gional recurrence, whereas this is seen in 22% of patients with stage IIIA disease. These results suggest that patients with stage IIIA disease, at least, could benefit from postoperative mediastinal irradiation, whereas those with stage I or II disease might not need to undergo radiotherapy. Thus, postoperative chemoradiotherapy might be used in a future trial for stage IIIA disease.

Auperin and associates[20] reported that PCI improved both overall survival and disease-free survival among patients with SCLC in complete remission. Surgically resected SCLC would be considered SCLC in complete remission, and PCI would be indicated. Overall, 15% of the patients in our study showed brain metastasis. Even among patients with stage IA disease, more than 10% of the patients had brain metastasis. Therefore, PCI might be necessary for all patients with completely resected SCLC, whereas some authors have insisted that patients with pathologic stage IA SCLC can be cured without any adjuvant treatment.[19]

Noda and coworkers[21] reported that combination chemotherapy consisting of irinotecan (CPT-11) and cisplatin was superior to PE for extensive SCLC. Although concurrent radiotherapy with CPT-11 would be harmful, we would use the new regimen for very limited SCLC, especially for stage II or IIIA SCLC.

Major lung resection with complete hilar and mediastinal lymph node dissection followed by postoperative PE is a feasible treatment and results in a favorable survival profile. Survival was especially good for patients with stage I disease. Our strategy could be used as a standard treatment arm in a future trial for very limited SCLC.

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Multi-institutional phase II trial of irinotecan, cisplatin, and etoposide for sensitive relapsed small-cell lung cancer

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Irinotecan (CPT-11) has been shown to exhibit excellent antitumour activity against small-cell lung cancer (SCLC). A multi-institutional phase II study was therefore conducted to evaluate the efficacy and toxicity of CPT-11 combined with cisplatin (CDDP) and etoposide (ETOP) (PEI regimen) for the treatment of sensitive relapsed SCLC. Patients who responded to first-line chemotherapy but relapsed more than 8 weeks after the completion of first-line therapy ($n = 40$) were treated using the PEI regimen, which consisted of CDDP (25 mg m^{-2}) weekly for 9 weeks, ETOP (60 mg m^{-2}) for 3 days on weeks 1, 3, 5, 7, and 9, and CPT-11 (90 mg m^{-2}) on weeks 2, 4, 6, and 8 with granulocyte colony-stimulating factor support. Five complete responses and 26 partial responses were observed, and the overall response rate was 78% (95% confidence interval 61.5–89.2%). The median survival time was 11.8 months, and the estimated 1-year survival rate was 49%. Grade 3/4 leucocytopenia, neutropenia, and thrombocytopenia were observed in 55, 73, and 33% of the patients, respectively. Nonhaematological toxicities were mild and transient in all patients. In conclusion, the PEI regimen is considered to be highly active and well tolerated for the treatment of sensitive relapsed SCLC.
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Small-cell lung cancer (SCLC) is one of the most chemosensitive solid tumours, and first-line combination chemotherapy improves survival. However, despite a high response rate to chemotherapy, the majority of SCLC patients relapse. At the time of recurrence, the tumour is broadly resistant to second-line chemotherapy and is lethal within a few to several months (Glisson, 2003). The further development of not only first-line chemotherapy but also of effective salvage chemotherapies is needed.

In predicting the efficacy of salvage chemotherapy, two major factors are important: the response to the initial chemotherapy and the duration of time between the last exposure to chemotherapy and the confirmation of recurrence (Postmus *et al*, 1987; Giaccone *et al*, 1988; Ardizzoni *et al*, 1997; Ebi *et al*, 1997). Based on these factors, relapsed SCLC is now commonly classified into two main groups. Patients who both respond to the initial chemotherapy and relapse more than 2 or 3 months after the completion of chemotherapy are considered to be 'sensitive relapse' patients, while patients whose tumour is stable or progresses during the initial chemotherapy or who have a recurrence within 2 or 3 months after the completion of chemotherapy are considered to be 'refractory relapse' patients (Giaccone *et al*, 1988). Since the outcomes of salvage chemotherapy for relapsed SCLC patients are different between these two groups, the ratios of sensitive and refractory cases must be carefully considered when evaluating the results of clinical trials for second-line chemotherapy.

The combination of cisplatin (CDDP) and etoposide (ETOP) (PE regimen) has been the standard chemotherapeutic regimen for SCLC (Fukuoka *et al*, 1991; Ihde, 1992; Roth *et al*, 1992; Aisner, 1996). Moreover, PE is a reasonable second-line chemotherapy for relapsed SCLC after combination chemotherapy consisting of cyclophosphamide, doxorubicin (ADM), and vincristine (VCR) (CAV regimen); the likelihood of a response to this regimen is 40–50% (Evans *et al*, 1984; Porter *et al*, 1985). Since PE has a relatively mild toxicity profile, other cytotoxic agent can be combined with PE.

Irinotecan (CPT-11), a camptothecin derivative topoisomerase I inhibitor, has been shown to exhibit excellent antitumour activity against SCLC in monotherapy and in combination with CDDP (Masuda *et al*, 1992; Kudoh *et al*, 1998). Based on these results, the Japan Clinical Oncology Group (JCOG) conducted a randomised phase III trial comparing CPT-11 and CDDP (IP regimen) with standard PE for previously untreated extensive stage (ED) SCLC (JCOG 9511) (Noda *et al*, 2002). The response rates were significantly higher for IP than for PE, and overall survival was also significantly better for IP than for PE. This was the first study to show the superiority of any one regimen over PE for the

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treatment of ED SCLC, and IP has become one of the standard regimens for ED SCLC in Japan. Thereafter, several clinical trials of CPT-11-containing regimens for patients with limited disease (LD), ED, and relapsed SCLC have been conducted by Japanese clinical study groups (Masuda *et al*, 1998; Mori *et al*, 2002; Sekine *et al*, 2002).

Consequently, a phase I trial of CPT-11 combined with weekly CDDP (25 mg m^{-2}) and biweekly ETOP (60 mg m^{-2}) (PEI regimen) was conducted, and the recommended dose of 90 mg m^{-2} of CPT-11 was repeated every 2 weeks (JCOG 9507) (Sekine *et al*, 2003). This regimen showed promising antitumour activity in patients with untreated ED SCLC (response rate, 91%, 1-year survival rate 46%). Moreover, since the drug dose and treatment schedule can be easily modified in a weekly regimen, this protocol is considered to be suitable for relapsed SCLC patients, who usually present with severe haematological toxicities during salvage chemotherapy because of poor bone marrow reserve (Masuda *et al*, 1990; Faylona *et al*, 1995).

Based on these results, we conducted two phase II trials to evaluate the efficacy and toxicities of PEI in patients with sensitive and refractory relapsed SCLC, separately. In this paper, the final results for the sensitive relapsed SCLC group are reported.

PATIENTS AND METHODS

Patient selection

Patients with histologically or cytologically confirmed SCLC who respond to first-line chemotherapy or chemoradiotherapy and relapsed more than 8 weeks after the completion of first-line treatment were candidates for the present study. Additional eligibility criteria were as follows: (1) age of 75 years or younger; (2) performance status of 0–2 on the Eastern Cooperative Oncology Group scale; (3) measurable disease; (4) adequate organ function as documented by a $4.0 \times 10^9 l^{-1} \leqslant$ WBC count $\leqslant 12.0 \times 10^9 l^{-1}$, haemoglobin level of $\geqslant 9.0$ g dl^{-1}, platelet count of $\geqslant 100 \times 10^9 l^{-1}$, total serum bilirubin level of $\leqslant 1.5$ mg dl^{-1}, a hepatic transaminase level of $\leqslant 2$ times the institutional upper limit of normal, a serum creatinine level of $\leqslant 1.5$ mg dl^{-1}; and (5) written informed consent. Patients were not eligible for the study if they had experienced any of the following events: (1) massive pleural effusion requiring drainage; (2) prior radiotherapy with an irradiated area larger than one-third of the bone marrow volume; (3) active infection; (4) contraindications for the use of CPT-11, including diarrhoea, ileus, interstitial pulmonary fibrosis, massive ascites, or hypersensitive reaction to CPT-11; (5) serious concomitant medical illness, including severe heart disease, uncontrollable diabetes mellitus or hypertension; or (7) pregnancy or lactation. This study was approved by the institutional review board at each participating institution.

Treatment schedule

Figure 1 shows the treatment schema of the PEI regimen. CDDP (25 mg m^{-2}) was administered intravenously (i.v.) over 60 min on day 1 and at 1-week intervals for 9 weeks; ETOP (60 mg m^{-2}) was administered i.v. over 60 min on days 1–3 of weeks 1, 3, 5, 7, and 9; and CPT-11 (90 mg m^{-2}) was administered i.v. over 90 min on day 1 on weeks 2, 4, 6, and 8. Hydration (2000 ml) and granisetron (40 μg kg^{-1}) were given on day 1. After day 1 on week 2, granulocyte colony-stimulating factor (G-CSF) (50 μg m^{-2}) was administered routinely according to JCOG 9507 on days when the cytotoxic drugs were not given, unless the WBC count exceeded $10.0 \times 10^9 l^{-1}$. Patients were expected to complete at least six cycles of this regimen; if the toxicities were acceptable and the tumour responded to the treatment, a maximum of nine cycles of chemotherapy were performed.

