Original article

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Randomized phase II study of cisplatin, irinotecan and etoposide combinations administered weekly or every 4 weeks for extensive small-cell lung cancer (JCOG9902-DI)

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Background: The purpose of this study was to evaluate the toxicity and antitumor effect of cisplatin, irinotecan and etoposide combinations on two schedules, arms A and B, for previously untreated extensive small-cell lung cancer (E-SCLC), and to select the right arm for phase III trials.

Patients and methods: Sixty patients were randomized to receive either arm A (cisplatin 25 mg/m^2 day 1, weekly for 9 weeks, irinotecan 90 mg/m^2 day 1, on weeks 1, 3, 5, 7 and 9, and etoposide 60 mg/m^2 days 1–3, on weeks 2, 4, 6, 8), or arm B (cisplatin 60 mg/m^2 day 1, irinotecan 60 mg/m^2 days 1, 8, 15, and etoposide 50 mg/m^2 days 1–3, every 4 weeks for four cycles). Prophylactic granulocyte colony-stimulating factor support was provided in both arms.

Results: Full cycles were delivered to 73% and 70% of patients in arms A and B, respectively. Incidences of grade 3–4 neutropenia, anemia, thrombocytopenia, infection and diarrhea were 57, 43, 27, 7 and 7%, respectively, in arm A, and 87, 47, 10, 13 and 10%, respectively, in arm B. A treatment-related death developed in one patient in arm A. Complete and partial response rates were 7% and 77%, respectively, in arm A, and 17% and 60%, respectively, in arm B. Median survival time was 8.9 months in arm A, and 12.9 months in arm B.

Conclusions: Arm B showed a promising complete response rate and median survival with acceptable toxicity in patients with E-SCLC, and should be selected for the investigational arm in phase III trials.

Key words: cisplatin, etoposide, irinotecan, randomized phase II, small-cell lung cancer

Introduction

Small-cell lung cancer (SCLC), which accounts for approximately 12% of all malignant pulmonary tumors in Japan [1], pursues an aggressive clinical course with rapid growth and early widespread metastases. Whereas chemotherapy combined with thoracic radiotherapy yields a high response rate and significant prolongation of survival in patients with limited disease, treatment of extensive disease remains palliative, and long-term survivors beyond 2 years are extremely rare [2]. A combination of cisplatin and etoposide (PE) has been the standard treatment, with response rates ranging from 60% to 90% and median survival times (MSTs) from 8 to 11 months in this patient population [3–5].

Irinotecan, a water-soluble camptothecin derivative, has been shown to exhibit excellent antitumor activity against SCLC in monotherapy and in combination with cisplatin [6, 7].

A previous phase III trial of the PE regimen versus a combination of cisplatin and irinotecan (PI) in patients with extensive SCLC showed that the PI regimen produced an MST of 12.8 months and a 2-year survival of 21%, which were significantly better than the results with the PE regimen [8]. However, since etoposide is still considered one of the key drugs for the treatment of SCLC, a combination of these three drugs, cisplatin, irinotecan and etoposide (PIE), seemed to be a promising strategy for advanced SCLC. We previously determined the recommended doses of the PIE regimens for two schedules, weekly and every 4 weeks, independently [9, 10]. In this phase II study, we evaluated the two PIE regimens.

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Patients and methods

Protocol objectives

The objectives of this study were: (i) to evaluate the toxicity and antitumor effect of PIE combination regimens administered weekly (arm A) and every 4 weeks (arm B) to patients with extensive stage SCLC; and (ii) to select the right arm for subsequent phase III trials. The primary endpoint was the response rate, with MST and toxicity profiles as the secondary endpoints.

Patient selection

Patients were enrolled in this study if they met the following criteria: (i) a histological or cytological diagnosis of SCLC; (ii) no prior treatment; (iii) measurable disease; (iv) extensive disease, defined as having distant metastasis or contralateral hilar lymph node metastasis; (v) performance status of 0 to 2 on the Eastern Cooperative Oncology Group (ECOG) scale; (vi) predicted life expectancy of ≥3 months; (vii) age between 20 and 70 years; (viii) adequate organ function as documented by a WBC count ≥4.0 × 10^9/l, neutrophil count ≥2.0 × 10^9/l, hemoglobin ≥9.5 g/dl, platelet count ≥100 × 10^9/l, total serum bilirubin ≤1.5 mg/dl, hepatic transaminases ≤100 IU/l, serum creatinine ≤1.2 mg/dl, creatinine clearance ≥60 ml/min, and PaO_2 ≥60 Torr; and (ix) written informed consent.

Patients were not eligible for the study if they had any of the following: (i) uncontrollable pleural, pericardial effusion or ascites; (ii) symptomatic brain metastasis; (iii) active infection; (iv) contraindications for the use of irinotecan, including diarrhea, ileus, interstitial pneumonitis and lung fibrosis; (v) synchronous active malignancies; (vi) serious concomitant medical illness, including severe heart disease, uncontrollable diabetes mellitus or hypertension; or (vii) pregnancy or breast feeding.

Pretreatment evaluation

Pretreatment assessment included a medical history, physical examination, complete blood cell count, differential counts, routine chemistry measurements, creatinine clearance, blood gas analysis, electrocardiogram, chest X-ray, chest computed tomography (CT) scan, brain CT scan or magnetic resonance imaging, abdominal CT scan or ultrasound sonography, and if patients complained of symptoms suggesting bone metastasis, a radionuclide bone scan.

Treatment schedule

In arm A, cisplatin 25 mg/m^2 was administered intravenously (i.v.) over 60 min on day 1 and at 1-week intervals for 9 weeks; irinotecan 90 mg/m^2 was administered i.v. over 90 min on day 1 on weeks 1, 3, 5, 7 and 9; and etoposide 60 mg/m^2 was administered i.v. over 60 min on days 1–3 of weeks 2, 4, 6 and 8. Hydration (2000 ml) and $5HT_3$-antagonist were given on day 1, followed by an additional infusion if indicated. Granulocyte colony-stimulating factor (G-CSF) was administered prophylactically on days when the cytotoxic drugs were not given, unless the WBC count exceeded 10.0 × 10^9/l (Figure 1). In arm B, cisplatin 60 mg/m^2 was administered i.v. over 60 min on day 1; irinotecan 60 mg/m^2 was administered i.v. over 90 min on days 1, 8 and 15; and etoposide 50 mg/m^2 was administered i.v. over 60 min on days 1–3. Hydration (2500 ml) and $5HT_3$-antagonist were given on day 1, followed by an additional infusion if indicated. G-CSF was subcutaneously injected from day 5 to the day when the WBC count exceeded 10.0 × 10^9/l. This treatment was repeated every 4 weeks for a total of four cycles (Figure 1).

Toxicity assessment and treatment modification

During the course of treatment, complete blood cell counts and differential counts were analyzed twice a week, and routine chemistry measurements and

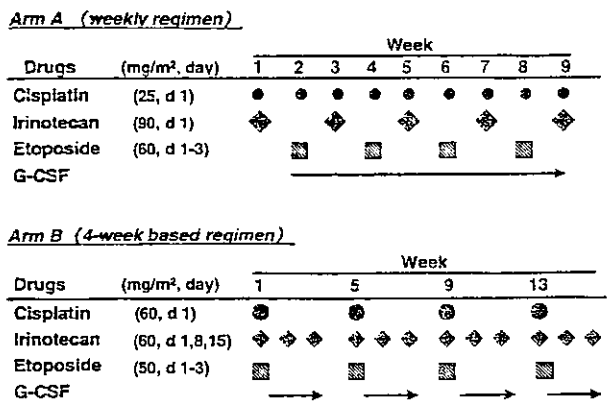

Figure 1. Treatment schema of arm A (weekly regimen) and arm B (4-week based regimen).

a chest X-ray were performed once a week. Toxicity was graded according to the toxicity criteria of the Japan Clinical Oncology Group (JCOG), a modified version of the National Cancer Institutes-Common Toxicity Criteria (NCI-CTC) issued in 1991 [11]. In arm A, subsequent cycles of chemotherapy were delayed for 1 week if one of the following toxicities was noted on day 1: WBC count <2.0 × 10^9/l, platelet count <75 × 10^9/l, serum creatinine level ≥2.0 mg/dl, elevated hepatic transaminase level or total serum bilirubin grade ≥2, fever ≥38°C, diarrhea grade 1–3, presence of ileus, massive pleural effusion or ascites, or a performance status of three or greater. The dose of irinotecan was reduced by 25% in all subsequent cycles if grade 2–3 diarrhea was noted. In arm B, irinotecan administration was omitted if one of the following toxicities was noted on day 8 or 15: WBC count <2.0 × 10^9/l, platelet count <75 × 10^9/l, elevated hepatic transaminase level or total serum bilirubin grade ≥2, fever ≥38°C, grade 1–3 diarrhea, presence of ileus, massive pleural effusion or ascites, or a performance status of three or greater. The subsequent cycle of chemotherapy was delayed if one of the following toxicities was noted on day 1: a WBC count <3.0 × 10^9/l, a platelet count <100 × 10^9/l, a serum creatinine level ≥1.6 mg/dl, an elevated hepatic transaminase level or total serum bilirubin grade ≥2, fever ≥38°C, diarrhea of grade 1–3, presence of ileus, massive pleural effusion or ascites, or a performance status of three or greater. If grade 4 leukopenia, grade 4 neutropenia lasting over 7 days, neutropenic fever or grade 4 thrombocytopenia was noted, the doses of irinotecan and etoposide were reduced by 25% in all subsequent cycles, and if grade 2–3 diarrhea was noted, the dose of irinotecan was reduced by 25% in all subsequent cycles. In both arms, treatment was terminated if grade 4 diarrhea, drug-induced interstitial pneumonitis or grade 3–4 peripheral neuropathy was noted.

