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Phase I and pharmacokinetic study of paclitaxel and irinotecan for patients with advanced non-small cell lung cancer

T. Kasai[a], M. Oka[a,b,*], H. Soda[a], J. Tsurutani[a], M. Fukuda[a], Y. Nakamura[a], S. Kawabata[a], K. Nakatomi[a], S. Nagashima[c], H. Takatani[a], M. Fukuda[d], A. Kinoshita[e], S. Kohno[a,b,1]

[a]*Second Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan*
[b]*Division of Molecular and Clinical Microbiology, Department of Molecular Microbiology and Immunology, Nagasaki University Graduate School of Medical Sciences, Nagasaki, Japan*
[c]*Internal Medicine, Sasebo City General Hospital, Nagasaki, Japan*
[d]*Internal Medicine, Japanese Red Cross Nagasaki Atomic Bomb Hospital, Nagasaki, Japan*
[e]*Internal Medicine, National Nagasaki Medical Center, Nagasaki, Japan*

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Abstract

We conducted a phase I study of paclitaxel and irinotecan (CPT-11) in advanced non-small cell lung cancer (NSCLC). This study aimed to determine the maximum tolerated doses (MTD). The pharmacokinetics of CPT-11 and its major active metabolite, SN-38, were also analysed. Patients received paclitaxel (day 1) followed by CPT-11 (days 1, 8 and 15), in a 4-week cycle, and paclitaxel and CPT-11 were escalated from 120 and 40 mg/m^2, respectively. 28 patients were enrolled, who were evaluated for toxicity. 2 of 6 patients at 210 mg/m^2 paclitaxel and 50 mg/m^2 CPT-11, and 2 of 4 at 180 and 60 mg/m^2 developed dose-limiting toxicity (DLT) (neutropenia, fever, neurotoxicity and diarrhoea). The area under the plasma concentration–time curve (AUC) of CPT-11 on day 1 was significantly higher than that on days 8 or 15 at each dose level ($P=0.002$). The AUC of SN-38 on day 1 was significantly increased using paclitaxel doses $\geqslant$150 mg/m^2. A preceding paclitaxel administration changed the pharmacokinetics of CPT-11 and SN-38. However, the toxicity was tolerable. Paclitaxel 180 mg/m^2 and CPT-11 50 mg/m^2 were the recommended doses for further phase II study of this combination.

Keywords: Lung cancer; Non-small cell lung cancer; Chemotherapy; Clinical trial; Taxane; Topoisomerase I inhibitor; Pharmacology; Drug interaction

1. Introduction

Non-small cell lung cancer (NSCLC) is a relatively chemoresistant cancer, and several chemotherapeutic agents and various treatment strategies have been extensively investigated. Platinum-based chemotherapy regimens have been most extensively studied in the treatment of advanced NSCLC. Meta-analysis of randomised clinical studies has shown modest benefits using platinum-based chemotherapy with regard to the survival of patients with advanced NSCLC [1–3]. However, the prognosis remains poor.

Recently, newer active agents for NSCLC have been used such as paclitaxel, irinotecan (CPT-11), vinorelbine and gemcitabine [4]. The combination chemotherapy of these newer agents with platinum has produced results that are superior to the older chemotherapy regimens [5]. Therefore, the effects of the combination therapies of two or three newer agents are now under investigation [4]. Paclitaxel is a new antimicrotubular agent extracted from the bark of the Pacific yew. The antitumour activity of paclitaxel is due to the promotion of tubulin polymerisation and stabilisation of microtubules against depolymerisation [6,7]. However, CPT-11 is a semi-synthetic derivative of camptothecin, and inhibits

* Corresponding author: Tel.: +81-95-849-7274; fax: +81-95-849-7285.
E-mail address: okamikio@net.nagasaki-u.ac.jp (M. Oka).
[1] For the Nagasaki Thoracic Oncology Group.

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the function of DNA topoisomerase I by stabilising a reversible enzyme–DNA cleavable complex. This leads to single-strand DNA breaks and to the death of cancer cells [8,9]. The underlying mechanisms of antitumour activity of paclitaxel and CPT-11 are different, and additive effects were observed when paclitaxel was used in combination with 7-ethyl-10-hydroxy-camptothecin (SN-38), the major active metabolite of CPT-11, in lung cancer cell lines [10].

