SD	PD	NE	Response rate (%) (95% CI)
All	44	4	35	3	0	2	88.6 (75.4–96.2)
Treated at RD	41	4	32	3	0	2	87.8 (73.8–95.9)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated; 95% CI, 95% confidence interval; RD, recommended dose.

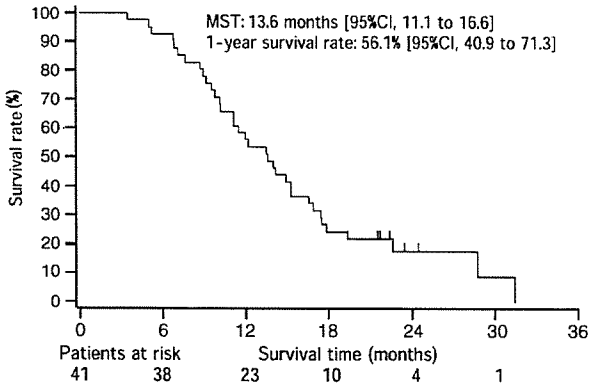

Figure 1. Overall survival of patients with extensive-stage small-cell lung cancer who were treated with amrubicin and cisplatin at the recommended dose. MST, median survival time; 95% CI, 95% confidence interval.

Toxicity in patients treated at the RD

The worst grades of hematological and non-hematological toxicities experienced by each patient are listed in Table 7. Hematological toxicity, especially leukopenia and neutropenia, was common and relatively severe. Grade 3 or worse leukopenia and neutropenia occurred in 65.9% and 95.1% of patients, respectively. Febrile neutropenia was observed in two patients at level 2. Grade 3 or worse anemia and thrombocytopenia occurred in 53.7% and 24.4% of patients, respectively. Four patients received platelet transfusions. Common non-hematological toxicities were gastrointestinal toxicity, such as anorexia, nausea, vomiting, constipation, diarrhea and stomatitis. Gastric ulcers developed in three patients. Hepatic and renal toxicity were not common in this study. Grade 3 or worse hyponatremia and hypokalemia occurred in 22% and 9.8% of patients, respectively. One patient developed myocardial infarction; however, cardiac toxicity was not common. No treatment-related deaths were observed.

Discussion

Doxorubicin and epirubicin are classified as active agents for SCLC, for which single-agent activity is a >20% response rate [19]. Doxorubicin has been used as a constituent of combination therapy for SCLC in the CAV (cyclophospamide, doxorubicin and vincristine) and CAP (cyclophosphamide, doxorubicin and cisplatin) regimens. Epirubicin has shown

Table 7. Toxicity in patients treated at the recommended dose ($n=41$)

	Grade (NCI CTC)					Grade 3/4 (%)
	0	1	2	3	4	
Leukopenia	1	0	13	20	7	65.9
Neutropenia	0	1	1	7	32	95.1
Febrile neutropenia	41	–	–	0	0	0.0
Hemoglobin	1	8	10	17	5	53.7
Thrombocytopenia	9	14	8	10	0	24.4
Stomatitis	22	13	5	1	0	2.4
Anorexia	1	14	13	13	0	31.7
Nausea	3	15	14	9	0	22.0
Vomiting	20	8	11	2	0	4.9
Constipation	24	1	13	3	0	7.3
Diarrhea	26	12	1	2	0	4.9
Gastric ulcer	38	0	1	2	0	4.9
Bilirubin	24	12	4	1	0	2.4
Hyponatremia	18	14	–	7	2	22.0
Hypokalemia	31	6	–	4	0	9.8
Hyperkalemia	33	3	4	1	0	2.4
Hypocalcemia	31	5	4	0	1	2.4

NCI CTC, National Cancer Institute Common Toxicity Criteria.

50% and 48% response rates in two clinical studies in 41 and 80 previously untreated patients, respectively, with ED-SCLC [20, 21]. However, currently, combination modalities containing doxorubicin or epirubicin are not being used in the therapy of SCLC, in preference to combination therapy with cisplatin and etoposide. Since amrubicin has shown excellent single-agent activity [15], it can be expected to be superior to other anthracyclines in the treatment of SCLC. Additionally, the present results of combination therapy with cisplatin support the view that amrubicin may be a promising agent that overcomes the therapeutic plateau of SCLC.

Amrubicin is one of the most promising new agents for the treatment of SCLC. In a previous phase II study of amrubicin 45 mg/m^2 on days 1–3 every 3 weeks as a monotherapy for chemonaive ED-SCLC, a 76% overall response rate and 11.7 month MST were observed [15]. The overall response rate and MST were comparable to those achieved with standard combination chemotherapy, such as etoposide plus cisplatin [5, 6]. Moreover, only a few patients treated in the phase II study received salvage chemotherapy consisting of cisplatin and etoposide [15]. The major toxicity of amrubicin as a monotherapy was hematological toxicity: grade 4 leukopenia and neutropenia were seen in 12.1% and 39.4% of patients, respectively, and thrombocytopenia and anemia of grade 3 or worse in 21.2%. Hepatic, renal and cardiac toxicities with amrubicin were not common. Cisplatin is a key drug for the treatment of SCLC and its hematological toxicity, such as leukopenia and neutropenia, is not severe. Thus, we conducted a phase I–II study of amrubicin and cisplatin treatment for chemonaive ED-SCLC to determine the MTD of this combination therapy, to

assess the efficacy and safety of the drugs delivered at their RD in chemonaive ED-SCLC, and to examine pharmacokinetics.

The topoisomerase I inhibitor, irinotecan, is also very effective for SCLC [6]. Combinations of topoisomerase I and topoisomerase II inhibitors, such as irinotecan plus etoposide, have been reported as active combination chemotherapy for SCLC [22]. Thus, combination of irinotecan and amrubicin is another candidate for new combination chemotherapy for SCLC. A phase I study of irinotecan and amrubicin for chemonaive non-SCLC was performed in National Cancer Center Hospital (unpublished data). However, the MTD was less than irinotecan 60 mg/m^2 on days 1 and 8 and amrubicin 35 mg/m^2 on days 2–4, due to relatively severe myelotoxicity. We considered that amrubicin <35 mg/m^2 on days 2–4 with irinotecan 60 mg/m^2 on days 1 and 8 was insufficient to treat SCLC.

In this study, we determined the RD to be amrubicin 40 mg/m^2 on days 1–3 and cisplatin 60 mg/m^2 on day 1 every 3 weeks, and 41 patients were treated at the RD. Main toxicities of this combination chemotherapy were myelosuppression, especially leukopenia and neutropenia, and gastrointestinal toxicities including anorexia, nausea, vomiting, constipation, diarrhea, stomatitis and gastric ulcer. Of 41 patients, 32 (78%) patients received four or more courses of chemotherapy, and 22 (54%) patients completed four courses of chemotherapy without dose modification. One patient developed myocardial infarction; however, other cardiac toxicity, including decrease in left ventricle ejection fraction, was not observed in up to six courses of chemotherapy. The total dose of amrubicin was 720 mg/m^2. Grade 3 or 4 hyponatremia occurred in nine (22%) patients; however, most of the patients were asymptomatic. No unexpected toxicities and no treatment-related deaths were observed in this study. Toxicities observed in this study were manageable.