Response evaluation

Objective tumor response was evaluated according to the World Health Organization (WHO) criteria issued in 1979 [12].

Study design, data management and statistical considerations

This study was designed as a multi-institutional, prospective, randomized phase II trial by 20 institutions in the Lung Cancer Study Group of JCOG. The protocol and consent form were approved by the Clinical Trial Review Committee of JCOG and the Institutional Review Board of each institution. Registration and randomization was conducted at the Registration Center. Data management, periodical monitoring and the final analysis were performed by the Study Coordinator. Simon's randomized phase II selection design was used to determine the sample size. Assuming response rates of a

poor and better arm of 70% and 85%, respectively, and a correct selection probability of 90%, the estimated required number of patients was 26 for each arm [13]. Accordingly, 30 patients for each arm and their accrual period of 24 months were planned for this study.

The dose intensity of each drug was calculated for each patient who received at least two cycles of chemotherapy by using the following formula:

Dose intensity (mg/m^2/week) = Total milligrams of a drug in all cycles per body surface area/[(Total days of therapy)/7]

where total days of therapy is the number of days from day 1 of cycle 1 to day 1 of the last cycle plus 7 days for arm A or 28 days for arm B [14]. The median dose intensity was then calculated.

The survival distribution was estimated by the Kaplan–Meier method [15]. The final analysis was planned 15 months after the last patient accrual. The investigational arm in a phase III trial was proposed based on the response rate, survival, toxicity and compliance data in the final analysis.

Results

Patient characteristics

From August 1999 to October 2000, 30 patients each were entered in arms A and B, and the last follow-up was performed in February 2002. All enrolled patients were included in the analyses of toxicity, tumor response and patient survival. The demographic details are listed in Table 1. Information on weight loss during the 6-month period before study entry was available for all patients. There were no differences between the two arms in any characteristics listed.

Treatment delivery

Treatment with respect to the number of cycles delivered was well tolerated in both arms. Of the 30 patients in arm, 22 (73%) in arm A and 21 (70%) in arm B received full cycles of chemotherapy, i.e. nine cycles in arm A and four cycles in arm B (Table 2). Therapy was stopped because of toxicity in four (13%) patients in arm A and in six (20%) patients in arm B, and because of tumor progression in three (10%) patients each in both arms. The treatment delays in arm A and skipping in arm B, however, were significant (Table 2). Only eight (27%) patients in arm A completed the treatment without delay, and only seven (23%) patients in arm B received all doses planned in the protocol. A total of 105 chemotherapy cycles were administered to 30 patients in arm B, but eight (8%) doses of irinotecan on day 8, and 33 (31%) doses of irinotecan on day 15 were omitted because of toxicity according to the criteria in the protocol.

The median total doses of cisplatin and etoposide administered per patient were maintained at the planned dose levels in both arms (Table 3). The median total dose of irinotecan as a percent-

Table 1. Patient characteristics

Characteristics	Arm A ($n = 30$)		Arm B ($n = 30$)	
	n	(%)	*n*	(%)
Sex				
Female	3	(10)	3	(10)
Male	27	(90)	27	(90)
Age				
Median	64		63	
Range	(47–70)		(46–68)	
Performance status				
0	2	(7)	3	(10)
1	25	(83)	25	(83)
2	3	(10)	2	(7)
Body weight loss				
<5%	23	(77)	21	(70)
5–10%	6	(20)	8	(27)
>10%	1	(3)	1	(3)

Table 2. Treatment delivery

No. of cycles	*n*	(%)
Arm A ($n = 30$)		
9	22	(73)
8	4	(13)
5	1	(3)
4	1	(3)
2	1	(3)
1	1	(3)
Delay (weeks)		
0	8	(27)
1	7	(23)
2	6	(20)
3	4	(13)
4	3	(10)
7	1	(3)
NE	1	(3)
Arm B ($n = 30$)		
4	21	(70)
3	5	(17)
2	2	(7)
1	2	(7)
Delay (weeks)		
0	22	(73)
1	3	(10)
2	2	(7)
3	1	(3)
NE	2	(7)
No. of missed cycles		
0	7	(23)
1	11	(37)
2	4	(13)
3	6	(20)
4	2	(7)

NE, not evaluable.

Table 3. Actual total dose and dose intensity delivered

	Median (range) total dose or dose intensity administered per patient			
	Arm A		Arm B	
	Actual	Relative (%)*	Actual	Relative (%)*
Total dose (mg/m^2)				
Cisplatin	225 (25–225)	100 (11–100)	240 (60–240)	100 (25–100)
Irinotecan	450 (90–450)	100 (20–100)	563 (60–720)	78 (8–100)
Etoposide	720 (0–720)	100 (0–100)	600 (150–600)	100 (25–100)
Dose intensity (mg/m^2/week)				
Cisplatin	21 (13–25)	82 (52–100)	15 (12–15)	100 (80–100)
Irinotecan	40 (21–50)	80 (41–100)	35 (19–45)	77 (42–100)
Etoposide	70 (47–80)	88 (59–100)	37 (28–38)	99 (75–100)

*Relative (%): actual/planned × 100.

Table 4. Grade 3 and 4 toxicity

Toxicity	Arm A ($n = 30$)				Arm B ($n = 30$)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Leukocytopenia	9	(30)	6	(20)	12	(40)	4	(13)
Neutropenia	5	(17)	12	(40)	14	(47)	12	(40)
Anemia	12	(40)	5	(17)	12	(40)	2	(7)
Thrombocytopenia	8	(27)	0	(0)	3	(10)	0	(0)
Elevated creatinine	1	(3)	0	(0)	1	(3)	0	(0)
Hyponatremia	4	(13)	0	(0)	6	(20)	0	(0)
Hypokalemia	0	(0)	0	(0)	2	(7)	0	(0)
Infection	1	(3)	1	(3)	2	(7)	2	(7)
Nausea/vomiting	1	(3)	0	(0)	2	(7)	0	(0)
Stomatitis	0	(0)	0	(0)	1	(3)	0	(0)
Diarrhea	2	(7)	0	(0)	1	(3)	2	(7)
Arrhythmia	2	(7)	0	(0)	0	(0)	1	(3)
Dyspnea	0	(0)	1	(3)	1	(3)	1	(3)

age of the scheduled dose (the relative total dose) was 100% in arm A, but only 78% in arm B, reflecting the skips of irinotecan on days 8 and 15. The dose intensity was evaluable in 29 patients in arm A and 28 patients in arm B (Table 3). Median relative dose intensity was well maintained at a level of 80% or higher except that of irinotecan in arm B (77%). The median actual dose intensity of etoposide was 70 mg/m^2/week in arm A and 37 mg/m^2/week in arm B.

Toxicity

Toxicity was evaluated in all patients. The major toxicity was neutropenia in both arms: grade 3 or 4 neutropenia was noted in 17 (57%) patients in arm A and in 26 (87%) patients in arm B (Table 4). The median duration of G-CSF administration was 33 days (range 0–59) in arm A and 27 days (range 3–65) in arm B. One patient in arm A developed grade 4 septic shock, grade 3 diarrhea, arrhythmia, dyspnea and elevated serum creatinine, and died 16 days after the start of the treatment. There was a protocol violation in this case because the patient was given the second cycle of chemotherapy despite the presence of grade 1 diarrhea and decreased performance status of three. Two patients in arm B also developed grade 4 septic shock in the first and third chemotherapy cycle, respectively, but recovered completely from the toxicity. There were three episodes of grade 3 infection consisting of neutropenic fever, pneumonia and phlegmon. In all, grade 3 or 4 infection developed in two (7%) patients in arm A and four (13%) patients in arm B. The percentage of patients who developed grade 3 or 4 anemia was almost the same in both arms: 43% in arm A and 47% in arm B. Red blood cell transfusion, however, was required in 13 (43%) patients in arm A and four (13%) patients in arm B. Thrombocytopenia was mild in both arms. Diarrhea was mild in most patients, and grade 3 or 4

Table 5. Clinical responses

Response	Arm A		Arm B	
	n	(%)	*n*	(%)
Complete response	2	(7)	5	(17)
Partial response	23	(77)	18	(60)
No change	1	(3)	0	(0)
Progressive disease	3	(10)	4	(13)
Not evaluable	1		3	

diarrhea was noted in two (7%) patients in arm A and three (10%) patients in arm B. Grade 3 arrhythmia in one patient in arm A resolved shortly after treatment with an antiarrhythmic agent. The other two episodes of grade 3 or 4 arrhythmia were associated with septic shock. Three episodes of grade 3 or 4 dyspnea were associated with pneumonia and septic shock. All episodes of grade 3 hyponatremia and hypokalemia not associated with infection were asymptomatic and transient.