Based on the above background, we conducted a phase I study of paclitaxel combined with CPT-11 for advanced NSCLC patients. The main objectives of our study were to determine the maximum tolerated dose (MTD) and the clinical toxicity of this two-drug regimen. We also analysed the influence of paclitaxel on the pharmacokinetics of CPT-11 and SN-38 at each dose level, since little is known about the pharmacokinetic interactions between paclitaxel and CPT-11.

2. Patients and methods

2.1. Eligibility

Patients with histologically- or cytologically-documented NSCLC were candidates for this study. Other eligibility criteria included the following: stage IIIB (without indication of radiation therapy) or IV; age $\leqslant$75 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leqslant$2; no prior chemo- or radio-therapy within 4 weeks of study entry; adequate haematopoietic function (leucocyte count $\geqslant 4\times10^9$/l, haemoglobin count $\geqslant$90 g/l, platelet count $\geqslant 100\times10^9$/l), hepatic function (total serum bilirubin level $\leqslant$25.65 umol/l, and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels $\leqslant$twice the upper limit of normal value), and renal function (serum creatinine levels $\leqslant$normal value); and no coexisting severe medical problems. Specific exclusion criteria included massive pleural or pericardial effusion, interstitial pneumonia, uncontrolled brain metastasis, and unresolved bowel obstruction. The study protocol was approved by the ethical committee of the Nagasaki University School of Medicine, and each patient signed a written informed consent according to the protocol.

2.2. Treatment and dose escalation

Paclitaxel was administered on day 1 and CPT-11 on days 1, 8 and 15. Paclitaxel was administered in a 3-h infusion, followed by a 2-h rest, then CPT-11 was infused over a period of 90 min. Each patient received premedication with 20 mg of dexamethasone intravenously (i.v.) at 14 and 6 h before the paclitaxel infusion. In addition, 50 mg of oral diphenhydramine and 50 mg of i.v. ranitidine were administered 30 min before the paclitaxel infusion. CPT-11 on day 8 or 15 in each cycle was cancelled if the leucocyte count was $<3\times10^9$ cells/l, platelet count $<50{,}000\times10^9$ cells/l, or if any grade of diarrhoea or fever of 38 °C developed on each of these days. The next cycle at each level commenced after the leucocyte and platelet counts reached at least 3×10^9 cells/l and 100×10^9 cells/l, respectively. Each treatment cycle was 4 weeks long (3 weeks of therapy followed by one week of rest). The starting doses of paclitaxel and CPT-11 were 120 and 40 mg/m^2, respectively. The doses of paclitaxel and CPT-11 were escalated as shown in Table 1. After determining the MTD of paclitaxel when combined with 50 mg/m^2 of CPT-11, the dose of paclitaxel was decreased to the lower level, and the dose of CPT-11 was increased up to 60 mg/m^2.

Dose-limiting toxicity (DLT) was defined during the first cycle of treatment as the presence of one or more of the following adverse effects: (1) grade 4 neutropenia lasting $\geqslant$5 days, (2) grade 4 neutropenia with fever of $>$ 38 °C, (3) grade 4 thrombocytopenia, (4) grade 3 or worse non-haematological toxicity, except for nausea, vomiting and alopecia, and (5) cancellation of CPT-11 on both days 8 and 15. These toxicities were assessed according to the World Health Organization (WHO) toxicity criteria [11].

3 patients were assigned to each dose level. When there was no evidence of DLT after one complete treatment cycle in all 3 patients, the next dose level was initiated. When 1 of 3 patients demonstrated DLT, an additional 3 patients were entered at that dose level before dose escalation. When 2 or more of 6 patients demonstrated DLTs, or 2 patients demonstrated DLTs in the first three patients, the dose was defined as MTD. Intrapatient dose escalation was not permitted.