Four CRs and 32 PRs occurred, for an objective response rate of 87.8% (95% CI 73.8% to 95.9%) in 41 patients treated at the RD. In most patients, ProGRP levels changed in parallel with tumor responses. The MST of the 41 patients was 13.6 months, and the 1-year survival rate was 56.1%. These results were better than recently reported results for irinotecan and cisplatin in chemonaive ED-SCLC: an objective response rate of 84% and MST of 12.8 months [6]. The combination of amrubicin and cisplatin has demonstrated an impressive response rate and MST in patients with previously untreated ED-SCLC. A possible reason for the better results is overselection of patients, because we used unusual exclusion criteria such as non-steroidal anti-inflammatory drug or adrenal cortical steroid use for >50 days, and gastric and/or duodenal ulcer. However, in a phase II study, this kind of bias is not uncommon.

Combination chemotherapy with etoposide plus cisplatin or etoposide plus cisplatin, alternating with cyclophosphamide, doxorubicin and vincristine, had been considered as standard chemotherapy for SCLC in North America and Japan. A Japanese phase III trial (JCOG 9511) demonstrated that treatment with four cycles of irinotecan plus cisplatin every 4 weeks yielded a highly significant improvement in survival in ED-SCLC patients over standard etoposide plus cisplatin, with less myelosuppression [6]. Based on the results of the JCOG 9511 trial, irinotecan plus cisplatin is considered to be the reference chemotherapy arm for ED-SCLC in future trials in Japan [23]. The JCOG are preparing a phase III clinical trial of amrubicin and cisplatin for previously untreated ED-SCLC to compare combination therapy of irinotecan with cisplatin.

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Randomised phase II study of docetaxel/cisplatin *vs* docetaxel/irinotecan in advanced non-small-cell lung cancer: a West Japan Thoracic Oncology Group Study (WJTOG9803)

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Docetaxel plus cisplatin and docetaxel plus irinotecan are active and well-tolerated chemotherapy regimens for advanced non-small-cell lung cancer (NSCLC). A randomised phase II study compared their efficacy and toxicity in 108 patients with stage IIIb/IV NSCLC, who were randomised to receive docetaxel 60 mg m^{-2} and cisplatin 80 mg m^{-2} on day 1 (DC; $n=51$), or docetaxel 60 mg m^{-2} on day 8 and irinotecan 60 mg m^{-2} on day 1 and 8 (DI; $n=57$) every 3 weeks. Response rates were 37% for DC and 32% for DI patients. Median survival times and 1- and 2-year survival rates were 50 weeks (95% confidence interval: 34–78 weeks), 47 and 25% for DC, and 46 weeks (95% confidence interval: 37–54 weeks), 40 and 18% for DI, respectively. The progression-free survival time was 20 weeks (95% confidence interval: 14–25 weeks) with DC and 18 (95% confidence interval: 12–22 weeks) with DI. Significantly more DI than DC patients had grade 4 leucopenia and neutropenia ($P<0.01$); more DC patients had grade $\geqslant 2$ thrombocytopenia ($P<0.01$). Nausea and vomiting was more pronounced with DC ($P<0.01$); diarrhoea was more common with DI ($P=0.01$). Three treatment-related deaths occurred in DC patients. In conclusion, although the DI and DC regimens had different toxicity profiles, there was no significant difference in survival.
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Keywords: combination chemotherapy; doublets; irinotecan; cisplatin; docetaxel; non-small-cell lung cancer; carboplatin

Unfortunately, non-small-cell lung cancer (NSCLC) is a member of the group of neoplastic diseases that is relatively chemoresistant. Recent meta-analyses show that cisplatin-based chemotherapy improves survival (Non-Small Cell Lung Cancer Collaborative Group, 1995), and it is considered a standard treatment for NSCLC, Most cisplatin-based regimens have substantial toxicities that require close monitoring and supportive care. Thus, there is a need to develop active and less toxic chemotherapy regimens that include new active compounds with novel mechanisms of action.

In the 1990s, several new, active therapies with single-agent response rates of 15–30% became available for NSCLC, including irinotecan, docetaxel, paclitaxel, vinorelbine, and gemcitabine. Because irinotecan and docetaxel were approved for NSCLC earlier than the other drugs in Japan, development of regimens containing irinotecan or docetaxel is more advanced. Docetaxel 60 mg m^{-2} showed good antitumour activity against advanced NSCLC (Kunitoh *et al*, 1996), and the combination of docetaxel plus cisplatin (DC) is one of the most effective regimens for advanced NSCLC (Rodriguez *et al*, 2001; Schiller *et al*, 2002). Studies in Japan included a phase II study in which DC yielded a response rate of 42% (Okamoto *et al*, 2002), and a phase III study in which DC was associated with better survival than the vindesine and cisplatin (VC) combination (Kubota *et al*, 2002).

Irinotecan demonstrated activity similar to that of VC in stage IIIb/IV NSCLC (Negoro *et al*, 2003), and significant longer overall survival time than VC in stage IV NSCLC (Fukuoka *et al*, 2000). We reported a phase I study of docetaxel plus irinotecan (DI) in patients with advanced NSCLC, in which a promising response rate of 48% and the median survival time of 48 weeks were achieved with acceptable toxicities (Masuda *et al*, 2000). Thus, DI appeared to be a promising non-cisplatin-containing regimen.

Based on the above findings, we conducted a randomised trial of DC *vs* DI in patients with advanced NSCLC to compare the respective response rates, survival data, and toxicity profiles of the two regimens. This was a multicentred phase II study.

PATIENTS AND METHODS

Patients

Patients enrolled in this trial had histologically or cytologically confirmed stage IIIb or IV NSCLC. Patients with stage IIIb disease who were not candidates for thoracic radiation and patients with stage IV disease were eligible if they had not received previous therapy, had measurable disease, and had a life expectancy of at least 3 months. Additional entry criteria were age $\geqslant 20$ years, performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale, adequate bone marrow function (leucocyte

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count 4000–12 000 μl^{-1}, haemoglobin concentration $\geqslant$9.5 g dl^{-1} platelet count $\geqslant$100 000 μl^{-1}), kidney function (creatinine $\leqslant$ upper limit of normal, 24-h creatinine clearance $\geqslant$60 ml min^{-1}), liver function (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leqslant$2.0 times the upper limit of normal, total bilirubin $\leqslant$1.5 mg dl^{-1}), and pulmonary function ($PaO_2 \geqslant 60$ torr). Patients with active concomitant or a recent (<3 years) history of any malignancy, symptomatic brain metastases, past history of drug allergy reactions, complication by interstitial pneumonia, watery diarrhoea, ileus, treatment with nonsteroidal anti-inflammatory drugs, or other serious complications, such as uncontrolled angina pectoris, myocardial infarction within 3 months, heart failure, uncontrolled diabetes mellitus or hypertension, massive pleural effusion or ascites, or serious active infection were excluded. All patients gave written informed consent, and the institutional review board for human experimentation approved the protocol.

clinical

Study evaluations

Pretreatment studies included a complete medical history and physical examination, chest X-ray, electrocardiography, computed tomography (CT) scan of the brain and chest, CT or ultrasound examination of the abdomen, and bone scintigraphy. Blood and blood chemistry studies included complete blood cell count, liver function test, serum electrolytes, serum creatinine, and blood urea nitrogen. Chest X-ray, blood and blood chemistry analyses, and urinalysis were repeated weekly.