Response and survival

Two complete responses (CRs) and 23 partial responses (PRs) were obtained in arm A, resulting in the overall clinical response rate of 83% with 95% confidence interval (CI) of 65–94%, whereas five CRs and 18 PRs were obtained in arm B, and the overall response rate was 77% (95% CI 58% to 90%) (Table 5). The MST and 1-year survival rate were 8.9 months and 40%, respectively, in arm A, and 12.9 months and 57%, respectively, in arm B (Figure 2).

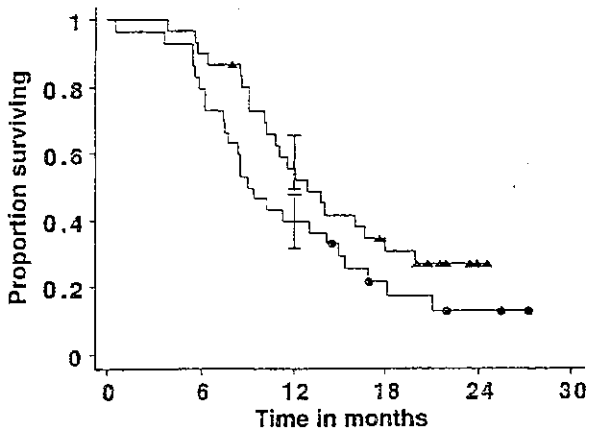

Figure 2. Survival by treatment arm. Arm A, thin line with closed circle; arm B, thick line with closed triangle.

Discussion

This is the first study to evaluate PIE combinations in patients with extensive SCLC. Myelosuppression was the major toxicity observed frequently, and was comparable in both arms. We observed one (3%) treatment-related death in arm A, but it was associated with a protocol violation, and there were two (7%) and four (13%) grade 3 or 4 infections in arms A and B, respectively. Diarrhea and other non-hematological toxicities were not significant. Thus, toxicity was acceptable in both arms, and the recommended doses determined in our previous combination phase I studies proved reasonable [9, 10]. The clinical response and survival in both arms were comparable with those reported in the literature [3–8]. The results of this study suggested that the PIE combinations in both schedules have significant activity against extensive SCLC with acceptable toxicity.

Randomized phase II trials are a useful method of selecting one arm for subsequent phase III trials [13]. It is not always easy, however, to determine the right arm on the basis of the results of this kind of study, because the sample size is not large enough to detect statistically significant differences between the arms. The response rate, the primary endpoint of this study, was slightly higher in arm A (83% in arm A and 77% in arm B), but the CR rate and MST were both higher in arm B (7% and 8.9 months in arm A, and 17% and 12.9 months in arm B, respectively). Since patients with various characteristics were equally distributed in the two arms, it seems reasonable to attribute the difference in survival to the difference in treatment arms. We therefore concluded that arm B should be selected for future phase III studies. The CR rate and MST in arm B were more promising than the historical control data [3–8].

The reasons for the difference in survival between the arms are unknown. The proportion of patients who discontinued treatment because of severe toxicity did not differ between the arms. The cumulative total doses of cisplatin, irinotecan and etoposide were comparable in both arms. Since the dose intensity of the three agents in arm A was higher than in arm B, the dose intensity did not contribute to the better survival in arm B. Because of the negative results of recent phase III studies comparing dose intensive versus standard chemotherapy [16–18], increasing dose intensity is not considered a major strategy for the treatment of extensive SCLC.

Although compliance with the treatment cycles appeared good in arm B, irinotecan administration often needed to be skipped, especially on day 15. Thus, a 3-week schedule in which irinotecan is administered only on days 1 and 8 and the chemotherapy cycle is repeated every 3 weeks may improve treatment delivery and antitumor efficacy. A recent randomized phase II study of cisplatin and gemcitabine chemotherapy in patients with non-small cell lung cancer showed that a 3-week schedule was better than a 4-week schedule [19].

In conclusion, combinations of cisplatin, irinotecan and etoposide on two schedules were effective against extensive SCLC with acceptable toxicity. Arm B, in which these agents were administered on a 4-week basis, was considered to be more appropriate as the investigational arm in phase III trials.

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Phase I study of cisplatin, vinorelbine, and concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer

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To determine the recommended phase II dose of vinorelbine in combination with cisplatin and thoracic radiotherapy (TRT) in patients with unresectable stage III non-small cell lung cancer (NSCLC), 18 patients received cisplatin (80 mg/m²) on day 1 and vinorelbine (20 mg/m² in level 1, and 25 mg/m² in level 2) on days 1 and 8 every 4 weeks for 4 cycles. TRT consisted of a single dose of 2 Gy once daily for 3 weeks followed by a rest of 4 days, and then the same TRT for 3 weeks to a total dose of 60 Gy. Fifteen (83%) patients received 60 Gy of TRT and 14 (78%) patients received 4 cycles of chemotherapy. Ten (77%) of 13 patients at level 1 and all 5 patients at level 2 developed grade 3–4 neutropenia. Four (31%) patients at level 1 and 3 (60%) patients at level 2 developed grade 3–4 infection. None developed ≥grade 3 esophagitis or lung toxicity. Dose-limiting toxicity was noted in 33% of the patients in level 1 and in 60% of the patients in level 2. The overall response rate (95% confidence interval) was 83% (59–96%) with 15 partial responses. The median survival time was 30.4 months, and the 1-year, 2-year, and 3-year survival rates were 72%, 61%, and 50%, respectively. In conclusion, the recommended dose is the level 1 dose, and this regimen is feasible and promising in patients with stage III NSCLC. (Cancer Sci 2004; 95: 691–695)

Stage III locally advanced non-small cell lung cancer (NSCLC) accounts for about 25% of all lung cancer cases.[1] Successful treatment of this disease rests on the control of both clinically apparent intrathoracic disease and occult systemic micrometastases, and therefore a combination of systemic chemotherapy and thoracic radiotherapy is indicated in many patients with good performance status and no pleural effusion.[2] Concurrent chemoradiotherapy is superior to the sequential approach, as shown by recent phase III trials in unresectable stage III NSCLC, in which the median survival time was 15.0 to 17.0 months in the concurrent arm and 13.3 to 14.6 months in the sequential arm, although acute esophagitis was more severe in the concurrent arm.[3–5] Chemotherapy regimens combined with simultaneous thoracic radiotherapy have consisted of cisplatin plus etoposide and cisplatin plus vinca alkaloids,[3,4] and a combination of cisplatin plus vindesine, with or without mitomycin, has been widely used in Japan.[5–8]

Vinorelbine, a new semisynthetic vinca alkaloid with a substitution in the catharanthine ring, interacts with tubulin and microtubule-associated proteins in a manner different from the older vinca alkaloids, and it more selectively depolymerizes microtubules in mitotic spindles.[9] Several randomized trials have shown vinorelbine to be more active against advanced or metastatic NSCLC than vindesine as a single agent or in combination with cisplatin.[10–13] Thus, incorporation of vinorelbine into concurrent chemoradiotherapy instead of vindesine is an important strategy for the treatment of locally advanced NSCLC. The objective of this study was to determine the maximum tolerated dose (MTD) and recommended dose of vinorelbine for phase II studies in combination with cisplatin, with or without mitomycin, and thoracic radiotherapy for patients with unresectable stage III NSCLC. We planned to start with the cisplatin and vinorelbine combination and then add mitomycin.

Patients and Methods

Patient selection. The eligibility criteria were: histologically or cytologically proven NSCLC; unresectable stage IIIA or IIIB disease; no previous treatment; measurable disease; tumor within an estimated irradiation field no larger than half the hemithorax; age between 20 years and 74 years; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1[14]; adequate bone marrow function (12.0×10^9/liter ≥white blood cell [WBC] count ≥4.0×10^9/liter, neutrophil count ≥2.0×10^9/liter, hemoglobin ≥10.0 g/dl, and platelet count ≥100×10^9/liter), liver function (total bilirubin ≤1.5 mg/dl and transaminase ≤twice the upper limit of the normal value), and renal function (serum creatinine ≤1.5 mg/dl and creatinine clearance ≥60 ml/min); and a PaO_2 of 70 Torr or more. Patients were excluded if they had malignant pleural or pericardial effusion, active double cancer, a concomitant serious illness, such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonia or lung fibrosis identified by a chest X-ray, chronic obstructive lung disease, infection or other diseases contraindicating chemotherapy or radiotherapy, pregnancy, or breast-feeding. All patients gave their written informed consent.