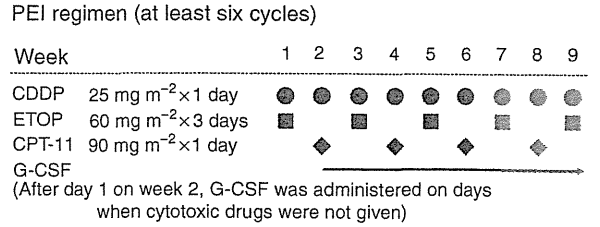

Figure 1 Treatment schedule.

Toxicity assessment and treatment

During the course of treatment, complete blood cell counts and differential counts were analysed twice a week, and routine chemistry measurements and a chest X-ray were performed once a week. Toxicity was graded according to the toxicity criteria of the JCOG (Tobinai *et al*, 1993), a modified version of the NCI Common Toxicity Criteria issued in 1991. Grade 4 neutropenia was defined as $<0.5 \times 10^9 l^{-1}$, and grade 3 neutropenia was defined as between (and including) $0.5-1.0 \times 10^9 l^{-1}$, according to the JCOG criteria. The second and subsequent cycles of chemotherapy were delayed for 1 week if one of the following toxicities was noted on day 1: a WBC count of $<2.0 \times 10^9 l^{-1}$, a platelet count of $<50 \times 10^9 l^{-1}$, a serum creatinine level of $\geqslant 2.0$ mg dl^{-1}, an elevated hepatic transaminase level or total serum bilirubin of grade 2 or higher, diarrhoea of grades 1–2, fever $\geqslant 38$°C, or a performance status of 3. The treatment was terminated if the above-mentioned criteria did not disappear in 3 weeks or if one of the following severe nonhaematological toxicities was noted: diarrhoea of grade 2 lasting for more than 1 week, diarrhoea of grade 3, neurotoxicity of grade 3, or drug-induced pneumonitis.

Dose modifications for toxicity

The CPT-11 dosage was reduced to 67.5 mg m^{-2} (25% reduction) in subsequent cycles if one of the following toxicities was noted: a WBC count of $<1.0 \times 10^9 l^{-1}$, or a platelet count of $<25 \times 10^9 l^{-1}$. If the above-mentioned toxicities reappeared after a 25% reduction in the dosage, the CPT-11 dosage was further reduced to 50 mg m^{-2} (44% reduction). Since CDDP (25 mg m^{-2}) and ETOP (60 mg m^{-2}) in this regimen were relatively low dose, no dose modifications for these drugs were permitted.

Pretreatment evaluation

Pretreatment assessment included a complete blood cell count, differential counts, routine chemistry measurements, creatinine clearance, blood gas analysis, electrocardiogram, chest X-rays, computed tomography (CT) scan of the chest, brain CT scan or magnetic resonance imaging (MRI), abdominal CT scan or ultrasound sonography, radionuclide bone scan, and bone X-rays, if indicated.

Response evaluation

Objective tumour responses were evaluated in all enrolled patients according to the WHO criteria issued in 1979 (WHO, 1979). 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) referred to a decrease in the total tumour size of at least 50% 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 and the appearance of no progressive or new lesions for at least 4 weeks. Progressive disease (PD) was

defined as a 25% or greater increase in the size of any measurable lesion or the appearance of new lesions. Patients whose responses were not evaluated were included in the analysis as not evaluable (NE).

Statistical methods

The primary end point of this study was the response rate, defined as the proportion of patients whose best response was CR or PR among all eligible patients, and its confidence interval was based on an exact binomial distribution. Simon's two-stage minimax design was used to determine the sample size and decision criteria. Assuming that a response rate of 40% in eligible patients would indicate a potential usefulness of the regimen while a rate of 20% would be the lower limit of interest and that alpha = 0.05 and beta = 0.20, the estimated number of required patients was 33 (Simon, 1989). Finally, this regimen would be considered worthy of further testing if 11 (33%) or more eligible patients showed an objective response. At the first stage decision, this regimen would be rejected if four (22%) or fewer of 18 eligible patients had an objective response. Thus, we determined that the sample size would be 35 registered patients. The planned accrual period was 2 years, and the follow-up period was set as 1 year after the completion of accrual. Secondary end points were toxicity and overall survival. The duration of overall survival was measured from the date of registration to the date of death from any cause or the last follow-up examination. Progression-free survival was calculated from the date of registration until evidence of PD. All patients started the treatment within 1 week of registration. The survival distribution was estimated by the method of Kaplan and Meier (1958).

RESULTS

Patient characteristics

From October 1998 to March 2001, 40 patients were enrolled in this study. The first-stage decision was made in October 1999, when 22 patients were registered. Three CRs and 13 PRs were observed in 18 analysed patients, resulting in a response rate of 89% (95% confidence interval (CI), 65.3–98.6%). This result did not meet the criteria for stopping the study as defined in the protocol, and the study was continued. At the time of the final analysis, there were three censored cases (8%). The median follow-up period for these cases was 25.5 months (range, 4.4–46.1 months).

The clinical characteristics of the enrolled patients are listed in Table 1. Of the 40 patients in the total, 29 (73%) were male and 11 (27%) were female; the median age was 67 years. A total of 39 patients (97%) had a good performance status of 0 or 1. The extent of the disease at the time of recurrence was LD in five patients (12%) and ED in 35 (88%). All 40 patients had been previously treated using platinum-based chemotherapy, such as PE in 11 patients, carboplatin plus ETOP in 11, PE plus weekly CDDP/VCR/ADM/ETOP (CODE) in six, CDDP plus CPT-11 in six, PEI in two, and other regimens in four. Eight (20%) of these patients received thoracic radiotherapy. All patients were eligible, and the toxicity and efficacy of the regimen was evaluated in all 40 patients.

Compliance with treatment

A total of 251 treatment cycles were administered, with a median of six cycles per patient (range, 1–9 cycles). A total of 32 patients (80%) completed six or more cycles of chemotherapy, and the median number of weeks for completing six cycles of chemotherapy was 7 weeks (range 6–10 weeks). Eight patients could not complete the planned six or more cycles for the following reasons: toxicities in four cases (grades 4 and 3 diarrhoea, grade 3 liver dysfunction, and grade 3 erythema); patient refusal in three cases; and PD in one case. Six patients (15%) had their dosage of CPT-11 reduced because of leucocytopenia in three, thrombocytopenia in two, and both in one.

Clinical response and survival

All the patients were included in the analyses of tumour response and survival. Five CRs (13%) and 26 PRs (65%) were observed, for an overall response rate of 78% (31 out of 40 patients; 95% CI, 61.5–89.2%). Four NC, four PD, and one NE were also observed. One patient was lost to follow-up and only two patients were still alive as of April 16, 2003. The median survival time (MST) was 11.8 months (95% CI, 10.1–13.5 months), and the estimated 1-year survival rate was 49% (Figure 2).

Table 1 Patient characteristics

Total no. of patients	40
Age, median (range)	67 (41–74)
Sex	
Male	29
Female	11
ECOG performance status	
0	9
1	30
2	1
Disease extent at relapse	
Limited disease	5
Extensive disease	35
Prior chemotherapy	
CDDP/ETOP	11
CBDCA/ETOP	11
CDDP/ETOP/CODE	6
CDDP/CPT-11	6
PEI	2
Others	4
Prior thoracic radiotherapy	8

ECOG = Eastern Cooperative Oncology Group; CDDP = cisplatin; ETOP = etoposide; CBDCA = carboplatin; CODE = cisplatin/vincristine/doxorubicin/etoposide; CPT-11 = irinotecan; PEI = cisplatin/etoposide/irinotecan.

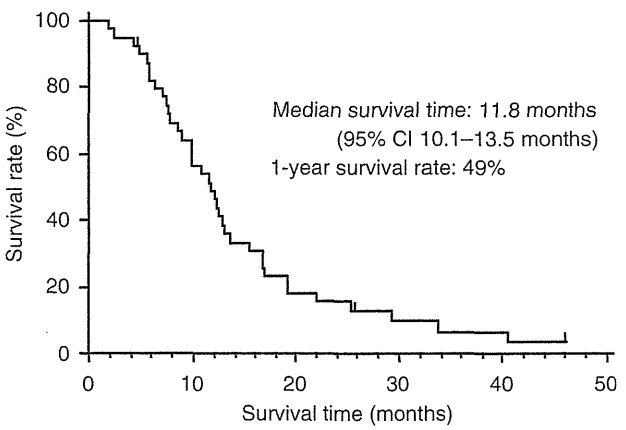

Figure 2 Overall survival ($n = 40$).