Randomisation and treatment schedule

Patients were randomly assigned to receive the DC regimen or the DI regimen by a minimisation method using stage (IIIB/IV) and treatment institution. The DC regimen was consisting of docetaxel 60 mg m^{-2} on day 1 and cisplatin 80 mg m^{-2} on day 1, and the DI regimen was consisting of docetaxel 60 mg m^{-2} as a 60-min intravenous infusion on day 8 and irinotecan 60 mg m^{-2} as a 90-min intravenous infusion on days 1 and 8 (Figure 1). Both regimens were repeated every 3 weeks. Participating researchers at each institution decided the amount of fluid replacement and the type of antiemetic therapy to administer. Standard antiemetic treatment in the DC arm consisted of 5-HT_3 receptor antagonist plus 16 mg dexamethasone intravenously on day 1, before cisplatin administration. In the DI arm, standard antiemetic treatment consisted of 5-HT_3 receptor antagonist intravenously before chemotherapy administration on days 1 and 8. Patients received at least two treatment cycles, and those with a complete or partial response after two cycles had treatment continued until there was evidence of disease progression, intolerable toxicity, or patient refusal.

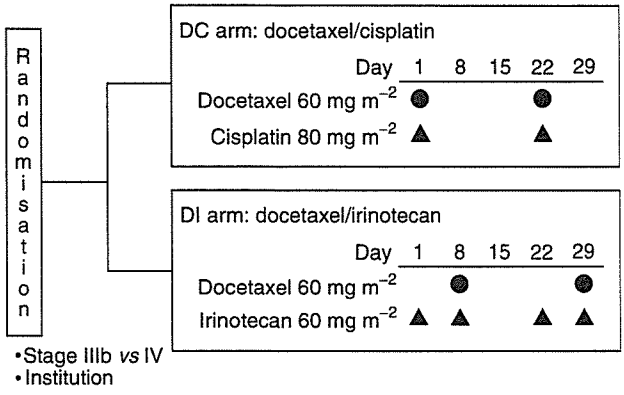

Figure 1 *Treatment schema*: after stratification by stage and institution, enrolled patients were randomly allocated to receive docetaxel plus cisplatin (DC) or docetaxel plus irinotecan (DI).

Dose modifications

Toxicity assessment was based on the National Cancer Institute–Common Toxicity Criteria version 2.0. Dose levels and treatment schedule were modified to avoid severe adverse effects. Patients receiving DI had the day-8 docetaxel and irinotecan doses postponed to day 15 if any of the following toxicities was present on day 8: leucocyte count <3000 μl^{-1}, platelet count <100 000 μl^{-1} diarrhoea consisting of bloody or watery stools, or increased to two or more diarrhoea within 24 h, abdominal pain rated mild or worse, hepatic toxicity $\geqslant$grade 3, or fever >38°C. If these toxicities occurred on day 15 after skipping the day-8 treatment, DI was stopped in that course.

Patients could receive the next treatment course only if the following criteria were met: leucocyte count $\geqslant$4000 μl^{-1}, platelet count $\geqslant$100 000 μl^{-1} AST/ALT <2.0 times the upper limit of normal, total bilirubin $\leqslant$1.5 mg dl^{-1} serum creatinine $\leqslant$ the upper limit of normal, ECOG PS$\leqslant$2, neurotoxicity $\leqslant$grade 1, no diarrhoea or oedema. However, if more than 6 weeks passed before these criteria were satisfied, the patient was removed from the study.

Dose modification criteria for each drug are shown in Table 1. If during the previous course, grade 4 leucopenia, grade 4 neutropenia lasting $\geqslant$3 days, or grade 4 thrombocytopenia had occurred, doses of all drugs were reduced by 10 mg m^{-2}. Doses of both cisplatin and docetaxel were reduced by 10 mg m^{-2} in subsequent cycles if chemotherapy induced grade $\geqslant$2 neurotoxicity. Moreover, dose of docetaxel was reduced by 10 mg m^{-2} if grade $\geqslant$2 hepatic toxicity or grade $\geqslant$3 stomatitis had occurred. Dose of cisplatin was reduced by 20 /mg/m^2 if grade $\geqslant$2 renal toxicity occurred. Dose of irinotecan was reduced by 5 mg m^{-2} if grade $\geqslant$2 hepatic toxicity had occurred and by 10 mg m^{-2} if grade $\geqslant$2 diarrhoea or cancellation of day-8 treatment had occurred.

Evaluation of response and survival

Tumour response was classified according to World Health Organization (WHO) criteria (World Health Organization, 1979). Complete response was defined as complete disappearance of all measurable and assessable disease for at least 4 weeks, Partial response was a $\geqslant$50% decrease in the sum of the products of the two IL largest perpendicular diameters of all measurable tumours lasting at least 4 weeks and without appearance of any new lesions. No change was defined as a <50% decrease or a <25% increase of tumor lesions for at least 4 weeks with no new lesions.

Table 1 Dose modification criteria

Toxicities in previous cycle	Decrease in docetaxel dose (mg/m^{-2})	Decrease in cisplatin dose (mg/m^{-2})	Decrease in -irinotecan dose (mg/m^{-2})
Grade 4 neutropenia lasting $\geqslant$3 days, leucopenia or thrombocytopenia	10	10	10
Grade $\geqslant$2 neurotoxicity	10	10	—
Grade $\geqslant$2 renal toxicity	—	20	—
Grade $\geqslant$2 hepatic toxicity	10	—	5
Grade $\geqslant$3 stomatitis	10	—	—
Grade $\geqslant$2 diarrhoea	—	—	10
Cancellation of day-8 treatment	—	—	10

Progressive disease was defined as development of new-lesions or a 25% increase in the sum of the products of the two largest perpendicular diameters of all measurable tumors. Duration of response in patients who achieved complete or partial response was measured from the start of treatment to the date of disease progression.

Statistical methods

Results of this study were evaluated to determine whether the docetaxel plus irinotecan combination warranted further assessment in a phase III trial. Thus, this study was designed to conduct two randomised phase II studies concurrently. We calculated the number of patients required for each of the two studies based on the Fleming's single-stage procedure (Fleming, 1982). In both studies, we set response rates of 40% as target activity level and 20% as the lowest level of interest with a power of 0.9 at a one-sided significance level of 0.05. As a result, a total of 100 qualified patients were to be enrolled, with 50 patients in each treatment arm. The primary objective was to estimate the response rate to both regimens, particularly to irinotecan plus docetaxel.

Overall survival and progression-free survival were analysed by the Kaplan–Meier method. The overall survival was measured from study entry to death. The progression-free survival was measured from study entry until the day of the first evidence of disease progression. If the disease had not progressed by the time of this analysis, progression-free survival was considered censored at the time of the analysis. All comparisons between patient characteristics, response rates, and toxicity incidences were performed by Pearson's χ^2 contingency table analysis.

RESULTS

Patient characteristics

From October 1998 to August 1999, 108 patients were assigned to receive DC ($n=51$) or DI ($n=57$). Baseline patient characteristics according to treatment arm are shown in Table 2. Patients were well balanced between the two treatment arms in terms of gender, age, performance status, disease stage, and histologic subtypes. There were 23% stage IIIb patients and 74% had adenocarcinoma. All patients were included in the survival evaluation, and all were assessable for antitumor efficacy and toxicity.

Treatment delivery

Patients in both treatment arms received a median of two treatment courses. Two or more courses were delivered to 72.5 and 71.9%, and four courses to 17.6 and 19.1% of patients in the DC and DI arms, respectively. Differences between arms in the number of chemotherapy courses administered were not statistically significant.