Pretreatment evaluation. The pretreatment assessment included a complete blood cell count and differential count, routine chemistry determinations, creatinine clearance, blood gas analysis, electrocardiogram, lung function testing, chest X-rays, chest computed tomographic (CT) scan, brain CT scan or magnetic resonance imaging, abdominal CT scan or ultrasonography, and radionuclide bone scan.

Treatment schedule. The dose levels and doses of each anticancer agent are shown in Table 1. Cisplatin and vinorelbine were administered at dose levels 1 and 2. It was planned to give cisplatin, vinorelbine, and mitomycin at dose levels 3–5, but because the MTD was determined to be dose level 2, dose levels 3–5 were not used. Cisplatin was administered on day 1 by intravenous infusion over 60 min together with 2500 to 3000 ml of fluid for hydration. Vinorelbine diluted in 40 ml of normal saline was administered by bolus intravenous injection on days 1 and 8. All patients received prophylactic antiemetic ther-

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apy consisting of a 5HT3-antagonist and a steroid. This chemotherapy regimen was repeated every 4 weeks for 4 cycles.

Thoracic radiotherapy with photon beams from a liniac or microtron accelerator with energy between 6 and 10 MV at a single dose of 2 Gy once daily given 15 times over 3 weeks was begun on day 2 of the first cycle of cisplatin and vinorelbine chemotherapy, and followed by a short rest period of 4 days. The same radiotherapy was begun on day 1 of the second cycle of chemotherapy to a total dose of 60 Gy. The clinical target volume (CTV) was based on conventional chest X-ray and CT scans, and included the primary lesion (CTV1), involved lymph nodes whose short diameter was 1 cm or larger (CTV2), and the ipsilateral pulmonary hilum and bilateral mediastinum area (CTV3). Anterior and posterior parallel opposed fields encompassed the initial planned target volume (PTV), consisting of CTV1–3 with the superior and inferior field margins extended to 1 to 2 cm and the lateral field margins extended to 0.5 cm for respiratory variation and fixation error. The boost PTV included only CTV1–2 based on the second CT scans with the same margins. The spinal cord dose was limited to 40 Gy by using oblique parallel opposed fields.

Toxicity assessment and treatment modification. Complete blood cell counts and differential counts, routine chemistry determinations, and a chest X-ray were performed once a week during the course of treatment. Acute toxicity was graded according to the NCI Common Toxicity Criteria version 2.0 issued in 1998, and late toxicity associated with thoracic radiotherapy was graded according to the RTOG Late Radiation Morbidity Scoring Schema.[15] Vinorelbine administration on day 8 was omitted if any of the following toxicities was noted: WBC count $<3.0\times10^9$/liter, neutrophil count $<1.5\times10^9$/liter, platelet count $<100\times10^9$/liter, elevated hepatic transaminase level or total serum bilirubin ≥grade 2, fever ≥38°C, or performance status ≥2. Subsequent cycles of chemotherapy were delayed if any of the following toxicities was noted on day 1: WBC count $<3.0\times10^9$/liter, neutrophil count $<1.5\times10^9$/liter, platelet count $<100\times10^9$/liter, serum creatinine level ≥1.6 mg/dl, elevated hepatic transaminase level or total serum bilirubin ≥grade 2, fever ≥38°C, or performance status ≥2. The doses of cisplatin and vinorelbine were reduced by 25% in all subsequent cycles if any of the following toxicities was noted: WBC count $<1.0\times10^9$/liter, platelet count $<20\times10^9$/liter, or grade 3 or severer non-hematological toxicity, except for nausea and vomiting. The dose of cisplatin was reduced by 25% in all subsequent cycles if the serum creatinine level was elevated to 2.0 mg/dl or higher. Thoracic radiotherapy was suspended if any of the following toxicities was noted: WBC count $<1.0\times10^9$/liter, platelet count $<20\times10^9$/liter, esophagitis ≥grade 3, fever ≥38°C, performance status ≥3, or PaO_2 <70 Torr. Thoracic radiotherapy was terminated if this toxicity persisted for more than 2 weeks. Granulocyte colony-stimulating factor support was used if the neutrophil count was $<0.5\times10^9$/liter for more than 4 days, the WBC count was $<1.0\times10^9$/liter, or febrile neutropenia ≥grade 3 was noted.

Dose-limiting toxicity, MTD, and recommended dose for phase II studies. The dose-limiting toxicity (DLT) was defined as a neutrophil count $<0.5\times10^9$/liter lasting 4 days or longer, febrile neutropenia ≥grade 3, platelet count $<20\times10^9$/liter, grade 3 or more severe non-hematological toxicity other than nausea and vomiting, and patient's refusal to receive subsequent treatment. Doses were escalated according to the frequency of DLT evaluated during the first and second cycles of chemotherapy and thoracic radiation. Six patients were initially enrolled at each dose level. If one or none of them experienced DLT, the next cohort of patients was treated at the next higher dose level. If 2 of the 6 patients experienced DLT, then 6 additional patients were enrolled at the same dose level to make a total of 12 patients. If 4 or fewer patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If 5 or more of the 12 patients experienced DLT, that level was considered to be the MTD. If 3 of the initial 6 patients experienced DLT, that level was considered to be the MTD. The recommended dose for phase II trials was defined as the dose preceding the MTD.

Table 1. Dose level and the dose of each anticancer agent

Dose level	Cisplatin (mg/m²)	Vinorelbine (mg/m²)	Mitomycin (mg/m²)
−1	80	15	—
1	80	20	—
2	80	25	—
3	80	15	8
4	80	20	8
5	80	25	8

Response evaluation. Objective tumor response was evaluated according to the WHO criteria issued in 1979.[16] A complete response (CR) was defined as the disappearance of all known disease for at least 4 weeks with no new lesions appearing. A partial response (PR) was defined as an at least 50% decrease in total tumor size for at least 4 weeks without the appearance of new lesions. No change (NC) was defined as the absence of a partial or complete response with no progressive or new lesions observed for at least 4 weeks. Progressive disease was defined as a 25% or greater increase in the size of any measurable lesion or the appearance of new lesions.

Study design, data management, and statistical considerations. This study was designed as a phase I study at two institutions, the National Cancer Center Hospital and Kanagawa Cancer Center. The protocol and consent form were approved by the Institutional Review Board of each institution. Registration was conducted at the Registration Center. Data management, periodic monitoring, and the final analysis were performed by the Study Coordinator. A patient accrual period of 24 months and a follow-up period of 18 months were planned. Overall survival time and progression-free survival time were estimated by the Kaplan-Meier method.[17] Survival time was measured from the date of registration to the date of death due to any cause. Progression-free survival time was measured from the date of registration to the date of disease progression or death. Patients who were lost to follow-up without event were censored at the date of their last known follow-up.

Results

Registration and characteristics of the patients. From October 1999 to August 2000, 13 patients were registered at dose level 1 and 5 patients at dose level 2. The detailed demographic characteristics of the patients are listed in Table 2. All patients had unresectable IIIA-N2 or IIIB disease. One of the 6 patients enrolled at dose level 1 developed bacterial meningitis during the second cycle of chemotherapy, and that case is described in detail elsewhere.[18] We did not include it in the assessment of DLT, because the bacterial meningitis was not specifically related to treatment. We registered another patient at the same dose level, and 2 cases of DLT were noted among the initial 6 patients evaluable for DLT. We added another 6 patients, and DLT was noted in 4 of the 12 patients registered at the dose level 1. Of the 5 patients registered at level 2, 3 patients developed DLT. This dose level was determined to be the MTD, and patient accrual to this study was terminated.

Treatment delivery. Treatment delivery was generally well maintained, and it did not differ between the two dose levels (Table 3). Full dose (60 Gy) thoracic radiotherapy was completed in 77% and 100% of the patients at dose levels 1 and 2,

Table 2. Patients' characteristics

		Median (range)	N (%)
Number of patients			18
Gender	male		16 (89)
	female		2 (11)
Age	median (range)	59 (48–69)	
PS	0		4 (22)
	1		14 (78)
Body weight loss	<5%		12 (67)
	5–9%		4 (22)
	≥10%		2 (11)
T-factor	1		1 (6)
	2		6 (33)
	3		7 (39)
	4		4 (22)
N-factor	2		11 (61)
	3		7 (39)
Clinical stage	IIIA		9 (50)
	IIIB		9 (50)
Histology	adenocarcinoma		14 (78)
	squamous cell carcinoma		3 (17)
	adenosquamous carcinoma		1 (6)

Table 3. Treatment delivery

	Dose level 1 (N=13)	Dose level 2 (N=5)
	N (%)	N (%)
Initial irradiation field (cm²)		
median (range)	171 (128–529)	182 (128–248)
Total dose of radiotherapy (Gy)		
60	10 (77)	5 (100)
50–59	1 (8)	0
<50	2 (15)	0
Delay of radiotherapy (days)[1]		
<5	6 (60)	3 (60)
5≤	4 (40)	2 (40)
Number of chemotherapy cycles		
4	10 (77)	4 (80)
3	0	1 (20)
2	2 (15)	0
1	1 (8)	0
Omission of vinorelbine administration on day 8		
0	9 (69)	2 (40)
1	4 (31)	2 (40)
3	0	1 (20)

1) Evaluated in patients who received 60 Gy radiotherapy (N=15).

respectively. Delays in radiotherapy evaluated in patients who completed the full course of radiotherapy amounted to less than 5 days in 60% of the patients at both levels. Full cycles (4 cycles) of chemotherapy were administered to 77% and 80% of the patients at dose levels 1 and 2, respectively, but vinorelbine administration on day 8 was more frequently omitted at dose level 2 (Table 3).