Site of first relapse and progression-free survival

The majority of patients ($n=30$, 75%) experienced a systemic relapse after completing PEI, including 17 patients (43%) with central nerve metastases. Six patients (15%) developed only a locoregional recurrence, and one had no recurrence and died of acute myocardial infarction. No data on recurrence patterns were available in three patients because these patients were followed up at other hospitals. In all, 13 patients received additional chemotherapy treatment after recurrence (no data on response to third-line chemotherapy were available), while four patients underwent palliative chest radiotherapy and 18 underwent whole-brain irradiation for cerebral metastases. One patient, who achieved a CR by this regimen, developed a locoregional recurrence and underwent a right upper lobectomy. He has not experienced any further relapse and is still alive. The median progression-free survival period was 5.0 months (95% CI, 4.1–5.9 months) (Figure 3).

Toxicities

All the patients were included in the toxicity analysis. Severe toxicities were mainly haematological. Grades 3–4 leucopenia, neutropenia, and thrombocytopenia were observed in 22 (55%), 29 (73%), and 13 (33%) patients, respectively (Table 2). Nonhaematological toxicities were mild and transient in all patients. Grades 3–4 diarrhoea was noted in only three patients (8%) (Table 3). No treatment-related deaths occurred.

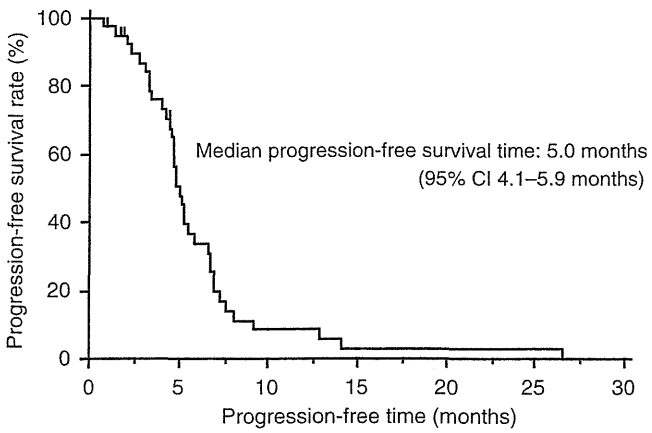

Figure 3 Progression-free survival ($n=40$).

Table 2 Haematological toxicities (JCOG toxicity criteria)

	0	1	2	3	4	% of Grs 3 and 4
Leucocytopenia	2	3	13	17	5	55
Neutropenia	3	4	4	12	17	73
Anemia	2	4	16	18	—	45
Thrombocytopenia	10	7	10	7	6	33
Elevated total bilirubin	33	—	6	1	0	3
Elevated GOT	32	7	0	1	0	3
Elevated GPT	30	7	2	1	0	3
Elevated creatinine	37	3	0	0	0	0
Hyponatremia	28	4	6	0	2	5
Hypokalemia	32	5	3	0	0	0

Grs = grades; GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase.

Table 3 Nonhaematological toxicities (JCOG toxicity criteria)

	0	1	2	3	4	% of Grs 3 and 4
PS	1	30	4	5	0	13
Infection	28	4	7	1	0	3
Fever	29	7	4	0	0	0
Nausea/vomiting	11	15	11	3	—	8
Diarrhoea	15	16	6	2	1	8
Mucositis	36	4	0	0	0	0
Arrythmia	36	2	0	1	1	5
Eruption	37	1	1	1	0	3
Alopecia	16	17	7	—	—	—
Allergy	39	0	1	0	0	0

Grs = grades; PS = performance status.

DISCUSSION

Despite a high response rate to first-line chemotherapy, most patients with SCLC experience a relapse within a year of the completion of therapy (Hansen, 1992). Although many relapsed patients in good physical condition undergo second-line chemotherapy, the results are disappointing. The obtained response is usually brief, and the median survival period is generally less than 4 months (Albain *et al*, 1993; Glisson, 2003).

Although one phase III trial for patients with relapse SCLC comparing the use of topotecan with CAV has been reported (von Pawel *et al*, 1999), a standard treatment for relapsed SCLC has not been agreed upon. However, the repeated use of the original induction regimen is the most popular treatment for sensitive relapsed patients. Reinduction chemotherapy has been reported to produce a response rate of 50%, and patients who relapsed more than 3 months after the end of their previous chemotherapy regimen were sensitive to reinduction chemotherapy (Giaccone *et al*, 1987; Postmus *et al*, 1987). Giaccone *et al* (1988) suggested that sensitive tumour cells, which were not completely eradicated by the induction chemotherapy, regrow spontaneously after the suspension of chemotherapy, eventually constituting a clinically significant part of the tumour burden. In the present study, two patients received the PEI regimen as a reinduction chemotherapy, and both patients showed PRs.

Many clinical trials of salvage chemotherapy for relapsed SCLC have been reported. In these studies, the single administration of CPT-11 or ETOP produced good results, with response rates of 16–47% and an MST of 3.5–6.2 months (Einhorn *et al*, 1990; Johnson *et al*, 1990; Masuda *et al*, 1992; Le Chevalier *et al*, 1997). Moreover, CPT-11 or ETOP-containing combined chemotherapy regimens showed favourable results, with response rates of 20–88% and an MST of 4.7–8.7 months (Table 4) (Evans *et al*, 1985; Masuda *et al*, 1990; Sculier *et al*, 1990; Gridelli *et al*, 1991; Roth *et al*, 1992; Faylona *et al*, 1995; Kubota *et al*, 1997; Masuda *et al*, 1998; Groen *et al*, 1999; Nakanishi *et al*, 1999; von Pawel *et al*, 1999; Domine *et al*, 2001; Kosmas *et al*, 2001). Therefore, these two drugs are considered to be key drugs for the treatment of relapsed SCLC. In particular, the combination of CPT-11 and ETOP (a combination of topoisomerase I and II inhibitors) produced a high response rate (71%) and the best survival results (MST, 8.7 months) (Masuda *et al*, 1998). In addition, a weekly chemotherapy regimen containing ETOP (CODE) was highly active in patients with relapsed SCLC, with a favourable response rate (88%) and survival duration (MST, 8.2 months) (Kubota *et al*, 1997). In the two studies mentioned above, four patients (16%) with refractory relapsed SCLC were included in the CPT-11 and ETOP study, and six patients (35%) with refractory relapsed SCLC were included in the CODE study. Three and five of these patients achieved PR, respectively.

Table 4 Combination chemotherapy studies for relapsed small-cell lung cancer

Author	Regimen	No. of pts	% of ref pts (%)	RR (%)	RR in ref pts (%)	MST (month)
Sculier	CAV	61	75	21	5	6.2–7.5
von Pawel	CAV	104	20	18	5	6.2
Roth	CAV	41	32	12	8	NM
Roth	PE	59	46	22	15	NM
Evans	PE	78	50	55	28	NM
Masuda	PE	20	NM	50	NM	4.7
Gridelli	CCNU/MTX	33	100	21	21	4.0
Faylona	PE/IFO	46	41	55	50	6.8
Kubota	CODE	17	35	88	83	8.2
Masuda	CPT-11/ETOP	25	16	71	75	8.7
Nakanishi	CPT-11/CDDP	5	100	20	20	NM
Domine	GEM/PTX	31	58	50	40	NM
Groen	CBDCA/PTX	35	100	74	74	7.2
Kosmas	CDDP/IFO/PTX	33	61	73	70	6.5

Pts = patients; ref = refractory; RR = response rate; MST = median survival time; CAV = cyclophosphamide/doxorubicin/vincristine; PE = cisplatin/etoposide; CCNU = lomustine; MTX = methotrexate; IFO = ifosfamide; CODE = cisplatin/vincristine/doxorubicin/etoposide; CPT-11 = irinotecan; ETOP = etoposide; CDDP = cisplatin; GEM = gemcitabine; PTX = paclitaxel; CBDCA = carboplatin; NM = not mentioned.

The response and survival data from Japanese clinical trials for relapsed SCLC were generally better than those obtained in western countries. We have no proof that this difference depends on either drug metabolism or tumour sensitivity. It is possibly related to the difference in patient follow-up interval between Japan and western countries. Since intensive follow up after completion of first-line treatment is common in Japan, relapses can be detected in the early stage by CT or MRI before becoming symptomatic. Therefore, relapsed patients had a relatively good performance status, and showed good responses to second-line chemotherapy as well as better survival results.

The weekly regimen was designed to increase the overall relative dose intensity of the chemotherapeutic drugs (Murray *et al*, 1991). However, several phase III trials have made it clear that intensive weekly chemotherapy does not improve the survival of patients with SCLC (Furuse *et al*, 1998; Murray *et al*, 1999). On the other hand, drug dosages and treatment schedules are easy to modify in weekly chemotherapy regimens. Since patients with relapsed SCLC may have lower bone marrow reserve, a high-dose regimen or intensified dosage can lead to treatment-related death (Masuda *et al*, 1990; Faylona *et al*, 1995). In the PEI regimen, the individual dosage of each drug is within the commonly used range and the dose given at one time is lower than that of a standard 3-week cycle regimen. The PEI regimen therefore permits greater flexibility in dosage adjustment and treatment delays based on laboratory data or the physical condition of patients. Thus, this regimen is considered to be suitable for the treatment of patients with relapse SCLC. In addition, this weekly schedule may be of great advantage for enabling the synergistic effects of ETOP (a topoisomerase II inhibitor) and CPT-11 to be realised because the development of resistance to topoisomerase II inhibitors has been reported to increase tumour sensitivity to subsequent treatment with topoisomerase I inhibitors (Vasey and Kaye, 1997).