Table 2 Baseline patient characteristics

		Docetaxel/ cisplatin	Docetaxel/ irinotecan	χ^2 text
No. of patients		51	57	
Gender	Male/female	37/14	38/19	$P=0.537$
Age (years)	Median	62	60	
	Range	39–74	42–77	
PS	0/1	15/36	15/42	$P=0.830$
Histology	Adenocarcinoma	36	44	$P=0.520$
	Squamous cell carcinoma	13	9	
	Others	2	4	
Disease stage	IIIb/IV	11/40	14/43	$P=0.820$
Brain metastasis	(+)/(−)	4/47	11/46	$P=0.086$

PS = performance status.

Response to treatment and survival

There were no complete responses. In the DC arm, 19 patients had partial responses for an overall response rate of 37% (Table 3). Among DI patients, 18 had partial responses for an overall response rate of 32%. The difference in response rate between arms was not significant ($P=0.55$). Progressive disease was noted in twice as many DI (25%) than DC (12%) patients. Early deaths within 3 months of treatment initiation occurred in 10% ($n=5$) of DC and 5% ($n=3$) of DI patients. The early deaths were treatment-related (three patients, all in the DC arm) or due to disease progression (five patients).

Overall and progression-free survival curves for the two treatment arms are shown in Figures 2 and 3. The median progression-free survival time was 20 weeks (95% confidence interval: 14–25 weeks) in the DC arm *vs* 18 weeks (95% confidence interval: 12–22 weeks) in the DI arm. Median survival times, 1-year survival rates, and 2-year survival rates were 50 weeks (95% confidence interval 34–78 weeks), 47 and 25%, respectively, in the DC arm, and 46 weeks (95% confidence interval: 37–54 weeks), 40 and 18%, respectively, in the DI arm. No significant differences were noted between groups in progression-free survival ($P=0.33$) or overall survival ($P=0.50$), although there were trends toward higher 1-year and 2-year survival rates in the DC.

Table 3 Overall response to docetaxel/cisplatin (DC) or docetaxel/irinotecan (DI) in patients with stages IIIb/IV non-small-cell lung cancer

Response	DC ($n=51$) No. pts	DI ($n=67$) No. pts
Complete response	0	0
Partial response	19	18
No change	23	25
Progressive disease	6	14
NE (TRD)	3	0
Response rate	37.3%*	31.6%*
95% Confidence intervals	24.1–51.9%	19.9–45.2%

pts = patients; NE = not evaluable; TRD = treatment-related death. *$P=0.55$.

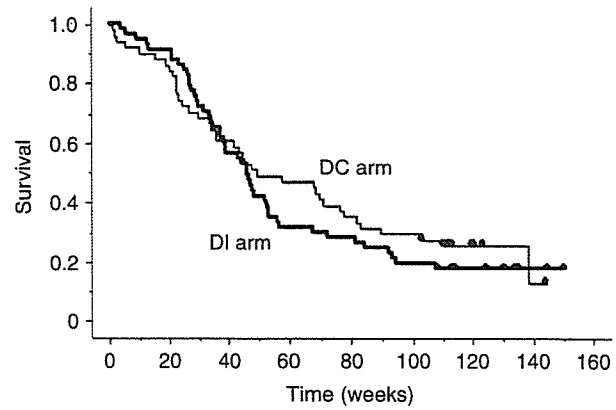

Figure 2 Overall survival according to treatment group, calculated by Kaplan–Meier method. Median survival times were 50 weeks for DC (docetaxel plus cisplatin) and 46 weeks for DI (docetaxel plus irinotecan). $P=0.50$ between treatment groups.

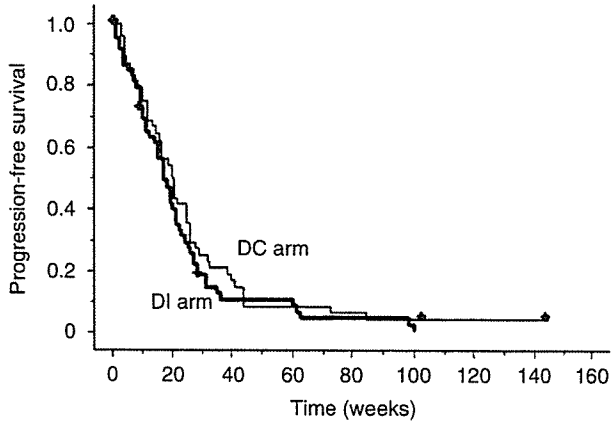

Figure 3 Progression-free survival according to treatment group, calculated by Kaplan–Meier method. Median progression-free survival times were 20 weeks for DC (docetaxel plus cisplatin) and 18 weeks for DI (docetaxel plus irinotecan). $P = 0.33$ between treatment groups.

Table 4 Haematologic toxicity: maximum toxicity grade in any course

	Docetaxel/ cisplatin (% pts)			Docetaxel/ irinotecan (% pts)		
Toxicity/grade	**2**	**3**	**4**	**2**	**3**	**4**
Leucopenia*	31	43	4	26	40	16
Neutropenia*	10	31	43	4	23	61
Anaemia	47	10	2	46	7	0
Thrombocytopenia**	10	4	0	0	0	0
Febrile neutropenia		20			28	

pts = patients. *$P<0.01$ for grade 4; **$P<0.01$ for the sum of grades 2 and 3.

Second-line chemotherapy was administered to 61 patients (24 DC and 37 DI patients). A total of 22 patients in the DI group received cisplatin-based second-line chemotherapy and five had partial responses to this treatment (overall response rate, 23%). In particular, nine patients were subsequently treated with vinorelbine containing regimen and three patients had a partial response. Only two patients in the DC group received an irinotecan-containing regimen, one of whom had a partial response. Concerning as second-line chest irradiation, 8 patients in the DC group and 13 patients the DI group received.

Toxicity

Haematologic and nonhaematologic toxicities are listed in Tables 4 and 5. Grade 4 leucopenia and neutropenia occurred in a significantly higher percentage of DI than DC patients (leucopenia 16 *vs* 4%, $P<0.01$; neutropenia 61 *vs* 43%, $P<0.01$). On the other hand, there was a higher rate of grade $\geqslant 2$ thrombocytopenia in the DC than in the DI arm (14 *vs* 0%, $P<0.01$). Rates of anaemia (decrease in haemoglobin) and febrile neutropenia were similar in both groups.

Nonhaematologic toxicities including grade $\geqslant 2$ nausea (88 *vs* 51%, $P<0.01$), vomiting (39 *vs* 14%, $P<0.01$), and renal toxicity (increased serum creatinine; 12 *vs* 2%, $P<0.01$) were significantly more prevalent in the DC than in the DI arm, respectively. On the other hand, grade $\geqslant 2$ diarrhoea occurred significantly more often in DI than in DC patients (24 *vs* 42%, $P=0.01$). Other nonhaematologic toxicities, such as hepatic toxicity and peripheral neuropathy, were mild and occurred with similar frequency in both groups.