Toxicity, MTD, and the recommended dose for phase II trials. Acute severe toxicity was mainly hematological (Table 4). Grade 3–4 leukopenia and neutropenia were noted in 77% and 100% of the patients at dose levels 1 and 2, respectively. Grade 3 anemia was observed in 23% and 20% of the patients at dose levels 1 and 2, respectively, but no blood transfusions were required. Thrombocytopenia was mild. Grade 4 transaminase elevation was observed in 1 patient during the first cycle of chemotherapy, but no subjective manifestations associated with liver dysfunction were noted. Chemotherapy was discontinued and the transaminases quickly decreased to within their normal ranges. Transient asymptomatic grade 3 hyponatremia was noted in 1 patient. Grade 3–4 infection was noted in 7 patients. Bacterial meningitis unassociated with neutropenia developed on day 6 of the second cycle of chemotherapy in 1 patient.[18] The other grade 3–4 infections were all associated with neutropenia. Esophagitis was mild in this study, and no grade 3–4 esophagitis was noted. No deaths occurred during or within 30 days of therapy.

DLT was noted in 4 of the 12 (33%) evaluable patients at dose level 1, and in 3 of the 5 (60%) at dose level 2. Six of these 7 DLTs were grade 3–4 infection associated with neutropenia, and the other 1 was grade 4 transaminase elevation. Thus, we determined that dose level 2 was the MTD, and dose level 1 was recommended as the dose for phase II trials.

Table 4. Acute toxicity

Toxicity	Dose level 1 (*N*=13), Grade					Dose level 2 (*N*=5), Grade				
	1	2	3	4	3–4 (%)	1	2	3	4	3–4 (%)
Hematological										
Leukopenia	0	2	9	1	(77)	0	0	4	1	(100)
Neutropenia	1	1	7	3	(77)	0	0	1	4	(100)
Anemia	4	6	3	0	(23)	2	2	1	0	(20)
Thrombocytopenia	1	2	0	0	(0)	1	0	0	0	(0)
Non-hematological										
AST	2	0	0	1	(8)	1	0	0	0	(0)
ALT	7	0	0	1	(8)	0	1	0	0	(0)
Total bilirubin	2	1	0	0	(0)	2	0	0	0	(0)
Creatinine	2	2	0	0	(0)	1	0	0	0	(0)
Hyponatremia	6	0	1	0	(8)	1	0	0	0	(0)
Infection	1	3	2	2	(31)	0	0	3	0	(60)
Nausea	4	1	0	0	(0)	3	0	0	0	(0)
Diarrhea	0	1	0	0	(0)	0	0	0	0	(0)
Stomatitis	2	0	0	0	(0)	0	2	0	0	(0)
Esophagitis	6	1	0	0	(0)	4	0	0	0	(0)
Sensory neuropathy	2	0	0	0	(0)	0	0	0	0	(0)

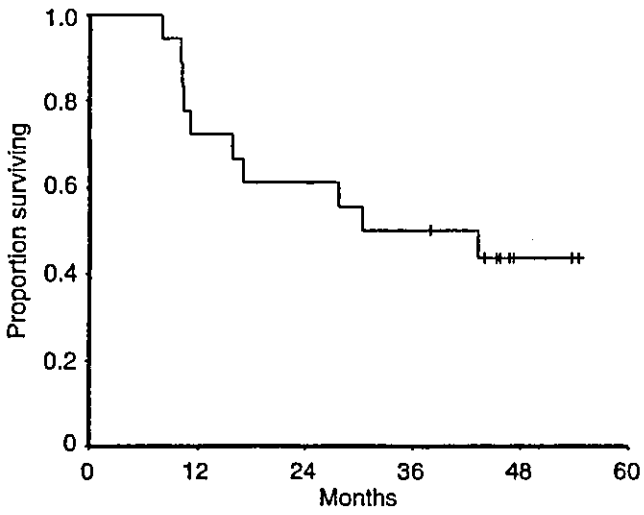

Fig. 1. Overall survival in 18 patients. The median (range) follow-up period of censored cases has been 35.4 (32.0–43.4) months, and the median overall survival time has not yet been reached.

Late lung toxicity associated with thoracic radiotherapy was grade 3 in 1 (6%) patient, grade 2 in 4 (22%) patients, and grade 1 in 8 (44%) patients. No late esophageal toxicity was noted.

Objective responses, relapse pattern, and survival. All patients were included in the analyses of tumor response and survival. No CR, 15 PRs, and 1 NC were noted, and the overall response rate (95% confidence interval) was 83% (59–96%). Relapse was noted in 12 (67%) of 18 patients. Initial relapse sites were locoregional alone in 5 (28%) patients, locoregional and distant in 3 (17%) patients, and distant alone in 4 (22%) patients. Brain metastasis was detected in 5 patients, and the brain was the most frequent site of distant metastasis. The median progression-free survival time was 15.6 months, and the median overall survival time was 30.4 months. The 1-year, 2-year, and 3-year survival rates were 72%, 61%, and 50%, respectively (Fig. 1).

Discussion

The combination of cisplatin, vindesine, and mitomycin with concurrent thoracic radiotherapy has been shown to yield an encouraging survival outcome, a median survival time of 17–19 months, and a 5-year survival rate of 16% in patients with unresectable stage III NSCLC.[5,7,8] A Japanese randomized trial revealed that replacement of vindesine by vinorelbine in combination with cisplatin and mitomycin yielded a promising response rate (57% versus 38%, $P=0.025$) and median survival time (15 months versus 11 months, $P<0.01$) in patients with stage IIIB or IV NSCLC.[13] Thus, the combination of cisplatin, vinorelbine, and mitomycin is a chemotherapy regimen with potential for combination with concurrent thoracic radiotherapy. The present study, however, showed that a DLT developed in 60% of patients who received cisplatin and vinorelbine 25 mg/m^2 days 1 and 8 (level 2), and since the DLTs were associated with myelosuppression, which is the major critical toxicity of mitomycin, we concluded that it would be impossible to incorporate mitomycin into this regimen.

The recommended doses of vinorelbine of 20 mg/m^2 on days 1 and 8 and cisplatin of 80 mg/m^2 on day 1 repeated every 4 weeks in this study are comparable to the doses used in the CALGB (vinorelbine 15 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1 repeated every 3 weeks),[19,20] and the Czech Lung Cancer Cooperative Group (vinorelbine 12.5 mg/m^2 on days 1, 8, and 15 and cisplatin 80 mg/m^2 on day 1, repeated every 4 weeks),[21] but lower than in a Mexican study (vinorelbine at 25 mg/m^2 on days 1 and 8 and cisplatin 100 mg/m^2 on day 1, repeated every 3 weeks).[22] These recommended doses are also lower than expected when compared with the recommended vinorelbine dose combined with cisplatin for metastatic NSCLC (vinorelbine 30 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1, repeated every 3 weeks),[23] and when compared with the results of vindesine, cisplatin, and mitomycin combined with thoracic radiotherapy, where the full doses can be administered concurrently.[8] Thus, vinorelbine can be safely administered with cisplatin and concurrent thoracic radiotherapy at a maximum dose of two-thirds the optimal dose without radiotherapy.

The results for response and survival in this study, however, were very encouraging. This may have been attributable to patient selection bias, but the percentage of patients who had stage IIIB disease in this study was similar to the percentage in the CALGB randomized phase II study.[20] In addition, 33% of the patients in this study had ≥5% body weight loss, whereas only 7% of the patients did in that study.[20] The median survival time was 30.4 months and exceeded the results of concurrent

chemoradiotherapy with old drug combinations that yielded a median survival time of 15–19 months.[3–8] Thus, it could be argued that the combination of cisplatin and vinorelbine is more active for locally advanced NSCLC than the older drug combinations, although there have not been any randomized trials comparing this regimen with old drug combinations in combination with thoracic radiotherapy in patients with stage III NSCLC. Our results also seem better than those of other trials using concurrent cisplatin, vinorelbine, and thoracic radiotherapy, in which the median survival time was 13 to 18 months.[20, 22] Those trials used induction chemotherapy followed by chemoradiotherapy. Since the response rate to induction chemotherapy is no more than 40%, induction chemotherapy may be disadvantageous. This issue is being evaluated in an on-going CALGB phase III trial.

Severe esophagitis and pneumonitis have been DLTs in many trials of concurrent chemoradiotherapy, but neither was observed in this study. Nevertheless, since the occurrence of these non-hematological toxicities associated with thoracic radiotherapy is sporadic, the sample size in this study may have been too small to detect them. Thus, careful observation for these toxicities is needed in further phase II and phase III trials to definitely establish the safety profile of this regimen.