Three cytotoxic drugs were used in this PEI regimen. However, three-drug combination chemotherapy was reportedly associated with more severe toxicity and showed no survival benefit as compared with the two-dug combination (Mavroudis *et al*, 2001; Niell *et al*, 2002). The main reason for mild toxicities was that the PEI regimen consists of a weekly schedule. With a weekly chemotherapy regimen, drug dosages and treatment schedules can easily be adjusted according to haematological data and the patient's physical condition. These careful modifications resulted in a mild toxicity profile with the PEI regimen. Moreover, the PEI regimen did not consist of concomitant administration of three drugs but rather weekly alternative administration of a two-drug combination chemotherapy, that is, PE and IP. As a result, the toxicity profile was similar with that of two-drug combination chemotherapy.

Although all the patients in this study were sensitive relapsed cases, the overall response rate of 78% is one of the best results reported for relapsed SCLC. Moreover, although only selected patients with a good performance status were included in this study, it is notable that the median survival time was 11.8 months and the 1-year survival rate was 49%. In JCOG- 9511, the MST was 12.8 months in the IP arm and 9.4 months in the PE arm for chemotherapy naive ED SCLC patients (Noda *et al*, 2002). Our survival data for PEI is almost equivalent to that of first-line treatment. Salvage chemotherapy may be possible to prolong the survival of sensitive relapsed SCLC patients who are in good physical condition.

Since second-line chemotherapy for relapsed SCLC patients is a palliative treatment, a reasonable toxicity profile is essential. The main toxicities of the PEI regimen were haematological. Although G-CSF was routinely administered, Grades 3–4 leucopenia and neutropenia were observed in 55 and 73% of patients, respectively. Grades 3–4 thrombocytopenia was observed in 33% of patients. However, the frequencies of these haematological toxicities were approximately equal to that of first-line PE treatment (Noda *et al*, 2002). Nonhaematological toxicities were mild and transient in all patients. Grades 3–4 diarrhoea was noted in only three patients (8%). Irinotecan dose modifications as a result of haematological toxicities were only performed in six patients (15%). All toxicities were easily manageable, and no treatment-related deaths occurred.

In conclusion, PEI is a highly active and well-tolerated treatment for sensitive relapsed SCLC. Another phase II trial restricted to refractory relapsed SCLC patients is presently being performed by our clinical group. Further phase III studies comparing PEI regimen with rechallenges of the same drugs used in the first-line chemotherapy regimen should clarify the role of second-line chemotherapy for sensitive relapsed SCLC and are now being planned.

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ORIGINAL ARTICLE

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Clinical and pharmacokinetic study of docetaxel in elderly non-small-cell lung cancer patients

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Abstract *Purpose*: To evaluate the usefulness and pharmacokinetics of docetaxel in the treatment of elderly patients with advanced non-small-cell lung cancer. *Patients and methods*: Chemotherapy-naive elderly patients (aged at least 76 years) with locally advanced or metastatic non-small-cell lung cancer were accrued. Eligible patients received at least two cycles of docetaxel at a dose of 60 mg/m^2 on day 1 over 1 h every 3 weeks. Patients who were considered ineligible for this study were also registered. Symptom control was assessed using a questionnaire during the treatment period. The pharmacokinetics of docetaxel were evaluated in the first cycle of chemotherapy. *Results*: Of 35 elderly patients, 15 (43%) met the study eligibility criteria. The reasons for ineligibility consisted mainly of poor performance status, poor bone marrow function, and hypoxemia (six patients each). A total of 49 cycles of chemotherapy (median 2 cycles, range 1–12 cycles) were administered to the eligible patients, six of whom achieved a partial response (overall response rate 40%, 95% confidence interval 15–65%). The major toxicity was hematologic, with grade 3 or greater neutropenia and grade 3 neutropenic fever developing in 13 patients (87%) and five patients (33%), respectively. Symptoms, as assessed in terms of the symptom control score, did not clearly decline during the treatment period. The values (mean ± SD) of C_{max}, $AUC_{0 \rightarrow inf}$, and $t_{1/2}$ were 1.35 ± 0.32 μg/ml, 1.79 ± 0.52 μg h/ml, and 4.1 ± 2.3 h, respectively. *Conclusions*: Although the validity of the results of this study is limited due to the small sample size, docetaxel appears effective in selected elderly patients with advanced non-small-cell lung cancer.

Keywords Docetaxel · Elderly · Non-small-cell lung cancer · Pharmacokinetics · Symptom control assessment

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Introduction

The incidence and mortality rate of lung cancer are increasing in Western countries and Japan. In the United States, the incidences of lung cancer per 100,000 persons from 1994 through 1997 were 565.5 for men and 294.1 for women, and peaked between the ages of 75 and 79 years [18]. In Osaka prefecture, Japan, the incidence also peaked above 74 years of age in the same period [18]. In addition, the mortality rates of lung cancer patients older than 74 years were 42.2% for men and 53.4% for women in Japan in 1999 [14]. Accordingly, treatment of elderly patients with lung cancer is of particular concern.

Cisplatin-based chemotherapy has been proven to improve survival of patients with advanced non-small-cell lung cancer (NSCLC) compared to best supportive care [11]. However, this benefit is modest and is limited to patients who have favorable conditions such as good performance status (PS) and younger age. In clinical trial, the upper age limit is usually set at 65 or 70 years, or 75 years at most; therefore, patients older than 75 years have been excluded from clinical trials.

The diversity of the elderly population makes it particularly difficult to determine the appropriateness of chemotherapy. The prevalence of comorbidity, functional limitations, socioeconomic restrictions, and geriatric syndromes appears to increase in patients greater than 74 years of age. Although no precise formulae are available for determining the physiologic age of patients, Balducci and Extermann have noted that an age of 75 years might represent a reasonable cut-off point to define older individuals [1]. In addition, it remains unclear how many patients can be treated with chemotherapy among all elderly patients with NSCLC, since there have been few reports on the proportion of patients eligible for chemotherapy among all elderly individuals with advanced NSCLC.

New anticancer agents such as vinorelbine, gemcitabine, and taxanes were developed and introduced for the treatment of NSCLC in the 1990s [2]. Among these agents, docetaxel is the first agent to be approved in Japan. The approved dose (60 mg/m^2) in Japan is lower than that (100 mg/m^2) in the United States and European countries [4]. However, this low dose of docetaxel is sufficiently effective with a low incidence of toxicities such as hypersensitivity and peripheral edema [4, 9].

On the basis of these considerations, a phase II study of docetaxel in elderly patients with advanced NSCLC was conducted in order to (1) evaluate the proportion of patients eligible for this study among all elderly patients with advanced NSCLC, (2) assess the efficacy and safety of docetaxel in the treatment of selected elderly patients, (3) examine the tolerability of this treatment from the view point of symptom control assessment during the treatment period, and (4) examine the pharmacokinetic profile of docetaxel in the elderly.

Patients and methods

Eligibility criteria

Chemotherapy-naive elderly patients (aged at least 76 years) with histologically or cytologically confirmed locally advanced (stage IIIA with N2 or IIIB) or metastatic (stage IV) NSCLC were accrued to this study. Eligibility criteria included an Eastern Cooperative Oncology Group PS of two or less, at least one measurable or assessable lesion, and life expectancy of 3 months or longer. Before enrollment, a complete medical history was obtained from each patient, and each underwent physical, laboratory, and staging work-up examinations. Laboratory examinations included complete blood cell counts with differential, routine serum chemistry and tumor marker analyses, 24-h creatinine clearance evaluation, arterial blood gas analysis, urinalysis, electrocardiogram, and pulmonary function tests. Staging work-up examination consisted of chest radiograph, computerized tomography (CT) of the chest and abdomen, magnetic resonance imaging of the brain, radionucleotide bone scan, and fiberoptic bronchoscopy. On laboratory examination, patients were required to have adequate organ function, as evidenced by a leukocyte count between 4000 and 12,000/μl, a neutrophil count of 2000/μl, a hemoglobin level of 9.5 g/dl, a platelet count of 100,000/μl, a total bilirubin level of 1.5 mg/dl, AST and ALT levels 2.5 times the upper limit of the normal range, a serum creatinine level not more than the upper limit of the normal range, and a PaO_2 of 65 mmHg. Patients with active infection, interstitial pneumonia, peripheral edema, or pleural or pericardial effusion that required drainage (patients with pleural effusion who had been successfully treated with agents other than anticancer drugs were eligible), a history of severe hypersensitivity, symptomatic brain metastasis, or active concomitant malignancy were excluded. Patients who were for other reasons considered not suited for study entry by the treating physician were also excluded. In addition, concomitant use of ketoconazole, miconazole, erythromycin, or clarithromycin was not permitted in this study, because it is possible that docetaxel metabolism is inhibited by these agents via liver cytochrome P450 isozyme CYP3A [7].