2.3. Assessment of treatment

Before commencement of therapy, a complete medical history, physical examination, and resting 12-lead elec-

Table 1
Dose-escalation and extension phase study

Dose level	Patients (*n*)	Paclitaxel (mg/m^2)	CPT-11 (mg/m^2)
1	3	120	40
2	3	120	50
3	3	150	50
4	6 (3)	180	50
5	6	210	50
6	4	180	60

The number in parentheses represents the number of patients in the extension phase study. Paclitaxel was injected on day 1, and CPT-11 was administered on days 1, 8 and 15 of each cycle. Paclitaxel was given as a 3-h infusion followed by a 90-min infusion of CPT-11 2 h after the paclitaxel infusion on day 1.

trocardiogram were performed. Tumour staging was determined by physical examination, routine chest radiography, computed tomography (CT) of the chest and abdomen, bone scintiscanning, and magnetic resonance imaging of the head. Staging was performed according to the tumour, node, metastasis (TNM) system [12]. A complete blood count including a differential leucocyte count, and urinalysis and biochemical analyses were performed two or three times per week. The following evaluations were performed weekly: history, physical examination, toxicity assessment according to WHO toxicity criteria. Tumours were evaluated radiologically after each course of therapy.

A complete response (CR) was defined as the resolution of all measurable and assessable disease for at least 4 weeks. A partial response (PR) required at least a 50% reduction in the sum of the products of the maximum perpendicular diameters of measurable lesions for at least 4 weeks. Progressive disease (PD) was defined as at least a 25% increase in measurable disease or the appearance of new tumour lesions. Stable disease (SD) was defined as a disease status failing to meet the above-described criteria.

2.4. Pharmacokinetic studies of CPT-11 and SN-38

Blood samples for pharmacokinetic analysis were obtained on day 1 and day 8 in the first cycle. The results of pharmacokinetic data on day 1 were compared with those of day 8. When CPT-11 administration was omitted on day 8, blood samples were obtained on day 15 instead of day 8. Differences in pharmacokinetic data between day 1 and day 8 (or 15) were considered to reflect the influence of paclitaxel on the pharmacokinetics of CPT-11 and SN-38.

Whole blood samples were obtained from an indwelling venous catheter placed in the arm contralateral to that used for drug infusion. For kinetic analyses of CPT-11 and SN-38, samples were collected in heparinised tubes at 0.75, 1.5, 2, 4, 6 and 19 h after the beginning of CPT-11 infusion. After centrifugation, the plasma samples were immediately mixed with the same volume of 0.1 N phosphoric acid, and stored at $-20\ ^{\circ}C$ until assay. The plasma concentrations of CPT-11 and SN-38 were measured by high-performance liquid chromatography (HPLC), as previously described in Ref. [13]. The area under the plasma concentration–time curve (AUC) from 0 to 19 h was calculated using the trapezoidal method. Differences in the AUCs between day 1 and day 8 or 15 were evaluated by the Wilcoxon-rank sum test. Differences in the plasma concentrations between day 1 and day 8 or 15 were evaluated by the paired Student's *t*-test. A two-tailed *P* value of less than 0.05 was considered significant.

3. Results

3.1. Patients' characteristics

A total of 28 patients from four institutes were enrolled in this study between August 1999 and January 2001. The patient's characteristics are listed in Table 2. All 28 patients were eligible and assessable for toxicity, and 26 patients were assessable for response to chemotherapy. 2 patients in level 1 and 1 patient in level 2 had received prior chemotherapy. The other patients had received no prior chemotherapy.

3.2. Recommended dose level

The total number of cycles was 59, and the median number of cycles per patient was two, and ranged from one to five cycles. 13 of 28 patients received only one cycle of treatment. The reasons for treatment discontinuation were PD in 6 patients, DLT in 6 and patient's refusal in 1. None of the patients at dose levels 1, 2 and 3 developed DLTs. One of 6 patients in level 4 was omitted from CPT-11 on both days 8 and 15, which was determined as a DLT. The reason for the omission of CPT-11 on day 8 was grade 2 neutropenia and on day 15 the reason was fever without grade 4 neutropenia. 2 of 6 patients in dose level 5 (210 mg/m^2 paclitaxel and 50 mg/m^2 CPT-11) developed DLTs including neutropenic fever and grade 3 neurotoxicity. Accordingly, the dose of paclitaxel was reduced to 180 mg/m^2 in combination with 60 mg/m^2 of CPT-11 (dose level 6). 2 of 4 patients at dose level 6 experienced DLTs including neutropenic fever and grade 4 diarrhoea

Table 2
Patients' characteristics

No. of patients	28
Sex	
Male	19
Female	9
Age (year)	
Median (range)	63 (39–73)
PS (ECOG)	
0	5
1	21
2	2
Clinical stage	
IIIB	8
IV	20
Histological type	
Adenocarcinoma	22
Squamous-cell carcinoma	4
Large-cell carcinoma	1
Undifferentiated carcinoma	1