In conclusion, cisplatin and vinorelbine chemotherapy combined with concurrent full-dose thoracic radiotherapy is feasible, and the recommended dose of vinorelbine for phase II trials is 20 mg/m^2 on days 1 and 8 repeated every 4 weeks. This regimen was highly active in patients with stage III NSCLC.

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Short Communication

Phase I study of cisplatin analogue nedaplatin (254-S) and paclitaxel in patients with unresectable squamous cell carcinoma

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The recommended phase II dose of paclitaxel 180 mg m^{-2} given as a 3-h infusion followed by nedaplatin 100 mg m^{-2} in a 1-h infusion every 3–4 weeks was determined in 52 chemo-naive patients with unresectable squamous cell carcinoma (SCC), with a promising response rate for lung SCC of 55%.

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Squamous cell carcinoma (SCC) arises from the epithelial tissue of many different organs. Although localised diseases can be treated using surgical resection or curative radiotherapy, advanced SCC continues to have a poor prognosis and the standard treatment has not been established (DeVita *et al*, 2001). Cisplatin-based chemotherapy has been used for the treatment of advanced SCC, regardless of the site of tumour origin (DeVita *et al*, 2001).

Nedaplatin (cis-diammine-glycolate-*O,O'*-platinum II, 254-S) is a second-generation platinum derivative that has an antitumour activity comparable to that of cisplatin (Kobayashi *et al*, 1991) but is less toxic to the kidney (Kameyama *et al*, 1990), as seen in preclinical experiments. Nedaplatin produced promising response rates in phase II trials for the treatment of SCC arising from the head and neck (Inuyama *et al*, 1992), lung (Yamamoto *et al*, 2000), oesophagus (Taguchi *et al*, 1992), and uterine cervix (Noda *et al*, 1992). Paclitaxel is another promising drug for the treatment of advanced SCC, as shown by the favourable response rates obtained in phase II trials for head and neck (Forastiere *et al*, 1998), non-small-cell lung (Sekine *et al*, 1996), oesophageal (Ajani *et al*, 1994), and cervical (McGuire *et al*, 1996) cancers.

A combination of nedaplatin and paclitaxel is a promising chemotherapeutic regimen because a significant synergistic effect was obtained for this combination in a preclinical mice tumour model (Yamada *et al*, 2001), and the combination of platinum compounds and paclitaxel is one of many standard regimens (Schiller *et al*, 2002). The objectives of this phase I trial were (1) to evaluate the toxicity of the regimen and to determine the maximum tolerated dose (MTD) and recommended phase II dose (RPTD) of nedaplatin and paclitaxel, and (2) to observe the antitumour effects of this regimen on SCC arising in various organs.

PATIENTS AND METHODS

Patient selection

The eligibility criteria for enrolment in the trial were as follows: histologically or cytologically proven SCC; unresectable disease; measurable disease; no previous chemotherapy; age between 20 and 75 years; performance status of 0 or 1 (Oken *et al*, 1982); adequate bone marrow function (white blood cell (WBC) count $\geqslant 4.0 \times 10^9 l^{-1}$, neutrophil count $\geqslant 2.0 \times 10^9 l^{-1}$, haemoglobin $\geqslant 10.0 g dl^{-1}$ and platelet count $\geqslant 100 \times 10^9 l^{-1}$), liver function (total bilirubin $\leqslant 1.5 mg dl^{-1}$ and transaminase $\leqslant 100 IU l^{-1}$), and renal function (serum creatinine $\leqslant 1.5 mg dl^{-1}$ and creatinine clearance $\geqslant 60 ml min^{-1}$); and a PaO_2 $\geqslant 60$ Torr. Patients were excluded from the trial for any of the following reasons: uncontrolled malignant pleural or pericardial effusion; a concomitant serious illness contraindicating chemotherapy; pregnancy; or breast-feeding. All patients gave their written informed consent.

Treatment schedule

The levels and respective doses of paclitaxel (mg m^{-2}) and nedaplatin (mg m^{-2}) are shown in Table 1. Paclitaxel diluted in 500 ml of 5% glucose was administered as a 3-h intravenous infusion with premedication as previously described (Sekine *et al*, 1996). Normal saline (500 ml) and granisetron (40 $\mu g kg^{-1}$) in 100 ml of normal saline were given intravenously, followed by nedaplatin diluted in 250 ml of normal saline administered in a 1-h intravenous infusion. This treatment was repeated every 3–4 weeks.

Toxicity assessment and treatment modification

Complete blood cell counts and differential counts, routine chemistry determinations, and a chest X-ray were performed at least once a week throughout the course of treatment. If grade 4 neutropenia was noted, the neutrophil count was repeated 4 days later to determine whether the grade 4 neutropenia had lasted for 5 days or longer. Acute toxicity was graded according to the NCI Common Toxicity Criteria, version 2.0, issued in 1998 (JCOG, 1998). Subsequent cycles of chemotherapy were delayed if any of the following toxicities were noted on day 1: WBC count $\leqslant 3.0 \times 10^9 l^{-1}$, neutrophil count $\leqslant 1.5 \times 10^9 l^{-1}$, platelet count $\leqslant 100 \times 10^9 l^{-1}$, serum creatinine level $\geqslant 1.6 mg dl^{-1}$, grade 2 elevated hepatic transaminase level or total serum bilirubin, fever $\geqslant 38°C$, or a performance status $\geqslant 2$.

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Table 1 Dose level and number of patients accrued

Level	Paclitaxel ($mg\,m^{-2}$)	Nedaplatin ($mg\,m^{-2}$)	No. of patients: Accrued	Evaluable for DLT[a]	Developing DLT[a]
1	135	60	6	6	2
2	150	60	3	3	0
3	150	80	3	3	0
4	180	80	7	6	1
5	180	100	12	12	4
6	210	100	21	19	8

[a]Dose-limiting toxicity.

The treatment was terminated if the above-mentioned toxicity did not disappear in 3 weeks. If grade 4 leukopenia, grade 4 neutropenia for 5 days or longer, grade 3–4 febrile neutropenia, or grade 3–4 neutropenia with infection was noted, $50\,mg\,m^{-2}$ of granulocyte colony-stimulating factor (G-CSF) was given subcutaneously, and the doses of paclitaxel and nedaplatin were reduced by 25% in subsequent chemotherapy cycles.

Dose-limiting toxicity, MTD, and RPTD

The dose-limiting toxicity (DLT) was defined as grade 4 neutropenia lasting 5 days or longer, grade 3–4 febrile neutropenia, grade 3–4 neutropenia with infection, grade 4 leukopenia, a platelet count $<20 \times 10^9 l^{-1}$, and grade 3 or greater nonhaematological toxicity other than nausea and vomiting. Doses were escalated according to the frequency of DLT evaluated during the first cycle of chemotherapy. Three patients were initially enrolled at each dose level. If none of the patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If one of the three patients experienced DLT, then three additional patients were enrolled at the same dose level, bringing the total to six patients for that dose level. If two or fewer patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If three or more of the six patients experienced DLT, that level was considered to be the MTD. If two or all the initial three patients experienced DLT, that level was considered to be the MTD. The recommended dose for phase II trials was defined as the dose preceding the MTD. Six to 15 additional patients were enrolled at the RPTD to confirm that the frequency of DLT was less than one-third.

Response evaluation

The objective tumour response was evaluated according to the WHO criteria issued in 1979 (WHO, 1979).

Study design, data management, and statistical considerations

The protocol and consent form were approved by the Institutional Review Board of the National Cancer Center, Tokyo Japan. Data management, periodic monitoring, and the final analysis were performed by the Study Coordinator. A patient accrual period of 24 months and a follow-up period of 12 months were planned. The overall survival time was estimated using the Kaplan–Meier method (Armitage and Berry, 1994). Survival time was measured from the date of study registration until the date of death from any cause.

RESULTS

Patient characteristics

Between August 1999 and December 2002, 53 patients were registered in the study. One patient at level 5 developed a bone fracture prior to treatment and did not receive chemotherapy. This patient was excluded from all the analyses. Of the remaining 52 patients (42 males and 10 females) with a median age of 62 years (range 49–75), 42 (81%) patients had lung SCC, followed by thymic SCC in five patients and head and neck SCC in four patients. Of the 52 patients, 24 and 24 had metastatic and locally advanced diseases, respectively.