Written informed consent was obtained from all patients. Three institutions participated in this study, and each of their Institutional Review Boards approved this study. The registration office (National Shikoku Cancer Center) entered the patients after verification of eligibility. Patients who were considered ineligible for this study were also registered in order to assess the reasons for ineligibility and estimate the proportion of eligible patients among the entire elderly population with advanced NSCLC.

Chemotherapy

Eligible patients received at least two cycles of docetaxel monotherapy. Docetaxel was given at a dose of 60 mg/m^2 on day 1 and repeated every 3 weeks. It was diluted in 500 ml 5% glucose or 0.9% saline solution, and was infused over a 1-h period. Antiemetic treatment was left to the treating physician. Prophylactic administration of dexamethasone was used to prevent fluid retention or hypersensitivity reaction, as well as for the prevention of emesis. Administration of granulocyte-colony stimulating factor (G-CSF) was allowed when grade 4 neutropenia or grade 3 neutropenic fever occurred. This administration was continued until the neutrophil count recovered to 5000/μl. The dose of docetaxel was reduced to 50 mg/m^2 in the presence of grade 4 hematologic toxicities lasting 3 days or when grade 3 non-hematologic toxicities had developed in the prior cycle of chemotherapy. Chemotherapy was withdrawn when similar toxicities were observed at this reduced dose level. In addition, docetaxel administration was postponed for up to 2 weeks (a maximum 6 weeks between administrations) when leukocyte, neutrophil, and platelet counts were less than 4000,

2000, and 100,000/μl, respectively. Chemotherapy was discontinued when delay of hematologic recovery continued for over 2 weeks. Other criteria for early interruption of this protocol treatment included progression of disease, emergence of intolerable toxicities, and withdrawal of consent. In addition, chemotherapy was discontinued for patients who were assessed as having stable disease after completion of two cycles of chemotherapy. Responders were allowed to continue this treatment until disease progression or the emergence of intolerable toxicities.

Toxicity and response evaluation

For evaluation of response and toxicity, all patients underwent as inpatients a series of examinations consisting of complete blood cell counts with differential, routine chemistry profiles, and chest radiograph on at least a weekly basis during the treatment period and then on a monthly basis. In addition, the patients' clinical characteristics such as symptoms, body temperature, and weight were periodically recorded. Evaluation of target lesions was performed after each cycle of chemotherapy, and the same examinations as for the staging work-up study were performed after completion of treatment.

Responses were assessed using the World Health Organization criteria [8]. The response to treatment, including eligibility and assessability, was determined for each patient by extramural reviewers. Complete response was defined as the disappearance of all measurable lesions for at least 4 weeks. Partial response (PR) was defined as a 50% decrease in the sum of the products of the greatest perpendicular diameters of all measurable lesions for at least 4 weeks without the development of new lesions. Progressive disease (PD) was defined as a 25% increase in the sum of the products of the perpendicular diameters of all measurable disease or the appearance of new lesions. If no response or progression of disease occurred during therapy, treatment outcome was considered to be no change (NC). Toxicities were assessed and graded using the National Cancer Institute Common Toxicity Criteria, version 2.0 (the Japan Clinical Oncology Group version) [10]. The worst degree of toxicity experienced throughout the treatment was computed for each patient.

Symptom control assessment

A quality-of-life (QOL) questionnaire for cancer patients treated with anticancer drugs (QOL-ACD) has been developed in Japan [5]. It is a 22-item questionnaire that covers four domains consisting of functional, physical, mental, and psychosocial well-being. In addition, global QOL is assessed using a face scale. In this study, assessment of symptoms during chemotherapy was performed using a questionnaire that consisted of four items selected from the QOL-ACD questionnaire (feeling, appetite, vomiting, and sleep) and an additional item concerning respiratory condition (cough and sputum). Assessment of global QOL using the face scale was also performed. Each patient was asked to fill in this questionnaire at the time of study entry (baseline symptom score) and immediately before each cycle of chemotherapy. Severity of each symptom during chemotherapy was scored using a visual analogue scale and was assessed compared with the baseline value.

Pharmacokinetic evaluation

The pharmacokinetics of docetaxel were studied in the first cycle of chemotherapy. Samples were taken at the following time points: predose, midinfusion, end of infusion, and 30 min and 2, 3, 5, 7, 23, 47 and 71 h after infusion. All blood samples were immediately centrifuged and the heparinized plasma was stored at −20°C until analysis. Subsequent assays and pharmacokinetic analysis were performed based on a previously described method [13]. Briefly, docetaxel concentrations in plasma were determined by high-performance liquid chromatography with UV detection. Docetaxel and internal standard were determined by a UV detector adjusted to 225 nm, and peak heights were used for quantification. Pharmacokinetic parameters were calculated using WinNonlin computer software (Pharsight, Mountain View, Calif.). The maximum plasma concentration (C_{max}) was obtained from the actual value. The terminal rate constant (k) was determined by log-linear regression analysis of the terminal phase of the plasma concentration vs time curve. The terminal half-life time ($t_{1/2}$) was calculated by the equation $t_{1/2} = 0.693/k$. The area under the concentration vs time curve (AUC) was calculated by the linear trapezoidal rule up to the last measurable data points with extrapolation to infinity. The clearance (CL) was calculated by dividing the dose received by the AUC.

Statistical considerations

The sample size of this study was determined with the assumption of an expected response rate of 20%, with a 95% confidence interval (CI) of ±10%. Accrual of 61 patients was therefore required for this study. Statistical analyses were performed using the SPSS Base System and Advanced Statistics programs (SPSS, Chicago, Ill.). The significances of differences between baseline and during-treatment or post-treatment symptom scores were determined using Student's paired *t*-test. The global QOL score was similarly analyzed. Survival time was defined as the period from initiation of treatment to death or last follow-up evaluation. In addition, time to progression was defined as the period from initiation of treatment to PD. Patients who received additional thoracic radiotherapy were censored at the start of

irradiation. Survival curves were calculated using the method of Kaplan and Meier.

Results

Patient characteristics

Between November 1999 and December 2001, 35 elderly patients with advanced NSCLC were accrued to this study. Of these, 15 (43%) met the study eligibility criteria. Although the sample size of this study was designed to be 61 patients on an eligible patient basis, the study was terminated early due mainly to the slow rate of accrual of patients.

The characteristics of the entire group of patients and eligible patients are listed in Table 1. The median ages and age ranges were similar for the two groups. However, the proportions of patients with a poor PS, adenocarcinoma, or metastatic disease were higher in the entire group than in the eligible group. The proportion of patients with weight loss was not determined in the entire group, since assessment of weight loss was not required for registration of patients ineligible for this study. The reasons for ineligibility for study entry were poor PS ($n=6$), poor bone marrow function ($n=6$), hypoxemia ($n=6$), life expectancy less than 3 months ($n=4$), physician's discretion ($n=4$), symptomatic brain metastasis ($n=2$), double cancer ($n=2$), poor renal function ($n=1$), infection ($n=1$), and interstitial lung disease ($n=1$). More than one reason was noted in seven patients. In addition, two patients refused chemotherapy. Among ineligible patients, two received chemotherapy; one with anemia received docetaxel at a dose of 60 mg/m^2, and the other with anemia and hypoxemia received vinorelbine monotherapy. The serum albumin values (means ± SD) were 3.6 ± 0.30 g/dl in 15 eligible patients and 3.9 ± 0.39 g/dl in 20 ineligible patients. In addition, the value of plasma alpha-1 acid glycoprotein (AAG), which was measured in ten eligible patients, was 1.22 ± 0.39 g/l.

Table 1 Patient characteristics (*NE* not evaluated)

	All patients ($n=35$)	Eligible patients ($n=15$)
Age (years)		
Median	78	78
Range	76–87	76–87
Sex		
Male	27	12
Female	8	3
ECOG performance status		
0	4	3
1	19	10
2	6	2
3	3	0
4	3	0
Histology		
Adenocarcinoma	18	7
Squamous cell	14	6
Adenosquamous cell	2	1
Not otherwise specified	1	1
Stage		
IIIA	8	3
IIIB	8	6
IV	19	6
Weight loss		
< 5%	NE	12
≥5%	NE	3

Chemotherapy outcome

A total of 49 cycles of chemotherapy were administered to 15 eligible patients. The median number of chemotherapy cycles was two (1 cycle in two patients, 2 cycles in six, 3 cycles in four, 5 cycles in one, 6 cycles in one, and 12 cycles in one). Two patients who had disease progression or developed docetaxel-related interstitial lung toxicity received only one cycle of chemotherapy. Four patients underwent reduction of dose of docetaxel because of grade 4 neutropenia lasting for 3 days ($n=3$), grade 3 neutropenic fever ($n=1$), or grade 3 nausea ($n=1$). One patient developed both grade 4 neutropenia and grade 3 nausea. In addition, the median interval between each cycle of chemotherapy was 22 days (range 19–30 days).