Table 5 Nonhaematologic toxicity: maximum toxicity grade in any course

	Docetaxel/ cisplatin (% pts)			Docetaxel/ irinotecan (% pts)		
Toxicity/grade	**2**	**3**	**4**	**2**	**3**	**4**
Diarrhoea*	18	6	0	26	12	4
Nausea*	53	33	0	33	18	0
Vomiting**	33	2	4	14	0	0
Peripheral neuropathy	2	0	0	2	0	0
AST increase	8	2	2	7	0	2
ALT increase	14	4	0	9	2	2
ALP increase	8	2	0	4	0	0
Creatinine increase*	10	0	2	0	0	2

pts = patients; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase. *$P<0.01$ for the sum of grades 2, 3, and 4; **$P=0.01$ for the sum of grades 2, 3, and 4.

There were three treatment-related deaths in the DC arm, which were due to febrile neutropenia and sepsis (one of these patients also developed perforation of the oesophagus). No treatment-related deaths occurred in the DI arm. The difference in incidence of treatment-related deaths was not significant.

DISCUSSION

Results of this randomised phase II study showed that the doublet chemotherapy regimens DC and DI had comparable activity in patients with advanced NSCLC. A primary goal of this study was to determine whether the DI combination should be studied in the phase III setting. Although there were no differences between DI and DC – a third-generation cisplatin-containing regimen – in overall and progression-free survival, patients who received DI tended to have lower 1-year and 2-year survival rates. Furthermore, overall toxicity was not reduced in the DI arm compared with the DC arm. Leucopenia and neutropenia were the major toxicities in both groups. As expected, emesis and renal toxicity were more prevalent in patients receiving DC, and diarrhoea occurred more frequently with DI.

Cisplatin has played a prominent role in the treatment of NSCLC, despite a relatively unimpressive single-agent response rate and a relatively severe toxicity profile. In 1995, the Non-Small Cell Lung Cancer Collaborative Group published a pivotal meta-analysis of chemotherapy in lung cancer and demonstrated the advantage of cisplatin-based regimens over best supportive care (Non-Small Cell Lung Cancer Collaborative Group, 1995). In the 1990s, third-generation chemotherapeutic agents, including paclitaxel, docetaxel, vinorelbine, gemcitabine and irinotecan, were shown to have higher response rates often coupled with fewer adverse effects (no renal toxicity, no massive dehydration, less emesis, etc.) than cisplatin. For example, single-agent paclitaxel (Ranson *et al*, 2000), docetaxel (Roszkowski *et al*, 2000), or vinorelbine (The Elderly Lung Cancer Vinorelbine Italian Study Group, 1999) significantly improved survival compared with best supportive care in patients with advanced NSCLC. Studies of single-agent gemcitabine (Perng *et al*, 1997) or irinotecan (Negoro *et al*, 2003) demonstrated a survival benefit comparable to that of second-generation chemotherapy regimens (cisplatin plus vindesine, cisplatin plus etoposide). Based on the above results, we thought that combination chemotherapy consisting of third-generation agents might improve outcome for patients with advanced NSCLC.

Only one published study compared cisplatin-based and noncisplatin-based regimens that included third-generation

agents. Georgoulias *et al* (2001) conducted a randomised study of cisplatin plus docetaxel (CD) *vs* gemcitabine plus docetaxel (GD) in 441 advanced NSCLC patients. The noncisplatin regimen provided a comparable response rate (CD 32.4%, GD 30.2%) and median survival time (CD 10 months, GD 9.5 months) but with less toxicity. The authors stated that the non-cisplatin GD regimen would likely be more acceptable to patients based on convenience of administration. However, several randomized trials reported at recent international meetings showed slightly shorter survival times with noncisplatin compared with cisplatin-based combinations. Preliminary results of the EORTC-Lung Cancer Group phase III study of cisplatin plus paclitaxel *vs* cisplatin plus gemcitabine *vs* paclitaxel plus gemcitabine in 480 patients with advanced NSCLC revealed superior overall survival and progression-free survival with the cisplatin-based regimens (Van Meerbeeck *et al*, 2001). Moreover, in a recent Italian–Canadian intergroup study of 501 patients comparing gemcitabine plus vinorelbine with cisplatin plus vinorelbine or gemcitabine, the noncisplatin regimen provided only short-term and sporadic advantages in some quality-of-life components, but there were no significant differences in overall and progression-free survival (Gridelli *et al*, 2002).

The best known noncisplatin platinum-based chemotherapy regimen is the paclitaxel plus carboplatin doublet. A Southwest Oncology Group study compared vinorelbine plus cisplatin with paclitaxel plus carboplatin. No differences in the overall survival or quality of life were noted between the two treatment groups, but toxicity rates were significantly lower in patients who received paclitaxel plus carboplatin (Chen *et al*, 2002). Results of a recent ECOG randomised phase III trial evaluating four platinum-based chemotherapy regimens showed no significant differences in the overall survival, while the paclitaxel plus carboplatin combination was less toxic than cisplatin-based chemotherapy (Schiller *et al*, 2002). Based on these findings, the paclitaxel plus carboplatin regimen is considered a standard therapy for previously untreated patients with advanced NSCLC, with activity comparable to that of cisplatin-based regimens and better tolerability.

The utility of doublet regimens containing third-generation chemotherapeutic agents for advanced NSCLC thus needs to be evaluated against the paclitaxel plus carboplatin combination, and several such studies were reported or are ongoing. The Hellenic Cooperative Oncology Group is conducting a phase III randomised study of paclitaxel plus carboplatin *vs* paclitaxel plus gemcitabine, and final results indicate comparable activity, toxicity and total cost of the two regimens in patients with inoperable NSCLC (Kosmidis *et al*, 2002). The Taiwan group conducted a similar study and found that paclitaxel plus carboplatin and paclitaxel plus gemcitabine had similar efficacy in the treatment of NSCLC, but that paclitaxel plus carboplatin was more cost-effective (Chen *et al*, 2002).

As mentioned in the introductory paragraphs, we conducted a phase I study of docetaxel plus irinotecan (DI) in patients with advanced NSCLC, and had a promising response rate of 48% and median survival time of 48 weeks (Masuda *et al*, 2000). Although we recommended docetaxel 50 mg m^{-2} on day 1 plus irinotecan 50 mg m^{-2} on days 1, 8, and 15 in the phase I study, more than half of patients could not receive irinotecan on day 15 because of haematologic toxicities. Accordingly, the day-15 irinotecan dose was omitted and the day-2 docetaxel dose moved to day 8 and increased from 50 to 60 mg m^{-2} in this randomised phase II trial.

It has been reported that second-line chemotherapy compared with best supportive care may increase the overall survival in patients with advanced NSCLC, and more studies in this regard are needed. In a recent study in which patients received cisplatin-based chemotherapy followed by docetaxel or supportive care alone, the median survival was significantly longer in the docetaxel-treated patients (Shepherd *et al*, 2000). In our study, 52% of patients were treated with second-line chemotherapy. Of these, 19 (33%) DI patients received cisplatin-based second-line chemotherapy, five of whom (26%) responded. Thus, cisplatin-based chemotherapy is capable of exerting antitumour activity in patients who have relapsed after having received noncisplatin-containing regimens.

Only two patients in the DC group received an irinotecan-containing regimen, one of whom had a partial response. As there were only two patients, we cannot judge whether irinotecan-containing regimen is effective for the patients after having received cisplatin-containing regimen.

In conclusion, docetaxel plus irinotecan combinations may be reasonable treatment options for NSCLC patients who cannot tolerate cisplatin. However, as there was no significant difference in the overall survival and no reduction in overall toxicity, DI has not improved on results obtained with DC. Thus, we will not select docetaxel/irinotecan as the experimental regimen in the next phase III study of first-line treatment of advanced NSCLC.