(bloody stool). Thus, MTDs in this regimen were dose levels 5 and 6, and the recommended dose was level 4 (180 mg/m^2 paclitaxel and 50 mg/m^2 CPT-11). To confirm the safety of the recommended dose, 3 patients in an extension study were entered into dose level 4. One of the 3 patients developed neutropenic fever. Taken together with the dose escalation study and the extension study, 2 of 9 patients experienced DLT at dose level 4. Paclitaxel at 180 mg/m^2 and CPT-11 at 50 mg/m^2 were considered to be tolerable doses for NSCLC.

3.3. Toxicity

Haematological toxicities in the first cycles are listed in Table 3. Neutropenia was the major haematological toxicity in the present study. Grade 3 neutropenia occurred in 6 (21%) of 28 patients in the first cycle, and grade 4 neutropenia in 20 (71%) patients. Grade 3 leucopenia occurred in 11 (39%) of 28 patients in the first cycle, and grade 4 leucopenia in 3 (11%) patients. The nadir of neutropenia occurred from day 8 to day 15 (median, day 12), but grade 4 neutropenia recovered to grade 2 or less in less than 5 days in all of the patients.

Table 3
Haematological toxicities (WHO grade) in the first cycle

Dose level	Patients (*n*)	Neutropenia		Thrombocytopenia		Anaemia	
		3	4	3	4	3	4
1	3	1	2	0	0	0	0
2	3	0	3	0	0	0	0
3	3	1	2	0	0	0	0
4	6 (3)	2	3 (2[a])	0	0	0	1
5	6	1	5[a]	0	0	0	0
6	4	1	3[a]	0	0	0	0

WHO, World Health Organization. Numbers in parentheses indicate those patients in the extension phase study.

[a] Grade 4 neutropenia with fever, which was considered as DLT, occurred in 1 patient in level 5, 2 in level 6, and 1 in the extension study.

Both thrombocytopenia and anaemia were mild. None of the patients developed thrombocytopenia of grade 2 or more in the first cycle. Grade 4 anaemia developed in only (4%) and grade 2 anemia in 4 (14%) of 28 patients in the first cycle. None of the remaining patients developed anaemia of grade 2 or higher in all of the cycles, and none developed thrombocytopenia of grade 2 or more in all of the cycles.

Non-haematological toxicities in the first cycle of chemotherapy are listed in Table 4. Diarrhoea was generally mild. Grade 4 diarrhoea, bloody stool and abdominal pain occurred in 1 (4%) patient at dose level 6, but grade 3 or 4 diarrhoea was not observed in the other 27 patients in the first cycle. In addition, there was no diarrhoea of grade 2 or more in all of the cycles for dose levels 1–4. Other toxicities such as peripheral neurotoxicity, arthralgia, and myalgia were observed. Grade 3 neurotoxicity was observed in 1 (4%) patient at dose level 5, and manifested itself as gait disturbance lasting for 6 days, and the same patient had grade 2 arthralgia. Arthralgia and myalgia were of grade 2 or less in the first cycle of chemotherapy. Nausea and vomiting were frequent adverse events. Grade 1 nausea and vomiting were observed in 13 (46%) patients, grade 2 in 2 (7%) patients and grade 3 was observed in 1 (4%) patient.

After the second cycle, grade 3 neutropenia occurred in 1 patient in each of the dose levels 4 (extension study), 5 and 6. Grade 4 neutropenia occurred in 1 patient in each of the dose levels 1, 2 and 5, and 2 patients at dose levels 3, 4 and 6. There was no thrombocytopenia of grade 2 or more and no anaemia of grades 3 and 4. Regarding non-haematological toxicities after the second cycle, there was no nausea or vomiting of grades 3 or 4. Grade 1 diarrhoea occurred in 1 patient in each of the dose levels 2, 4 (extension study) and 6. Grade 1 neurotoxicity was observed in 1 patient in each of the dose levels 1 and 6, and 2 patients at dose levels 4 and 5. There was no diarrhoea or neurotoxicity of grade 2 or more. Grade 1 arthralgia and myalgia