Of the 15 patients, 6 achieved PR, 6 NC, and 2 PD. Response was not evaluated for one patient who developed docetaxel-related interstitial pneumonia. The overall response rate was 40%, with a 95% CI of 15–65%. Four patients with stage IIIA ($n=3$) or IIIB disease ($n=1$) received additional thoracic radiotherapy. The plasma AAG levels of two patients with PD were 1.85 and 1.79 g/l, respectively, which were the highest and the second highest values in this study. With a median follow-up period of 27.9 months (range 16.2–42.5 months), median progression-free survival time was 6.1 months (95% CI 5.6–6.6 months). At the time of analysis, 11 patients had died and four were still alive. The cause of death was directly related to NSCLC in ten patients and unrelated in one (interstitial pneumonia). This complication of interstitial pneumonia, occurring in another patient who developed docetaxel-related lung toxicity, was observed more than 12 months after completion of chemotherapy. The median survival time was 15.6 months (95% CI 11.4–19.8 months), with 1-year and 2-year survival rates of 73.3% and 37.3%, respectively.

The toxicities observed in the 15 patients during treatment and the follow-up period are listed in Table 2. The major toxicity was myelosuppression, with grade 3 or higher leukopenia and neutropenia observed in 9 patients (60%) and 13 patients (87%), respectively. Grade 3 neutropenic fever occurred in five patients (33%). G-CSF was administered to 13 patients (87%) over a median duration of 4 days (range 2–6 days). Grade 3 nonhematologic toxicities observed in this study included fatigue (33%), dyspnea (13%), electrolyte dis-

Table 2 Maximum NCI-CTC toxicities by number of patients

	NCI-CTC grade				Grade 3/4 toxicity (% of patients)
	1	2	3	4	
Leukocytes	1	5	8	1	60
Neutrophils	0	2	1	12	87
Platelets	1	1	0	0	0
Hemoglobin	10	4	1	0	7
Nausea	7	1	2	–	13
Vomiting	1	0	1	0	7
Dyspnea	–	2	2	0	13
Neutropenic fever	–	–	5	0	33
Fatigue	2	3	3	0	20
Liver	7	1	0	0	0
Electrolytes	1	0	2	0	13
Worst hematologic toxicity	0	1	2	12	93
Worst non-hematologic toxicity	5	2	8	0	53

turbance (13%), nausea (13%), and vomiting (7%). Grade 3 dyspnea observed in two patients was associated with bacterial pneumonia and docetaxel-related interstitial lung toxicity. No patients experienced hypersensitivity reactions or peripheral edema. Overall, grade 3 or higher hematologic and nonhematologic toxicities were observed in 14 patients (93%) and 8 patients (53%), respectively. No treatment-related death occurred.

Changes in symptom scores during chemotherapy

A total of 39 questionnaires were collected throughout the study. The overall collection rate was 61% (39/64), with rates after the first, second, and third cycle of chemotherapy of 87% (13/15), 38% (5/13), and 43% (3/7), respectively. Changes in symptom and global QOL (face scale) scores up to the third assessment are shown in Fig. 1, where individual scores are presented as relative values as compared with the baseline value. At each assessment, patients exhibited improvement in feeling, appetite, and global QOL; whereas slight deterioration was found in vomiting, cough and sputum. However, there were no significant differences in the changes in these scores during the treatment period. In addition, no relationship was found between relative symptom score and response to treatment.

Pharmacokinetic results

Blood sampling for pharmacokinetic analysis was not performed in three patients because of patient refusal. The C_{max} (1.35 ± 0.32 μg/ml, mean ± SD), $AUC_{0 \rightarrow inf}$ (1.79 ± 0.52 μg h/ml), and $t_{1/2}$ (4.1 ± 2.3 h) in the 12 elderly patients were somewhat lower than those (C_{max}, 1.61 ± 0.59 μg/ml; $AUC_{0 \rightarrow inf}$, 2.44 ± 0.83 μg·h/ml; $t_{1/2}$, 7.5 ± 6.3 h; $n = 6$) in non-elderly patients in a phase I study in Japan (docetaxel dose 60 mg/m^2; infusion time 60–160 min) [15]. Conversely, the CL (38.5 ± 8.5 l/h/m^2) in this study was somewhat higher than that (27.8 ± 11.6 l/h/m^2) in the phase I study. The non-elderly pharmacokinetic participants were required to have an Eastern Cooperative Oncology Group PS of two or less, to be aged between 15 and 75 years old, and to have a leukocyte count ≥4000/μl, a neutrophil count ≥1500/μl, a hemoglobin level ≥9.5 g/dl, a total bilirubin level ≤ 1.5 mg/dl, AST and ALT levels not more than two times the upper limit of the normal range, and a serum creatinine level not more than the upper limit of the normal range [15].

Discussion

This is, to our knowledge, the first study of an every 3-weeks schedule of docetaxel in chemotherapy-naive elderly patients with advanced NSCLC. The percentage

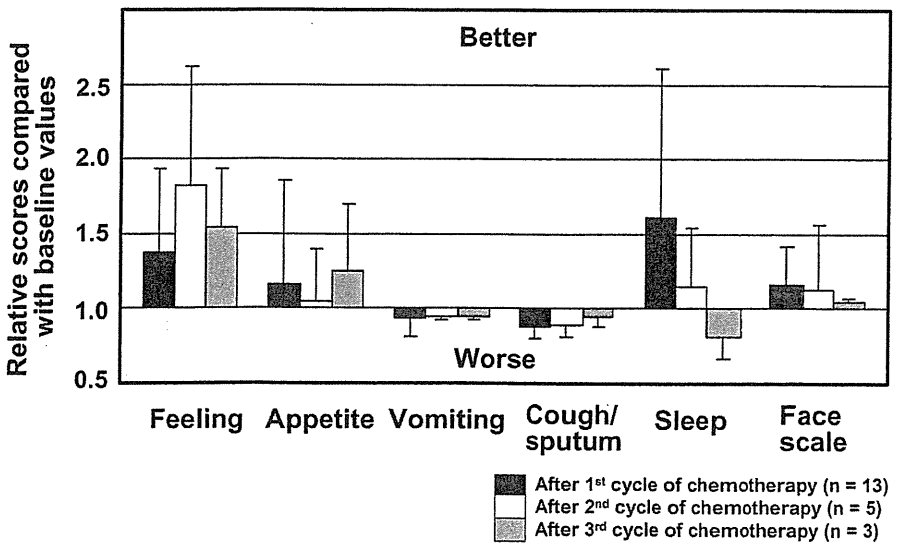

Fig. 1 Changes in relative symptom scores during the treatment period. The histograms represent mean and standard deviation

of patients who are reluctant to receive chemotherapy or who should not be treated with chemotherapy due to poor PS or comorbidity appears to be much higher among elderly patients than among younger patients [3]. In this study, we attempted to estimate the proportion of patients eligible for docetaxel among all elderly patients with advanced NSCLC who visited our hospitals. In a previous study by Oshita et al., 10 of 34 elderly (aged at least 75 years) patients (29%) with lung cancer were eligible for cisplatin-based chemotherapy [12]. In addition, in our retrospective series, 37% of elderly patients with advanced NSCLC underwent either cisplatin-based or non-platinum combination chemotherapy [16]. The results of these studies as well as that (proportion of eligible patients, 43%) of our own suggest that chemotherapy can be administered to approximately 30–40% of elderly patients with advanced NSCLC. However, these findings should be cautiously interpreted because the figures might include a considerable degree of physician discretion with regard to chemotherapy drug and dosing in the elderly.

The initial estimated sample size was 61 patients, which was determined with the efficacy endpoint (one of four primary endpoints) of this study. However, this study was terminated early due to the slow rate of patient accrual. Although the sample size was extremely small, the response rate (40%, 95% CI 15–65%) can be considered at least comparable to that (19%, 95% CI 11–29%) in a phase II study of docetaxel, which was conducted for the application for approval of docetaxel in Japan [4]. In that study, advanced NSCLC patients with a median age of 67 years (range 40–80 years) received docetaxel at a dose of 60 mg/m^2. In addition, the median survival time (15.6 months) in the present study is superior to that in the previous phase II study (9.8 months) [4], although four of nine patients with stage III disease underwent additional thoracic radiotherapy.

The major toxicity in our study was myelosuppression, with grade 3 or higher leukopenia and neutropenia, and grade 3 neutropenic fever observed in 60%, 87%, and 33% of patients, respectively. The incidence and severity of myelosuppression in our study were similar to those (49%, 87%, and 11%, respectively) in the Japanese phase II study [4]. However, hematologic toxicity was easily manageable, and did not lead to treatment-related death. Concerning non-hematologic toxicities, grade 3 or higher fatigue was more frequently observed in our study (20%) than in the phase II study (4%). However, there were no differences in the incidences of other non-hematologic toxicities between the two studies. In this study, relative symptom and global QOL scores did not decline during the treatment period. However, particularly after the second cycle of chemotherapy, only a small number of patients answered the questionnaire, adding limited information to this assessment.