Treatment delivery, toxicity, MTD, and RPTD

Treatment delivery was summarised in Table 2. Severe toxicity was mainly manifested as leucopenia, neutropenia, and associated infection, but the frequency of these symptoms did not differ between dose levels (Table 3). Grade 3 anaemia and thrombocytopenia were only noted in one patient (5%) each; both these patients had been treated at dose level 6. No grade 3–4 nausea, neuropathy, or myalgia was noted. A grade 3–4 elevation in creatinine, grade 3–4 hyponatremia, appetite loss, and diarrhoea were only observed at level 6. One patient treated at level 6

Table 2 Treatment delivery

	No. of patients (%): Levels 1–4 ($n=19$)	Level 5 ($n=12$)	Level 6 ($n=21$)
Chemotherapy cycles			
5	1 (5)	0 (0)	0 (0)
4	7 (37)	4 (33)	5 (24)
3	2 (11)	2 (17)	3 (14)
2	5 (26)	4 (33)	8 (38)
1	4 (21)	2 (17)	5 (24)
Median	3	3	2
Dose reduction in subsequent cycles			
None	12 (63)	9 (75)	12 (50)
Required	3 (16)	1 (8)	4 (19)
Not administered	4 (21)	2 (17)	5 (24)

Table 3 Toxicity in all courses

	Levels 1–4 ($n=19$)			Level 5 ($n=12$)			Level 6 ($n=21$)		
	3	4	3–4 (%)	3	4	3–4 (%)	3	4	3–4 (%)
Leukopenia	6	0	(32)	5	0	(42)	6	1	(33)
Neutropenia	3	10	(68)	2	9	(92)	3	12	(71)
Anaemia	0	0	(0)	0	0	(0)	1	0	(5)
Thrombocytopenia	0	0	(0)	0	0	(0)	1	0	(5)
AST	0	0	(0)	0	0	(0)	1	0	(5)
ALT	0	0	(0)	1	0	(8)	0	1	(5)
Creatinine	0	0	(0)	0	0	(0)	0	1	(5)
Hyponatremia	0	0	(0)	0	0	(0)	2	1	(14)
Infection	4	0	(21)	4	0	(33)	6	0	(29)
Appetite loss	0	0	(0)	0	0	(0)	1	0	(5)
Diarrhoea	0	0	(0)	0	0	(0)	2	0	(10)
Constipation	0	0	(0)	0	0	(0)	0	1	(5)
Arrhythmia	2	0	(11)	0	0	(0)	0	0	(0)
Lung toxicity	0	0	(0)	0	0	(0)	2	0	(10)

developed grade 2 leukopenia, fever, watery diarrhoea, and grade 4 ileus, but recovered in 5 days. Two patients at level 6 developed grade 3 interstitial pneumonitis, but quickly recovered with oxygen therapy alone in one patient and with oxygen and steroid therapy in the other patient. No treatment-related deaths occurred in the study.

In all, 19 DLTs were noted in 15 patients. Of the 1nine DLTs, 13 were neutropenic fever or documented infection and six were nonhaematological. At level 6, only two of the first six patients developed DLT; therefore, 15 additional patients were entered at this level to confirm the frequency of DLT. Two patients were excluded from the DLT analysis because G-CSF was administered before the duration of grade 4 neutropenia had been determined (protocol violation). Of the remaining 13 patients, six developed DLT. Thus, eight (42%) of the 19 patients evaluated for DLT developed DLT at level 6; this dose level was therefore determined to be the MTD. An additional six patients were registered at level 5, and four (33%) of the 12 patients at level 5 developed DLT; this level was determined to be the RPTD.

Objective responses and survival

Of the 42 patients with lung SCC, two CRs and 21 PRs were noted, and the overall response rate (95% confidence interval) was 55% (39–70%). No difference in the response rates for levels 1–4 and levels 5–6 were observed. One PR was noted in a patient with thymic SCC, and one PR was noted in a patient with head and neck SCC. The overall survival time (95% confidence interval) in all patients ($n = 52$) was 11.1 (6.4–15.8) months.

DISCUSSION

This study showed that the combination of nedaplatin and paclitaxel was feasible with acceptable toxicity, and that the RPTD of nedaplatin was 100 mg m^{-2} over 1 hour, which is the full dose of this agent, while that of paclitaxel was 180 mg m^{-2} over 3 h. These doses are comparable to doses for practical use and those determined by previous phase I trials of cisplatin or carboplatin in combination with paclitaxel, where 180–225 mg m^{-2} of paclitaxel was given with the full dose of platinum-agent (Akiyama *et al*, 2001; Kurata *et al*, 2001). The toxicity profile in the present study was similar to that of the carboplatin and paclitaxel combination (Akiyama *et al*, 2001).

The primary objectives of phase I trials are to evaluate toxicity and to establish a recommended drug dose for a given administration schedule; an additional goal of these trials is to look for evidence of the drug's antitumour activity. Objective tumour responses to newly investigated drugs are a promising clue for determining specific tumour types for subsequent phase II trials; therefore, patients with various tumours are usually registered in phase I trials (Sekine *et al*, 2002). In cases where some information on the antitumour activity of a drug is available, patients can be selected so that the chance of a response is maximised. This study was a histology-oriented phase I trial, and objective tumour responses were observed in about half of the patients.

The combination of nedaplatin and paclitaxel is particularly promising for the treatment of patients with lung SCC, as shown by the high response rate of 55%. Adenocarcinoma, large-cell carcinoma, adenosquamous carcinoma, and SCC of the lung have been grouped together as non-small-cell lung cancer because treatment response and prognosis are similar for these histologies. A recent cDNA microarray analysis of non-small-cell lung cancer tissue, however, showed that the gene expression profiles of SCC and adenocarcinoma are different (Kikuchi *et al*, 2003), and these differences may lead to different responses to anticancer agents, including nedaplatin. Thus, optimal chemotherapy regimens for the treatment of non-small-cell lung cancer should be established according to each tumour's histology. The numbers of patients with head and neck SCC and patients with thymic SCC were too small to comment on the antitumour effects of this regimen.

In conclusion, the combination of nedaplatin and paclitaxel is a feasible treatment, and the RPTD is paclitaxel 180 mg m^{-2} given as a 3-h infusion followed by nedaplatin 100 mg m^{-2} in a 1-h infusion every 3–4 weeks. This regimen was highly effective for the treatment of untreated lung SCC.

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ANTI-TUMOUR TREATMENT

Treatment of small cell lung cancer in the elderly based on a critical literature review of clinical trials

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KEYWORDS
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Summary At diagnosis, 25–40% of patients with small cell lung cancer (SCLC) are 70 years of age or older, and many of them have been undertreated because of fear of excessive toxicity associated with chemotherapy. Papers retrieved by a Medline search using the key words "elderly or older" and "small cell lung cancer" and by a manual search were classified into the three types: (1) case-series studies, (2) subgroup analyses of phase II and phase III trials by age, and (3) prospective clinical trials in the elderly. Treatment regimens, delivery, toxicity, antitumor activity, and patient survival were reviewed in elderly patients with good and poor general condition. The standard chemotherapy regimens for the general population could be applied to elderly patients in good general condition (performance status of 0–1, normal organ function, and no comorbidity), but etoposide and carboplatin regimen with dose modification was frequently used for unselected elderly patients. A combination of full-dose thoracic radiotherapy and chemotherapy was the treatment of choice for limited SCLC in the elderly. Full cycles of chemotherapy were tolerable by 80% of the elderly patients with good general condition, but two cycles may be optimal for unselected elderly patients. Although the evidence levels based on clinical trials available today are low, these results are helpful for clinical practice and future clinical trials for elderly patients with SCLC.

Introduction

Lung cancer is currently the most common cancer in the world, and it is the leading cause of cancer death in many countries.[1,2] Small cell lung cancer (SCLC) accounts for 15–25% of all lung tumors. For treatment purposes, it is considered separately from other histological types, which are known as non-small cell lung cancer, because by the initial diagnosis SCLC has already metastastized to distant organs in 60–70% of patients, and it is highly sensitive to chemotherapy and radiotherapy. The prognosis of the disease is extremely poor. The 5-year survival rate of patients with limited disease (LD), which is a disease confined to one hemithorax that can be encompassed in a tolerable radiation field, is less than 15–25%, and most patients with extensive disease (ED), which has spread

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beyond the range of LD, die within two years after diagnosis.[3]

At diagnosis, 25–40% of patients with SCLC are 70 years old or older, and the number of patients is expected to increase, because the geriatric population is growing.[3–5] There has been a general tendency among physicians to consider aged people to always have poor tolerance for chemotherapy, and as a result many elderly cancer patients have been undertreated because of fear of excessive toxicity.[5] Thus, it is one of the immediate tasks for medical oncologists to establish treatment of SCLC in the elderly based on evidence obtained in clinical trials.

The decreases in lean body mass, hepatic blood flow, and renal function that accompany aging affect drug distribution, metabolism, and excretion. The clearance of anticancer agents commonly used for the treatment of SCLC, including cisplatin, doxorubicin, etoposide, and ifosfamide, has been shown to be decreased in the elderly.[6] Myelotoxicity is also sometimes severer in this population than in younger populations, because the absolute amount of hematopoietic marrow decreases with age. The incidence of doxorubicin-induced cardiotoxicity is also increased in the elderly, although the mechanism is unknown.[6] These age-related changes in pharmacokinetics and phamacodynamics, however, have not been fully evaluated in the treatment for SCLC in the elderly.