Table 4
Non-haematological toxicities (WHO grade) in the first cycle

Dose level	Patients (*n*)	Diarrhoea				Peripheral neurotoxicity				Arthralgia and myalgia (pain score)		
		1	2	3	4	1	2	3	4	1	2	⩾3
1	3	0	0	0	0	1	0	0	0	0	0	0
2	3	1	0	0	0	0	0	0	0	1	0	0
3	3	0	0	0	0	1	0	0	0	0	0	0
4	6 (3)	3 (3)	0	0	0	5 (1)	0	0	0	2 (1)	0	0
5	6	3	1	0	0	4	1	1[a]	0	0	2	0
6	4	0	1	0	1[a]	3	0	0	0	2	0	0

Numbers in parentheses indicate those patients in the extension phase study. Grades 3 and 4 non-haematological toxicities were considered dose-limiting toxicities (DLT).

[a] Grade 3 neurotoxicity occurred in 1 patient in level 5, and grade 4 diarrhoea occurred in 1 patient in level 6.

occurred in 1 patient in each of the dose levels 2, 4 and 6. Grade 2 arthralgia and myalgia occurred in 1 patient in each of the dose levels 4 and 6. There was no arthralgia or myalgia of grades 3 and 4. Peripheral neurotoxicity, arthralgia and myalgia were almost relieved with non-steroidal anti-inflammatory drugs used over several weeks. Cumulative toxicity was not observed.

In all the cycles, there were no severe hepatic, pulmonary or renal toxicities. None of the patients showed increases of AST or ALT in the first cycle, and only 1 patient at dose level 6 showed grade 1 increases in AST or ALT levels after the second cycle. Treatment-related pulmonary fibrosis and increased serum creatinine level were not encountered during the treatment, and no treatment-related deaths were observed.

3.4. Dose intensity of CPT-11

Details of the CPT-11 delivery and the dose intensity (DI) at each level are shown in Table 5. Total planned administrations of CPT-11 on days 8 and 15 were 48, and 16 skips (33%) on days 8 or 15 were observed in the first cycles. Nineteen skips (35%) of 54 planned CPT-11 administrations were observed at the second cycle or later. The 16 skips in the first cycle were nine on day 8, and seven on day 15. Skips of CPT-11 on both days 8 and 15 in the first cycle were observed in 1 patient at dose level 4 and one patient at dose level 5. The main reasons for skips on both days were leucopenia and neutropenia.

3.5. Pharmacokinetics of CPT-11 and SN-38

Pharmacokinetic studies of CPT-11 and SN-38 were performed in 13 patients who agreed to participate in this protocol. 3 patients at dose level 1, 2 at dose level 2, 3 at dose level 3, 1 at dose level 4, and 4 at dose level 5. Blood samples were obtained on day 1 and day 8 (or 15) in the first cycle. Blood samples on day 15 were obtained in 1 of 3 patients at level 1, 1 patient at level 4, and 1 of 4 patients at level 5. The AUCs (ng h/ml) of CPT-11 and SN-38 on day 1 were compared with those of day 8 or 15. Fig. 1 shows the values of AUCs of CPT-11 and SN-38 on day 1 for each patient, relative to the respective values for day 8 or 15. Values higher than one denote higher AUCs on day 1 compared with those of day 8 or 15. All relative AUC values were > 1, suggesting that the AUC of CPT-11 on day 1 was higher than that of day 8 or 15 in all the patients at dose levels 1–5. These differences were significant ($P = 0.002$). The relative AUC values were higher at dose levels 3–5, suggesting that the AUC of SN-38 on day 1 was higher compared with that of day 8 or 15 at dose levels 3–5. These differences were also significant ($P = 0.025$). The dose of paclitaxel was 120 mg/m^2 for dose levels 1–2, and $\geqslant 150$ mg/m^2 for dose levels 3–5.

Table 5
Delivery and dose intensity of irinotecan

Dose level	First cycle			All cycles		
	Days 1/8/15	DI	%DI (%)	Days 1/8/15	DI	%DI (%)
1	3/2/3	26.7	88.9	5/3/5	26.0	86.7
2	3/3/1	29.2	77.8	8/8/3	29.7	79.2
3	3/2/2	29.2	77.8	8/6/4	28.1	75.0
4	6/2/4	25.0	66.7	14/8/8	26.8	71.5
5	6/3/5	29.2	77.8	10/5/7	30.6	73.3
6	3/3/2	40.0	88.9	6/6/4	40.0	88.9

DI, dose intensity (mg/m^2/week);%DI,% ratio of actual DI to planned DI. Irinotecan was administered on days 1, 8 and 15 of each cycle, and repeated every 4 weeks in patients showing a response.