It is believed that the pharmacokinetic profiles of docetaxel are not affected by patient age [6]. Compared with the result of a Japanese phase I study of docetaxel conducted in non-elderly patients [15], the values of C_{max}, $AUC_{0 \rightarrow inf}$, and $t_{1/2}$ were slightly lower in our study, with a slight increase in CL. We cannot explain why docetaxel was cleared more rapidly in this study population. In addition, we have no clear explanation for the relationship between relatively increased total body clearance of docetaxel and high incidence of severe neutropenia. It seems difficult to compare the pharmacokinetic profiles of docetaxel between these studies, since docetaxel in the phase I study was infused at a dose of 60 mg/m^2 over 60–160 min.

In conclusion, 43% of elderly patients with advanced NSCLC received single-agent docetaxel without a reduction in their symptoms in our study, although careful attention should be paid to the physiologic changes associated with ageing to ensure safe administration of anticancer drugs to the elderly. Based on the result of the "ELVIS" study, vinorelbine monotherapy has been considered the treatment of choice for elderly patients with advanced NSCLC [17]. Docetaxel monotherapy also appears to be useful for the treatment of elderly patients with advanced NSCLC, although the validity of the results is limited due to the small sample size. In future studies the endpoint should be limited and the age range should be reconsidered (e.g., 70 years or more). In addition, comorbidity, number of medications, and functional and cognitive status should be evaluated to ascertain the "physiologic age" of the elderly.

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Phase I Study of Irinotecan and Amrubicin in Patients with Advanced Non-Small-Cell Lung Cancer

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Abstract. *Background: Combination chemotherapy of irinotecan and amrubicin for advanced non-small cell lung cancer (NSCLC) has not been fully evaluated. To determine the maximum-tolerated dose (MTD), a phase I study in patients with advanced NSCLC was conducted. Materials and Methods: Patients with stage IIIB/IV NSCLC were enrolled in this study. Both patients with and without prior chemotherapy were also eligible. The drugs were administered on days 1 and 8, every 3 weeks. The starting doses of irinotecan and amrubicin were 60 and 35 mg/m^2, respectively. Results: Nineteen patients received a total of 53 courses. Grade 4 neutropenia was observed in 23% of courses. Anaemia and thrombocytopenia were generally mild. Grade 3 febrile neutropenia occurred in 5 courses. Other grade 3 or greater non-haematological toxicities were observed in only 4 out of 52 courses (grade 3 infection and hyponatremia). The maximum-tolerated doses (MTDs) of irinotecan and amrubicin were 100 and 45 mg/m^2, respectively. Objective response was obtained in 2 patients (10.5%), who had received prior chemotherapy. Conclusion: This combination was well tolerated, but produced only a modest anti-tumour effect for advanced NSCLC. Further investigation into the role of this regimen as a salvage chemotherapy may be warranted in relapsed patients.*

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Key Words: Irinotecan, amrubicin, non-small cell lung cancer, phase I study, non-platinum regimen, topoisomerase inhibitor.

Lung cancer is the leading cause of cancer deaths in many countries (1). Although cisplatin-based chemotherapy has been conducted extensively in patients with advanced non-small cell lung cancer (NSCLC) over the past two decades, the survival benefit remains modest and further improvement of treatment outcome is needed (2). Recently, several new agents with novel mechanisms have been developed and have shown to be highly effective for NSCLC (3). Irinotecan, a unique semi-synthetic derivative of camptothecin, is a topoisomerase I inhibitor shown to have favourable anti-tumour activity for advanced NSCLC as a single agent, with a response rate of 21-32% (4, 5). Amrubicin, a totally synthetic anthracycline, is a topoisomerase II inhibitor and also effective for NSCLC as a single agent, with a response rate of 25% (6), although other anthracyclines are now considered to have little benefit in the treatment of advanced NSCLC. Combined use of topoisomerase I and II inhibitors has been demonstrated to be complementary in preclinical studies (7, 8). The toxicity profiles of these two drugs are different (4-6). Although several large randomized phase III studies have been conducted to compare survival, response and toxicity from a platinum-based doublet containing a single new agents to a non-platinum-based doublet consisting of two new agents, it has not yet been determined which is more effective (9). Thus, there is still room for investigation of non-platinum regimens.

Table I. *Planned dose level.*

Dose level	Irinotecan (mg/m^2)	Amrubicin (mg/m^2)
1	60	35
2	80	35
3	80	40
4	100	40
5	100	45
6	100	50

Table II. *Patient characteristics.*

Number of patients		19
Age	median (range)	67 (48-74)
Gender	male	12
	female	7
Performance status	0 / 1	11 / 8
Histology	adenocarcinoma	16
	squamous cell carcinoma	3
Stage	IIIB	2
	IV	7
	postoperative recurrence	10
No. of prior chemotherapy regimens		
	0 / 1 / 2 / 3	12/ 6 / 0 / 1

Based on such a background, a phase I study of combination chemotherapy in patients with advanced NSCLC was designed. The primary objective was to determine the maximum-tolerated dose (MTD) for each drug, with a secondary objective of assessing anti-tumour activity.

Patients and Methods

Eligibility criteria. Patients were required to fulfil the following eligibility criteria: pathologically proven, advanced and inoperable NSCLC; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2; age ≤75 years; presence of evaluable lesions; adequate reserves of haematological function (white blood cell (WBC) count >4000 /μL, neutrophil count >2000 /μL, haemoglobin level >9.5 g/dL, platelet count >10x10^4 /μL), renal function (serum creatinine <1.5 mg/dL), hepatic function (total bilirubin <1.5 mg/dL, serum transaminases <2.5x upper limit of normal range) and pulmonary function (PaO_2 ≥60 Torr); and acquisition of written informed consent. Both patients with and without prior chemotherapy were included. Patients with symptomatic brain metastasis were excluded from the study. Baseline pretreatment evaluations included a complete history, physical examination, laboratory tests, chest radiograph, electrocardiogram, computed tomography (CT) scans of the chest and abdomen, magnetic resonance imaging (MRI) of the brain, and a radionuclide bone scan. Staging was assessed according to the tumour, node and metastasis system (10). The protocol was approved by the institutional review board of each participating institute.

Treatment schedules. Amrubicin, diluted in 20 mL physiological saline, was intravenously administered over 5 minutes on days 1 and 8. Soon after completion of amrubicin infusion, irinotecan, diluted in 250 mL physiological saline, was intravenously administered over 1 hour on the same days. Each patient was premedicated with intravenous administration of dexamethasone (8 mg) and granisetron (3 mg) 30 minutes before bolus infusion of amrubicin. Treatment was repeated every 3 weeks, with 5 dose levels planned. The starting doses of irinotecan and amrubicin were 60 and 35 mg/m^2, respectively, which were two-thirds of the recommended doses as single agents (Table I). Administration of irinotecan and amrubicin on day 8 was delayed until day 15 if haematological toxicity of grade 3 or greater, non-haematological toxicity of grade 2 or greater, or diarrhoea was observed on the day of administration. If these toxicities did not improve by day 15, this administration was cancelled in that course. Patients were treated with at least 2 courses of chemotherapy unless there was disease progression, unacceptable toxicity, or withdrawal of informed consent. Initiation of the next course of chemotherapy was delayed until recovery of WBC count to 3000 /μL or greater, neutrophil count to 1500 /μL or greater, platelet count to 10x10^4 /μL or greater, and resolution of non-haematological toxicities to grade 1 or less.

Assessment of toxicity and dose escalation. All toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC, Version 2.0). Dose-limiting toxicity (DLT) was defined as development of at least one of the following adverse events: any non-haematological toxicity of grade 3 or greater, except alopecia, nausea, or vomiting; platelet count <2x10^4 /μL; grade 4 leukopenia; grade 4 neutropenia lasting for 4 days or longer; cancellation of irinotecan and amrubicin administration on day 8; or inability to begin the next course of treatment by day 56 due to failure to recover from toxicity.

For each dose level, 3 or 6 patients were scheduled to enter. If fewer than 2 out of 3 or 3 out of 6 patients experienced DLT, the next group of patients was treated at the next higher dose level. MTD was defined as the dose level that produced any DLT in 3 or more patients out of a maximum of 6 patients, and further dose escalation was not permitted. All treatment courses were analysed to determine DLT and MTD, although the decision to elevate dose level was based on toxicity in the first course. Dose escalation above starting doses in an individual patient was not allowed. The recommended dose was defined as the dose level below MTD. If grade 4 leukopenia, grade 4 neutropenia, or febrile neutropenia were observed, use of granulocyte colony-stimulating factor was permitted. The dose could be reduced in subsequent courses if patients experienced DLT in the previous course.