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Phase I–II study of irinotecan (CPT-11) plus nedaplatin (254-S) with recombinant human granulocyte colony-stimulating factor support in patients with advanced or recurrent cervical cancer

Clinical

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Combination chemotherapy with irinotecan (CPT-11) and platinum compounds is effective for treating cervical cancer. Nedaplatin (254-S) is a new cisplatin analogue that achieves a high response rate (53%) in patients with primary cervical cancer. We performed a phase I–II study of combination chemotherapy with CPT-11 plus 254-S for advanced or recurrent cervical cancer. The inclusion criteria were stage IV disease or recurrence. CPT-11 and 254-S were administered intravenously on day 1, while rhG-CSF (50 μg) was given on days 3–12. This regimen was repeated after 4 weeks. Dose escalation was carried out in tandem (CPT-11/254-S: 50/70, 50/80, and 60/80 mg m^{-2}). A total of 27 patients (stage IV = seven, recurrence = 20) were enrolled. The phase I study enrolled eight patients. At dose levels 1 and 2, no dose-limiting toxicities were observed. At dose level 3, the first two patients developed DLTs. The maximum tolerated dose of CPT-11 and 254-S was 60 and 80 mg m^{-2}, respectively, and the recommended doses were 50 and 80 mg m^{-2}. Grade 3/4 haematologic toxicity occurred in 67% in phase II study, but there were no grade 3 nonhaematologic toxicities except fot nausea or lethargy. In all 27 patients, there were two complete responses (7%) and 14 Partial responses (52%), for an overall response rate of 59% (95% confidence interval: 39–78%). Among the 12 responders with recurrent disease, the median time to progression and median survival were 161 days (range: 61–711 days) and 415 days (range: 74–801 days). This new regimen is promising for cervical cancer.

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Cancer of the uterine cervix is one of the most common malignancies among women and remains the leading female malignancy in developing countries (Thigpen *et al*, 1994). In 1999, about 6500 patients developed cervical cancer in Japan (Sekiya, 2002). In the USA, approximately 13 000 patients developed cervical cancer in 2000 (Robert *et al*, 2001). This tumour is usually radiosensitive and highly curable at an early stage. For patients with stage IV disease or with recurrence after radiotherapy, however, the prognosis is still dismal (Thigpen *et al*, 1995). In such patients, most of the active chemotherapy agents achieve overall response rates of 20–35% when given as monotherapy, with a median response duration of 3–6 months and a survival time of 5–9 months (Thigpen *et al*, 1981; McGuire *et al*, 1996). Many combination chemotherapy regimens have also been explored during the last two decades. High response rates have been obtained in some studies, but it is difficult to assess the relative merits of the various regimens because of differences in patient selection (Buxton *et al*, 1989; Papadimitriou *et al*, 1999).

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Nedaplatin (254-S) is a new cisplatin analogue with the same carrier ligands of ammine as cisplatin but has a different leaving group, a five-membered ring structure in which glycolate is bound to the platinum ion as a bidentate ligand (Figure 1). This product has an approximately 10 times higher water solubility than cisplatin and, unlike cisplatin, shows very limited binding to plasma protein (Sugeno *et al*, 1991). The plasma concentration profile of unbound platinum after 254-S infusion has been reported to be similar to that of total platinum, and the protein binding of 254-S to be lower than that of CDDP (Ota *et al*, 1994). Nedaplatin has a short elimination half-life and a phamacokinetic profile similar to that of CBDCA (Sasaki *et al*, 1989). Nephrotoxicity and gastrointestinal toxicity often limits the clinical use of antitumour agents such as CDDP, but 254-S causes less nephrotoxicity and gastrointestinal toxicity than CDDP, although its haematological toxicity can be a limiting factor at high dosage, as found with CBDCA (Kameyama *et al*, 1990; Ota *et al*, 1992; Suzumura *et al*, 1989). The dose-limiting toxicity (DLT) of 254-S is myelosuppression, especially thrombocytopenia. In the Phase II studies, 254-S monotherapy generated a 46.3% response rate against cervical cancer, especially 53.1% in patients with squamous cell carcinoma (Kato *et al*, 1992).

Irinotecan hydrochloride (CPT-11) is a semisynthetic derivative of camptothecin, an alkaloid contained in plants such as *Camptotheca acuminate* (Nitta *et al*, 1987). Irinotecan inhibits

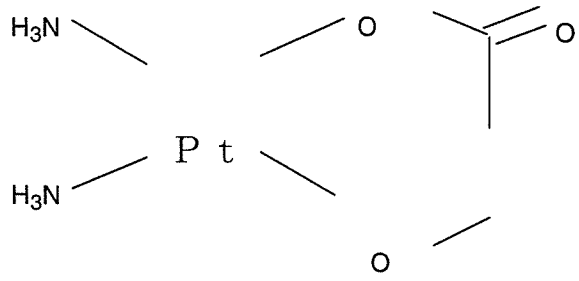

Figure 1 Structure of nedaplatin.

the activity of DNA topoisomerase I, which is necessary for replication of DNA. Several phase II studies have shown that CPT-11 is active against cervical cancer, and activity of CPT-11 monotherapy against recurrent or refractory cervical cancer was revealed in phase II studies performed by the Japan CPT-11 Study Group (24% response rate) and the MD Anderson Cancer Center (21% response rate) (Takeuchi *et al*, 1991; Verschraegen *et al*, 1997). However, a pilot study of CPT-11 in patients with platinum-resistant squamous cell carcinoma failed to show any tumour response (Ivrin *et al*, 1998).

Kanazawa *et al* (2001) reported that the combination of 254-S and CPT-11 showed marked synergistic activity against SBC-3 and PC-14 lung cancer cell lines. This synergistic effect was dependent on the treatment schedule and was produced by concurrent exposure to 254-S and CPT-11. They analysed the mechanism of synergy and demonstrated that the topoisomerase I inhibitory effect of CPT-11 was enhanced 10-fold in the presence of 254-S. Based on these findings, the combination of 254-S and CPT-11 may well be clinically useful. Machida *et al* (2003) performed a phase I study of chemotherapy using CPT-11 plus 254-S for advanced or recurrent cervical cancer. They concluded that the DLT was neutropenia, and their recommended doses of CPT-11 (days 1, 8, and 15) and 254-S (day 1) were 50 and 60 mg m^{-2}, respectively. Recombinant human granulocyte colony-stimulating factor (rhG-CSF) can activate haematopoiesis and thus prevent chemotherapy-induced neutropenia or accelerate recovery from this complication, allowing patients to receive full per protocol doses of anticancer drugs. The G-CSF was expected to increase the dose intensity of combination chemotherapy with 254-S plus CPT-11.

Accordingly, we performed a phase I–II study of CPT-11 plus 254-S with rhG-CSF support in patients with advanced or recurrent cervical cancer.