Fig. 2 shows the median plasma concentration–time curve of CPT-11 for all dose levels. The CPT-11 concentrations at 4 h or later on day 1 were higher than those of day 8 or 15 ($P < 0.05$).

Fig. 3 shows the median plasma concentration–time curves of SN-38, according to the different dose levels. In dose levels 1–2, there were no significant differences between the plasma SN-38 concentrations on day 1 and those of day 8 or 15 at each sampling point. However, the plasma SN-38 concentrations on day 1 became significantly higher compared with those of day 8 or 15 within 2 h after the CPT-11 administration at dose levels 3–5 ($P < 0.05$).

3.6. Antitumor activity

26 patients were evaluated for response to the combination chemotherapy. None of the patients achieved a CR, and 8 of 26 patients showed a PR. 11 (42%) of 26 patients achieved SD, and 7 (27%) showed PD. Finally, the overall response rate to chemotherapy was 31% (95% Confidence Interval (CI), 14–52%). The median duration of PR was 78 days, and ranged from 44 to 210 days. In the 11 patients that showed SD, 4 patients stopped treatment following a response before the recurrence of NSCLC. Reasons for stopping were DLT in 3 of these 4 patients. In the other 7 patients, the median duration of SD was 82 days, and ranged from 49 to 143 days.

4. Discussion

Newer active agents, such as paclitaxel and CPT-11, have been used for NSCLC. Recently, non-platinum-combination chemotherapy of these newer agents has been examined for NSCLC. Georgoulias and colleagues [15] reported a randomised trial comparing platinum-based chemotherapy with non-platinum-based chemo-

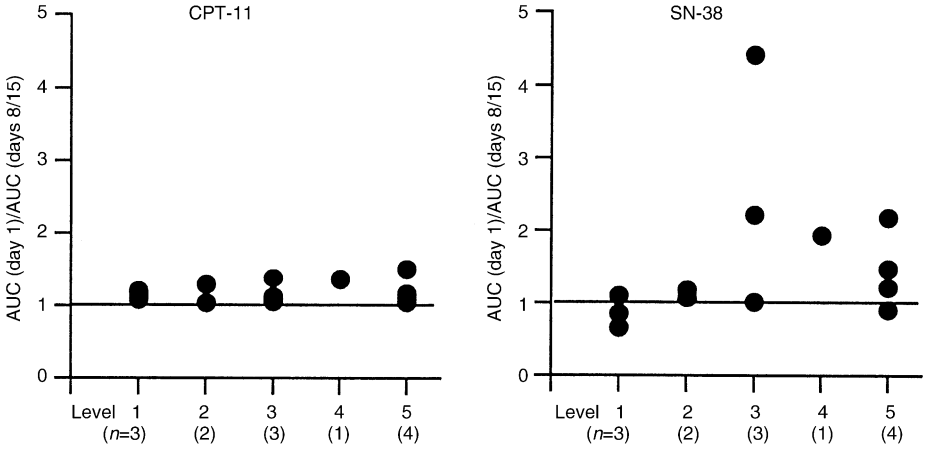

Fig. 1. The value of the area under the plasma concentration–time curves (AUCs) of CPT-11 and SN-38 on day 1 divided by those of day 8 or 15 for each patient. The AUC of CPT-11 on day 1 was higher than that of day 8 or 15 in levels 1–5 ($P=0.002$). The AUC on day 1 was 1.1 times higher than that of day 8 or 15 (median value, 3600 versus 3000 ng h/ml; 25–75%, 2700–4000 versus 2200–3700 ng h/ml). With regard to SN-38, there were no significant differences between the AUC_{0-19} of SN-38 on day 1 and that of day 8 or 15 at dose levels 1–2 (median value, 52 versus 47 ng h/ml; 25–75%, 29–82 versus 38–75 ng h/ml) ($P=0.893$). In contrast, the AUC_{0-19} of SN-38 on day 1 was approximately 1.7 times higher than that of day 8 or 15 at dose levels 3–5 (median value, 71 versus 48 ng h/ml; 25–75%, 59–83 versus 26–62 ng h/ml) ($P=0.025$).