Table III. *Haematological toxicity of grade 2 or greater (all courses).*

		Dose level				
Toxicity	Grade	1	2	3	4	5
No. of treated patients		3	3	3	6	4
No. of courses evaluated		4	5	8	31	5
No. (%) of courses encountered						
Leukopenia	2	2 (50%)	2 (40%)	3 (38%)	9 (29%)	0
	3	2 (50%)	0	0	5 (16%)	4 (80%)
	4	0	0	0	0	1 (20%)
Neutropenia	2	0	3 (60%)	1 (13%)	9 (29%)	0
	3	4 (100%)	0	3 (38%)	8 (26%)	1 (20%)
	4	0	1 (20%)	0	7 (23%)	4 (80%)
Thrombocytopenia	2	0	0	0	1 (3%)	0
	3	0	0	0	1 (3%)	0
	4	0	0	0	0	0
Anaemia	2	1 (25%)	4 (80%)	0	3 (10%)	2 (40%)
	3	0	0	0	0	0
	4	0	0	0	0	0

Assessment of anti-tumour activity. Standard Response Evaluation Criteria in Solid Tumours (11) was used to evaluate responses. The best overall response was defined as the best response recorded from the start of treatment until disease progression or recurrence.

Results

Patient characteristics and treatment delivery. Nineteen patients with advanced NSCLC were enrolled between May, 2003 and January, 2004 in 4 institutes. The patient characteristics are listed in Table II. A total of 53 courses were evaluated, with a median number of 2 courses (range: 1 to 8). Eight patients (42%) received only 1 course of chemotherapy, because of disease progression in 6 patients, patient refusal and unacceptable toxicity (1 patient each). The median total delivered dose of amrubicin was 140 mg/m^2, ranging from 70 to 640 mg/m^2. Administration of irinotecan and amrubicin on day 8 was delayed for 1 week in 1 course at dose level 4 because of diarrhoea. All patients and courses were assessable for safety.

Haematological toxicity. Grade 4 neutropenia occurred in 12 (23%) out of 53 courses (Table III). In 2 courses, grade 4 neutropenia continued for 4 and 6 days, and grade 4 leukopenia continued for 4 days in 1 course despite G-CSF support, but they were not accompanied by any febrile episodes. Anaemia and thrombocytopenia were relatively mild, and no transfusions were required.

Non-haematological toxicity. Non-haematological toxicity was generally mild and no patient experienced grade 4 or greater toxicitiy (Table IV). Febrile neutropenia occurred in 5 (9%) out of 53 courses. Grade 3 infection occurred in 3 out of 53 courses; 2 in the first course, on day 4 at dose level 2 and on day 25 at dose level 4. These toxicities were reversible with appropriate supportive care. Grade 3 hyponatremia was observed in 1 out of 53 courses, but was reversible and mild. No other severe toxicities, such as diarrhoea or cardiotoxicity, occurred.

Maximum-tolerated dose. In the first course, DLT was observed in 1 of 3 patients at dose level 2 (grade 3

Table IV. *Non-haematological toxicity of grade 2 or greater (all courses).*

		Dose level				
Toxicity	Grade	1	2	3	4	5
No. of treated patients		3	3	3	6	4
No. of courses evaluated		4	5	8	31	5
No. (%) of courses encountered						
Febrile neutropenia	3	1 (25%)	0	0	2 (6%)	2 (40%)
Nausea/vomiting	2	0	1 (20%)	4 (50%)	0	0
	3	0	0	0	0	0
Hepatotoxicity	2	1 (25%)	0	0	0	0
	3	0	0	0	0	0
Infection	2	0	0	0	0	0
	3	0	2 (40%)	0	1 (3%)	0
Diarrhoea	2	0	2 (40%)	0	0	1 (20%)
	3	0	0	0	0	0
Hyponatremia	2	0	0	0	0	0
	3	0	1 (20%)	0	0	0

No patient developed grade 4 or greater toxicity.

infection), in 2 of 6 at dose level 4 (grade 3 febrile neutropenia and grade 3 infection) and in 3 of 4 at dose level 5 (persistence of grade 4 neutropenia and grade 4 leukopenia, persistence of grade 4 neutropenia, and grade 3 febrile neutropenia). There were no treatment-related deaths. Accordingly, the MTDs of irinotecan and amrubicin were determined to be 100 and 45 mg/m^2, respectively (dose level 5). The recommended doses of irinotecan and amrubicin were therefore concluded to be 100 and 40 mg/m^2, respectively (dose level 4).

Anti-tumour activity. All patients were assessable for response. Objective tumour response was obtained in 2 (11%) of 19 patients. Both patients were treated at dose level 4 and had received prior chemotherapy (single agent vinorelbine therapy and combination chemotherapy of carboplatin and gemcitabine, respectively).

Discussion

The present study demonstrated that the two-drug combination of irinotecan and amrubicin using a fractionated administration schedule was well tolerated in patients with advanced NSCLC. MTDs of irinotecan and amrubicin were 100 and 45 mg/m^2, respectively. Dose-intensities of irinotecan and amrubicin at the MTD were 67 and 30 mg/m^2/week, respectively. The MTD for irinotecan was higher than in the two-drug combination with cisplatin (12) and the MTD for amrubicin was slightly lower than when used as a single agent (6).

As expected, myelosuppression was the major toxicity in this study, however, it was reversible and not life-threatening. One of the major toxicities associated with anthracyclines is cardiotoxicity (13). However, in a preclinical study using dogs, Noda *et al.* reported that amrubicin had neither cardiotoxicity nor deteriorating effects on pre-existing cardiomyopathy (14). Also, previous clinical trials involving 74 patients with small cell lung cancer demonstrated that amrubicin had no cardiotoxicity, consistent with our results (15, 16). Similarly, irinotecan is not reported to have any major potential cardiotoxicity (17). Thus, this regimen may be used safely even in patients with pre-existing cardiac dysfunction. Additionally, it is of note that diarrhoea was mild in our study, since one of the DLTs of single agent irinotecan was diarrhoea (17). The difference in incidence of diarrhoea might be attributable to the difference in treatment schedule or in supportive care. Further confirmation is warranted.

Previous studies have shown that development of cellular resistance to topoisomerase II inhibitors confers an increased sensitivity to topoisomerase I inhibitors (7). The reverse effect, in which resistance to a topoisomerase I inhibitor enhances the sensitivity to topoisomerase II inhibitors, has also been reported (8). This enhanced sensitivity may be related to a compensatory role by each topoisomerase

enzyme to a deficiency in the other. Despite positive experimental findings, combined use of topoisomerase inhibitors has produced controversial *in vitro* results. When administered simultaneously, some reports have indicated synergistic or additive cytotoxic effects in various tumour cell lines (18), while others have demonstrated antagonistic effects (19). However, Bertrand *et al.* have shown that sequential administration of camptothecin and etoposide resulted in additive cytotoxicity in colon cancer cell lines (20). Therefore, further characterisation of the maximum attainable effect from a topoisomerase I and II inhibitors combination is required.

In Japan, two phase II studies investigating a combination of irinotecan and topoisomerase II inhibitor, etoposide, have been conducted (21, 22). Masuda *et al.* evaluated this combination chemotherapy in patients with relapsed small cell lung cancer (21). Irinotecan was administered at a dose of 70 mg/m^2 on days 1, 8 and 15, and etoposide was given at a dose of 80 mg/m^2 on days 1 to 3. This combination produced a response rate of 71%, far exceeding the response rates of 40-50% previously reported for the combination of cisplatin and etoposide (23). However, Oshita *et al.* investigated the same combination using a different schedule in chemo-naïve patients with metastatic NSCLC, in which both irinotecan and etoposide were administered on days 1 to 3 (22). This concurrent administration yielded a disappointing response rate of 21%, less than the 32% response rate of irinotecan alone (4). Considering the data, it may be preferable to avoid simultaneous administration of topoisomerase I and II inhibitors. This scheduled-dependency, as well as insufficient doses of the two drugs (15 out of 19 were treated with doses lower than MTD) probably contributed to the lower efficacy in this study. More preclinical and clinical investigations are needed to clarify the optimum sequence and administration schedule for both drugs.

In this study, objective response was obtained in 2 patients who had prior chemotherapy, whereas no chemo-naïve patients achieved objective response. This may be attributed to differences in the expression levels of target molecules of chemotherapeutic agents, in addition to the small sample size. Naruse *et al.* reported that K562/TPA, a human leukemic phorbol ester-resistant subline, was 400-fold more sensitive to the EGFR tyrosine kinase inhibitor gefitinib than the K562 parental cell, and that EGFR protein expression was detected in K562/TPA but not in K562 parent cells. They speculated that the high sensitivity of the multiple drug-resistant cell line K562/TPA is due to acquired EGFR expression from exposure to cytotoxic agents (24). Similarly, determining protein levels of topoisomerases before and after chemotherapy may be useful for characterising differences in response to this regimen between relapsed and chemo-naïve patients.

In conclusion, the combination of irinotecan and amrubicin was well tolerated, but produced only a modest anti-tumour effect for advanced NSCLC. However, further investigation into the role of this regimen as salvage chemotherapy may be warranted in relapsed patients, because relapsed patients responded to the regimen and there have been no reports evaluating topoisomerase I and II inhibitors combination trials in relapsed patient with NSCLC.

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