MATERIALS AND METHODS

Patient selection

The chief eligibility criteria were as follows: (1) histologically proven cervical cancer (stage IV or recurrent disease), (2) at least one measurable tumour lesion documented radiographically, and (3) an interval >4 weeks between the end of previous treatment (including radiotherapy) and this study. Other eligibility criteria were an age <75 years, performance status (WHO) ⩽2 and life expectancy >3 months. Patients were also required to meet all of the following laboratory criteria: WBC count ⩾3000 mm^{-3} or absolute neutrophil count ⩾1500 mm^{-3}, platelet count ⩾100 000 mm^{-3}, serum transaminases ⩽60 IU ml^{-1}, total bilirubin ⩽1.5 mg dl^{-1}, serum creatinine ⩽1.5 mg dl^{-1}, and blood urea nitrogen ⩽20 mg dl^{-1}. The nature and purpose of the study were fully explained to each patient and all patients gave written informed consent. The study was also approved by the institutional review board of Osaka City General Hospital. Patients were excluded for any of the following conditions: other cancer (metachronous or synchronous); concurrent infection; pre-existing diarrhoea; intestinal paralysis or obstruction; interstitial pneumonia or pulmonary fibrosis; massive ascites; pleural effusion; uncontrolled diabetes; or a history of severe drug hypersensitivity.

Table 1 Dose escalation schedule

Dose level	Irinotecan (mg m^{-2})	Nedaplatin (mg m^{-2})
1	50	70
2	50	80
3	60	80

Treatment schedule

A 90-min intravenous infusion of CPT-11 (in 500 ml of 0.9% normal saline) was given on day 1, after which 254-S (in 500 ml of 0.9% normal saline) was also administered intravenously over 90 min. Then, patients received intravenous hydration with 1000 ml of 0.9% saline or 5% dextrose. All patients were treated with a 5-HT3 receptor antagonist before administration of the anticancer drugs. Recombinant human granulocyte colony-stimulating factor (50 μg) was given on days 3–12. Before starting the next cycle, it was confirmed that the leukocyte was ⩾3000 μl^{-1}, the neutrophil count was ⩾1500 μl^{-1}, and the platelet count was ⩾100 000 μl^{-1}, with no diarrhoea, and hepatorenal function meeting the eligibility criteria. Treatment was repeated every 4 weeks for at least two cycles, unless the disease progressed. Treatment was, generally, also stopped if the response was defined as no change (NC) after two cycles. The doses of the two anticancer agents were escalated in tandem, as shown in Table 1. Recombinant human granulocyte colony-stimulating factor was also administered when grade 4 neutropenia or grade 3 neutropenia associated with infection occurred. Additionally, if the leukocyte count was <1000 μl^{-1}, neutrophil count was <500 μl^{-1}, or platelet count was <25 000 μl^{-1} during any cycle, the doses of CPT-11 and 254-S were reduced by one level for the next cycle. Physical examination, complete blood count, and biochemistry tests were carried out weekly.

Evaluation of response and toxicity

Tumour response was evaluated according to World Health Organization (WHO) criteria (WHO, 1979). Tumours were measured using contrast-enhanced computed tomography (CT) after two cycles of chemotherapy and also 1 month after the end of the treatment. Computed tomography scans were subsequently performed every 3 months for 2 years. The response was assessed from the product of the two largest perpendicular diameters using the following criteria: complete response (CR) was defined as the disappearance of all detectable lesions with no new lesions for at least 4 weeks; partial response (PR) was defined as ⩾50% reduction of the sum of the products of measurable lesions for at least 4 weeks. Progressive disease (PD) was defined as a ⩾25% increase in the sum of the products of all measurable lesions, reappearance of any lesion that had disappeared, or appearance of a new lesion. No change was defined as any outcome that did not qualify as response or progression. Measurements were performed by an experienced radiologist who was blinded to patient information. Patients were considered evaluable for response if they received at least one full cycle of per protocol therapy.

Toxicity was evaluated by the Japan Clinical Oncology Group (JCOG) criteria (Tobina *et al*, 1993). Complete blood counts, biochemistry tests, and liver function tests were performed weekly.

Patients were considered evaluable for toxicity if they received at least one full cycle according to the protocol. Dose-limiting toxicity was defined as grade 4 haematologic toxicity (a leukocyte count $<1000\,\mu l^{-1}$, neutrophil count $<500\,\mu l^{-1}$, or platelet count $<25\,000\,\mu l^{-1}$), or grades 3–4 nonhaematologic toxicity (except for alopecia, nausea, and vomiting) or failure to recover sufficiently to start the second cycle within 6 weeks. At least three assessable patients were treated at each dose level. If none of these three patients experienced DLT, then the next dose level was started. If one patient developed DLT, the cohort was expanded to six patients. The maximum tolerated dose (MTD) was defined as the dose level at which at least two out of three patients or three out of six patients experienced DLT. The recommended dose (RD) of 254-S and CPT-11 for the subsequent phase II study was set at one level below the MTD.

Statistical analysis

When the number of subjects required for a 95% confidence interval (95% CI) of $\pm 20\%$ was calculated by setting the expected response rate as 35%, it was 22 subjects. Therefore, the target number of subjects for this study was set as 22. Primary statistical analysis consisted of estimation of the complete and partial response rates. The response rate was calculated as the percentage of complete plus partial responders relative to the total number of assessable patients and 95% CIs for the response were computed using the binomial distribution function.

RESULTS

Patient characteristics

A total of 27 patients were enrolled in this study between 10 January 1998 and 1 March 2003. Four patients were in stage IVA, three patients were in stage IVB, and 20 patients had recurrent cancer. Among those recurrent 20 patients, the duration from primary therapy to recurrence was <1 year for 10 patients, from $\geqslant 1$ to <2 years for seven patients, and >2 years for three patients. Their median age was 54 years (range: 32–67 years). In all, 22 patients had a PS of 0, four had a PS of 1, and one had a PS of 2. A total of 20 patients had squamous cell carcinoma, four had adenosquamous cell carcinoma, and three had adenocarcinoma. Seven patients had no prior therapy, two had received chemoradiotherapy, five had undergone surgery, and 13 had received both surgery and chemoradiation. The chemoradiotherapy consisted of radiotherapy for whole pelivis and intravenous weekly CDDP treatment ($30\,mg\,m^{-2}\,week^{-1}$) with or without brachytherapy. The tumour was located in the pelvic cavity in 11 cases, lung in nine cases, liver in five cases, paraaortic lymph nodes in four cases, and Virchow's node in one case. All patients were assessable for toxicity and response. A total of 71 cycles of therapy were administered. The clinical features of the patients are summarised in Table 2.

Toxicity

Phase I study The phase I study enrolled eight patients. At dose levels 1 and 2, no DLTs were observed. At dose level 1, three patients developed grade 3 neutropenia, while one out of three patients had grade 3 neutropenia at dose level 2. At dose level 2, one out of three patients only received one course because of PD. At dose level three, the first two patients developed grade 4 neutropenia and one of them had febrile neutropenia for 4 days. Both received rhG-CSF and one of them also received intravenous antibiotics. None of the patients experienced nonhaematologic DLTs. In five cases, treatment could be performed every 4 weeks, but treatment delay occurred in two cases (3 days and 7 days). Therefore, the MTD was set as 60 and $80\,mg\,m^{-2}$ for CPT-11 and 254-S, respectively, and the doses for the phase II study were set at 50 and $80\,mg\,m^{-2}$. Toxicities are summarised in Tables 3 and 4.