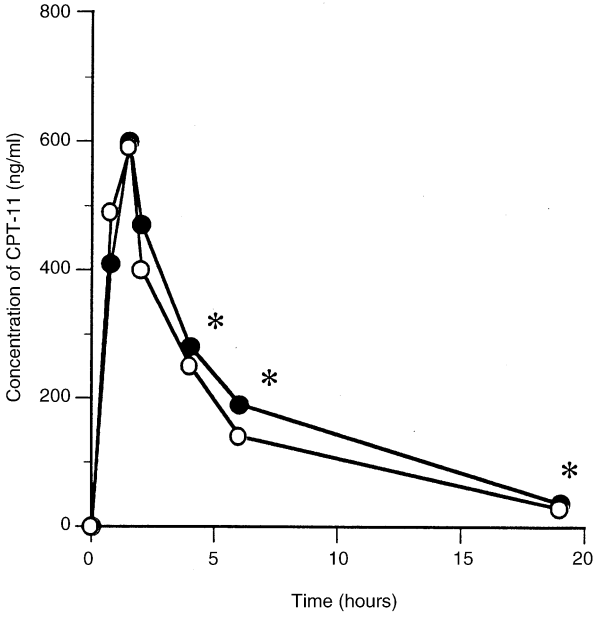

Fig. 2. The median plasma concentration–time curves of CPT-11 on day 1 (*closed circles*), and days 8 or 15 (*open circles*). * Significantly different from those of day 8 or 15 ($P=0.018$ at 4 h; $P=0.005$ at 6 h; $P=0.004$ at 19 h).

therapy. They reported that both regimens had comparable activity, however, the non-platinum-based chemotherapy regimen had the most favourable toxicity profile.

We conducted a phase I study of a combination of paclitaxel (day 1) with weekly CPT-11 (days 1, 8 and 15) for NSCLC. The recommended dose in this regimen was 180 mg/m^2 for paclitaxel and 50 mg/m^2 for CPT-11. This regimen was tolerable, although the main DLTs were neutropenic fever, neuropathy and diarrhoea. Earlier clinical studies of combination therapy of paclitaxel infused over 3 hours with other agents recommended a dose of 175 to 225 mg/m^2 of paclitaxel [16–18], while those of weekly CPT-11 when combined with other agents recommended a dose of CPT-11 of 50–60 mg/m^2 [19, 20]. Considered together with these results, the recommended dose determined in the present study seems appropriate. Recently, Murren and colleagues [14] also reported a phase I study of paclitaxel and CPT-11 in advanced cancer, where paclitaxel and CPT-11 were administered weekly for 4 weeks with a 2-week rest. Nineteen patients were entered into the first dose level (paclitaxel 75 mg/m^2, CPT-11 50 mg/m^2) and 2 patients in the second level (paclitaxel 75 mg/m^2, CPT-11 65 mg/m^2). All patients in the second level experienced DLT, thus determining the MTD. 8 of 19 patients in the first level also experienced serious adverse events, such as neutropenic fever, grade 3 diarrhoea, grade 3 fatigue, pulmonary embolism, pleural effusion and seizure. The administration schedule was different in these two phase I studies with paclitaxel and CPT-11, reflecting the different toxicity profiles.

In the present study, the preceding paclitaxel dose increased the AUC of CPT-11, and paclitaxel at a dose $\geqslant$150 mg/m^2 also increased the AUC of SN-38. Similarly, previous studies reported that paclitaxel increased the peak level of the active metabolite of doxorubicin and gemcitabine [21,22]. Although the exact mechanisms of these drug–drug interactions remain undetermined, the plasma CPT-11 concentration increased 4 h after CPT-11 administration and the AUC of SN-38 was within 2 h in the present study. We speculate that the increase of CPT-11 during the late phase might be due to the inhibition of CPT-11 excretion or metabolism, and that the increase of SN-38 in the early phase was due to the acceleration of CPT-11 metabolism by