Studies on the treatment of SCLC in the elderly can be classified into the following three types: (1) case-series studies, (2) subgroup analyses of phase II and phase III trials by age, and (3) prospective clinical trials in the elderly. The first type of studies retrospectively analyzes all the elderly cases of SCLC diagnosed at an institution in a given period. They may provide information on the general aspects of elderly patients with SCLC, including performance, comorbidity, and percentages of patients treated with chemotherapy or supportive care alone. The results for outcome of treatment, however, are thought to be highly biased, because the patient populations in these studies are heterogeneous in terms of various prognostic factors. In the second type of studies, treatment outcome is retrospectively compared between an elderly group and a younger group. The patients in these studies are highly selected, because only those who meet strict eligibility criteria are included in clinical trials. Thus, the results of the analyses are understandable, but they are only applicable to the limited population of elderly patients. The most reliable and clinically useful results are obtained in the third type of studies, because the subjects can be freely defined and biases are controlled. Thus far, however, only a limited number of prospective studies on elderly patients with SCLC have been available.

The interpatient variability in activities of daily living, performance status, and comorbidity in elderly patients is so large that it is difficult to establish a standard treatment applicable to all patients. In this review, treatments for patients with good and poor general condition were summarized separately. We believe these summaries are helpful for clinical practice and future clinical trials for elderly patients with SCLC.

Methods

We retrieved papers published during the period from 1981 to 2000 by means of a Medline search using the key words "elderly or older" and "small cell lung cancer" in the Medical Subject Headings and a manual search. The papers were then classified into the three types: (1) case-series studies, (2) subgroup analyses of phase II and phase III trials by age, and (3) prospective clinical trials in the elderly. Among the retrospective studies in the first two categories, only those in which "elderly" was defined as 70 years or older were selected for the analysis. Prospective trials of infirm as well as elderly patients, however, were included in the analysis, because both populations were frequently included in the same trial. Patient characteristics, treatment regimens, treatment delivery, toxicity, antitumor activity, and patient survival were reviewed. The general clinical characteristics of the elderly SCLC patients are summarized on the basis of the results of the first type of studies. In principle, our summary of treatment for elderly patients with good performance status and no comorbidity is based on the results of the second type of studies, and our summary for unselected elderly patients is based on the third type of studies. Evidence levels are provided according to the previously described scale (Table 1).[7]

General clinical characteristics of elderly patients with SCLC

Elderly patients 70 years of age or older accounted for 26–38% (average, 31%) of all of the patients (Table 2). The percentage of limited disease ranged from 36% to 50% in both age groups. The general condition of the elderly patients was worse than in the younger patients; patients with PS 0 or 1 accounted for only 52–69% of the elderly patients, and comorbidity was noted in 63–78%. Optimal treatment, defined as four or more treatment

Table 1 Levels of evidence

I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies. Randomized trials with low false-positive and low false-negative errors (high power)
II	Evidence obtained from at least one well-designed experimental study. Randomized trials with high false-positive and/or low false-negative errors (low power)
III	Evidence obtained from well-designed, quasi-experimental studies such as non-randomized, controlled single-arm, pre-post, cohort, time, or matched case-control series
IV	Evidence from well-designed, non-experimental studies such as comparative and correlational descriptive and case studies
V	Evidence from case reports and clinical examples

Table 2 Case-series studies on small cell lung cancer in the elderly

Authors (year)	Age	Number of patients (%)	Limited disease (%)	PS 0–1 (%)	Comorbidity (%)	Optimal treatment (%)[a]	TRD (%)	MST (month)
Nou (1996)[8]	<70	235 (68)	50	NA	NA	NA	7	11
	≤70	110 (32)	48	NA	NA	NA	8	7
Dajczman et al. (1996)[9]	<70	231 (74)	40	80	56	44	5	9
	≤70	81 (26)	43	52	75	23	5	6
Tebbutt et al. (1997)[10]	<70	102 (67)	46	60	NA	83	NA	No difference
	≤70	51 (33)	49	55	63	47	4	No difference
Jara et al. (1999)[11]	<70	59 (62)	42	71	58	59	NA	8
	≤70	36 (38)	36	69	78	39	NA	5

MST, median survival time; NA, not available; PS, performance status; TRD, treatment-related death.
[a]Optimal treatment was defined as four or more treatment cycles, relative total dose of 85% or higher, or no definition described.

cycles, relative total does of 85% or higher, or no definition available, was delivered to 23–47% of the elderly patients compared with 44–83% of the younger patients. The incidence of treatment-related death and patient survival, however, did not differ between the two age groups.

Chemotherapy for elderly patients in good general condition

Among elderly lung cancer patients, 10–30% are in good general condition without comorbidity,[9–13] and the standard chemotherapy for the general population, including cyclophosphamide, doxorubicin and vincristine (CAV), cisplatin and etoposide (PE), and CAV alternating with PE regimens, can be given to this population (Evidence level, IV). Subgroup analyses of phase II and phase III trials of SCLC by age showed that myelosuppression and doxorubicin-induced cardiotoxicity were severer in the elderly patients than in the younger patients, and that their incidence of treatment-related death tended to be higher. About 80% of elderly patients, however, received optimal treatment, and their survival was comparable to that of younger patients (Table 3).[14–16] Thus, the standard chemotherapy should be tried in these patients, although a reduction in treatment cycles and chemotherapy dose, or prolongation of treatment intervals may be needed more often than in younger patients.

Chemotherapy for unselected elderly patients

The standard chemotherapy for younger patients is not indicated for 70–90% of elderly patients because of poor performance status or the presence of complications. Oral etoposide and teniposide has been tried in these patients, but randomized trials showed that it was more toxic and had no survival benefit over the standard chemotherapy (Table 4).[17,18] A randomized trial of two-drug

Table 3 Subgroup analyses of phase III trials of small cell lung cancer by age

Authors (year)	Treatment	Age	Number of patients	Limited disease (%)	PS 0–1 (%)	Optimal treatment (%)[a]	Grade 3–4 toxicity (%)	TRD (%)	MST (month)
Paccagnella et al. (1996)[14]	CAV–PE (±TRT)	<70	254	58	ND	RDI 78	NA	3	12
		⩽70	32	56	ND	RDI 67	NA	9	12
Siu et al. (1996)[15]	CAV–PE (±TRT)	<70	520	100	88	92	Neutropenia[b] (60) Thrombocytopenia (10) Cardiac (0.2)	2	15
		⩽70	88	100	84	82	Neutropenia[b](64) Thrombocytopenia[15] Cardiac (3)	5	13
Yuen et al. (2000)[16]	PE+TRT	<70	331	100	96	90	Neutropenia[b](58) Thrombocytopenia (21) Infection (6)	1	22
		⩽70	50	100	90	78	Neutropenia[b](82) Thrombocytopenia (36) Infection (10)	10	14

CAV, cyclophosphamide, doxorubicin and vincristine; MST, median survival time; NA, not available; ND, no difference; PE, cisplatin and etoposide; PS, performance status; RDI, relative dose intensity; TRD, treatment-related death; TRT, thoracic radiotherapy.

[a] Optimal treatment was defined as four or more treatment cycles.

[b] Grade 4 only.

Table 4 Phase III studies comparing standard and low intensive chemotherapy in elderly or poor risk patients with small cell lung cancer

Authors (year)	Chemotherapy regimen	Number of patients	Age ⩾70 (%)	PS ⩾2 (%)	RR (%)	Grade 3–4 toxicty (%)	TRD (%)	MST (month)
Girling (1996)[17]	Oral E (50 mg) bid days 1–10	171	Median 67	100	61	Neutropenia[a](14), Infection (4)	14	4.3[b]
	Standard EV or CAV	168	Median 68	100	73	Neutropenia[a] (12), Infection (7)	10	6.1[b]
Souhami et al. (1997)[18]	Oral E (100 mg) bid days 1–5	75	52	48	33	Neutropenia (3), Infection (5)	2	4.8[b]
	Standard CAV/PE	80	44	56	46	Neutropenia (3), Infection (6)	1	5.9[b]
MRC (1996)[19]	EV	156	25	54	55	Leukopenia[a] (4)[b], Stomatitis[c] (34)[b]	1	4.6
	EVMC	154	27	52	54	Leukopenia[a] (16)[b], Stomatitis[c] (54)[b]	7	4.7
James et al. (1996)[20]	Half dose CAV/PE, q11 days	78	Median 63	63	59	Leukopenia (23)[b], Infection (5)	0	6.4
	Standard CAV/PE, q3w	89	Median 63	67	45	Leukopenia (7)[b], Infection (5)	1	5.8
Earl et al. (1991)[21]	Planned CEV	155	Median 65	31	NA	NA	NA	8.2
	Required CEV	145	Median 66	35	NA	NA	NA	6.8

CAV, cyclophosphamide, doxorubicin and vincristine; CEV, cyclophosphamide, etoposide and vincristine; E, etoposide; EV, etoposide and vincristine; EVMC, etoposide, vincristine, methotrexate and cyclophosphamide; MST, median survival time; NA, not available; PE, cisplatin and etoposide; PS, performance status; RR, response rate; TRD, treatment-related death.

[a] Including grade 2–4 toxicity.

[b] Statistically significant.

[c] Including grade 1–4 toxicity.