Phase II study A total of 22 patients, including three patients from the phase I study, were registered for the phase II study. In 7

Table 2 Characteristics of the eligible patients ($n=27$)

Characteristic	n
Age (years)	
Median	54
Range	32–67
WHO PS	
0	22
1	4
2	1
FIGO stage	
IVA	4
IVB	3
Recurrent	20
Site of recurrent	
Inside radiation field	5
Outside radiation field	22
Histology	
Squamous cell carcinoma	20
Adenosquamous cell carcinoma	4
Adenocarcinoma	3
Prior therapy	
None	7
Chemoradiation	2
Surgery	5
Surgery plus chemoradiation	13

Table 3 Haematologic toxicity

	Leukopenia				Neutropenia				Anemia			Thrombocytopenia				
Dose level	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G1**	**G2**	**G3**	**G4**	**Grade 3/4 toxicity (%)**
Phase I																
1 ($n=3$)	0	0	3	0	0	1	2	0	0	1	1	1	0	0	0	100
2 ($n=3$)	0	2	1	0	0	2	1	0	1	1	0	0	0	0	0	33
3 ($n=2$)	0	0	1	1	0	0	0	2	0	0	2	0	0	1	1	100
Phase II																
2 (cycles = 50)[a]	6	19	18	1	9	9	22	6	17	17	10	4	8	4	1	62[a]
1 (cycles = 8)	0	2	5	1	0	1	3	4	1	2	5	1	2	2	1	100
Total (cycles = 58)	6	21	23	2	9	10	25	10	18	19	15	5	10	6	2	67

[a]Three patients were from the phase I study.

Table 4 Nonhaematologic toxicity

	Nausea				Diarrhoea				Haematouria				Hepatotoxicity				alopecia		mucocitis				lethargy			
Dose level	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**
Phase I																										
1 ($n=3$)	2	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0	2	1	0	0	0	0	2	1	0	0
2 ($n=3$)	3	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	2	1	1	0	0	0	3	0	0	0
3 ($n=2$)	1	0	1	0	0	1	0	0	0	1	0	0	0	0	0	0	1	1	1	0	0	0	0	1	1	0
Phase II																										
2 (cycles = 50)[a]	30	12	4	0	12	7	0	0	5	0	0	0	12	0	0	0	17	8	5	0	0	0	24	7	0	0
1 (cycles = 8)	6	2	0	0	3	0	0	0	1	0	0	0	1	0	0	0	2	3	1	0	0	0	8	0	0	0
Total (cycles = 58)	36	14	4	0	15	7	0	0	6	0	0	0	13	0	0	0	19	11	6	0	0	0	32	7	0	0

[a]Three patients were from the phase I study.

of 22 patients, grade 4 neutropenia was observed and for these seven patients, the doses of CPT-11 and 254-S were reduced by one level for the next cycle. For phase II study, 50 cycles were administered at dose level 2 and eight cycles were administered at dose level 1. Finally, a total of 58 cycles were administered, with a median of two cycles per person (range: 1–6 cycles). Haematologic toxicities are summarised in Table 3. Grade 3 or 4 leukopenia, grade 3 or 4 neutropenia, grade 3 anemia, and grade 3 or 4 thrombocytopenia occurred in 43% (25 out of 58), 60% (35 out of 58), 26% (15 out of 58), and 14% (8 out of 58) of all cycles, respectively. The seven patients who had grade 4 neutropenia recovered after short-term therapy with rhG-CSF (median: 4 days; range: 3–9 days), and none of them developed febrile neutropenia. The median leukocyte count nadir occurred on day 16 (range: days 12–22). No patient required transfusion, including platelets or red blood cells. Nonhaematologoic toxicities are summarised in Table 4. There were no severe nonhaematologic toxicities. Only two patients received one cycle of chemotherapy because of PD. Treatment delays occurred in 12 patients (median: 7 days; range: 3–12 days). Occurrence of toxicity, including haematologic and nonhaematologic toxicity, did not appear to be associated with the cumulative dose.

Response

At dose level 1, one out of three patients achieved a clinical response, but there were no responders at dose level 3. In the phase II study ($n=22$), there were two CRs (9%) and 13 PRs (59%), for an overall response rate of 68% (95% CI: 49–84%).

In all 27 patients, there were two CRs (7%) and 14 PRs (52%), for an overall response rate of 59% (95% CI: 39–78%). Complete response occurred in patients with lung and Virchow's node metastasis as the measurable target lesions. Nine patients had NC (33%) and two patients had PD (7%) (Table 5). Among the 12 responders with recurrent disease, the median time to progression and median survival were 161 days (range: 61–711 days) and 415 days (range: 74–801 days). In one CR case, recurrence occurred at 534 days and the patient is now alive with disease at 801 days. Another CR case is now alive without disease at 711 days. In all, 27 cases, the median survival was 394 days (61–801 days).

Table 6 shows the responses stratified according to various clinical factors in all cases. The response rate was 57% (4 out of 7) and 60% (12 out of 20) for primary and recurrent cancer, respectively. The response rate was 53% (8 out of 15) and 67% (8 out of 12) for patients with and without prior treatment except for surgery, respectively. Among 22 patients with diseases outside the radiation field, 14 (two CRs and 12 PRs) achieved a clinical response (64%). Among five patients with disease inside the radiation field, two achieved a clinical response (PR: 40%). In the 10 patients less than 50 years old, the response rate was 80%, while it was 47% in the 17 patients more than 50 years old. After chemotherapy, three out of four stage IVA patients received surgery plus chemoradiation and one received chemoradiation alone, and two out of three stage IVB patients received chemoradiotherapy and one received radiotherapy. Among the remaining 20 recurrent patients, one patient received chemoradiation, two patients received radiotherapy, and two had further chemotherapy after CPT-11 plus 254-S. When the response of measurable lesions was analysed, it was seven of 11 (64%) at the primary site, four of nine (44%) for lung, three of five (60%) for liver, and four of five (80%) for lymph nodes.

Table 5 Outcome of treatment

	Response				
Dose level	**CR**	**PR**	**NC**	**PD**	**Total**
1 ($n=3$)	0	1	2	0	1/3
2 ($n=22$)	2	13	5	2	15/22
3 ($n=2$)	0	0	2	0	0/2
Total ($n=27$)	2	14	9	2	16/27

CR = Complete response; PR = Partial response; NC = No change; PD = Progressive disease.

DISCUSSION

We conducted a phase I–II study of combination chemotherapy with CPT-11 plus 254-S and rhG-CSF support for advanced or recurrent cervical cancer. At dose level 3 (CPT-11/254-S: 60/80 mg m^{-2}), the first two patients developed grade 4 neutropenia and one of them had febrile neutropenia for 4 days. Accordingly, we defined the MTD for CPT-11/254-S as 60/80 mg m^{-2} and the RD for the phase II study as 50/80 mg m^{-2}. In the phase II study ($n=22$), 73% of the 22 patients experienced grade 3 or 4 neutropenia, although the seven patients who had grade 4 neutropenia recovered with rhG-CSF support and a good clinical response rate (68%) was achieved. Grade 3 or 4 neutropenia occurred in 60% (35 out of 58) of all cycles in phase II study, respectively. In all 27 patients, there were two CRs (7%) and 14 PRs (52%), for an overall response rate of 59% (95% CI: 39–78%).

Machida *et al* (2003) conducted a phase I study of this therapy for advanced or recurrent cervical cancer and concluded that (1) the DLT was neutropenia, 2) the MTD of CPT-11 (days 1, 8, and 15)/254-S (day 1) was 60/60 mg m^{-2}, and (3) the RD was 50/60 mg m^{-2}. Their data are concordant with ours. However, Oshita *et al* (2003) performed a phase I–II study in patients with