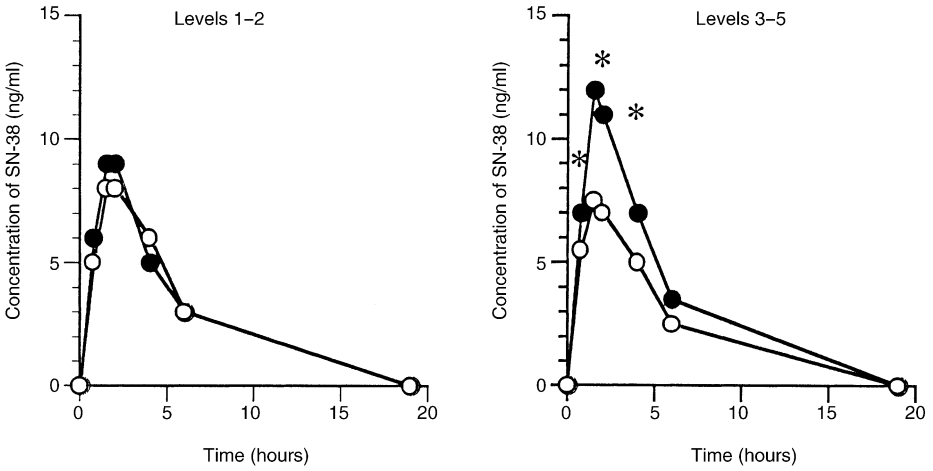

Fig. 3. The median plasma concentration–time curves of SN-38 on day 1 (*closed circles*), and days 8 or 15 (*open circles*). * Significantly different from day 8 or 15 at dose levels 3–5 ($P = 0.008$ at 45 min; $P = 0.002$ at 1.5 h; $P = 0.006$ at 2 h).

carboxylesterase or inhibition of SN-38 excretion. One of the possible mechanisms is competition of the metabolisms of paclitaxel and CPT-11. CPT-11 is mainly metabolised to its active metabolite SN-38 by carboxylesterase [23–25], and partially metabolised to 7-ethyl-10-[4-*N*-(5-aminopentanoic acid)-1-piperidino] carbonyloxycamptothecin (APC), and 7-ethyl-10-(4-amino-1-piperidino) carbonyloxycamptothecin (NPC) by cytochrome P450 (CYP) 3A4 [26–28]. Paclitaxel is also metabolised by CYP3A4 and CYP2C8 [29–32]. In the present study, CYP3A4 might have been consumed by the preceding paclitaxel, and then the metabolic pathway of CPT-11 to APC and NPC by CYP3A4 might have been inhibited. This inhibition of the CYP3A4 pathway possibly accelerated the metabolism of CPT-11 by carboxylesterase, resulting in an increased AUC of SN-38. Murren and colleagues [14] reported that the sequence of drug administration of paclitaxel followed by CPT-11 and CPT-11 followed by paclitaxel affected neither the elimination of CPT-11, nor the chemotherapy-related toxicity. However, the dose of paclitaxel used in their study was 75 mg/m^2 compared with more than 120 mg/m^2 in the present study. This difference in the paclitaxel dose probably affected the pharmacokinetics of CPT-11 and the toxicity.

The toxicities at our recommended dose were feasible, although the preceding paclitaxel increased the AUC of SN-38. 2 patients in level 1 and 1 patient in level 2 had received chemotherapy prior to this study, and this might have affected the analysis of toxicities. However, this did not affect the decision of the recommended dose, because they were entered in the low dose levels. Grade 3 or 4 neutropenia was observed in the first dose level, but recovery was seen within a few days. Anaemia and thrombocytopenia were mild. In addition, there were no grade 2 or higher non-haematological toxicities seen at dose levels 1–4. Grade 4 diarrhoea was observed at dose level 6 (CPT-11 60 mg/m^2), but grade 2 or less was observed at dose levels 1–5 (CPT-11 50 mg/m^2). We previously showed that various toxicities including diarrhoea might be more frequently observed when $\geqslant 60$ rather than 50 mg/m^2 of CPT-11 is combined with platinum agents [19]. Diarrhoea in the present study was consistent with this earlier suggestion, although paclitaxel increased the AUC of SN-38. Thus, when CPT-11 is combined with other agents, 50–60 mg/m^2 of this agent seems to be an appropriate dose.

The preceding paclitaxel increased the AUC of SN-38, therefore, other treatment schedules might be worth considering in order to reduce the toxicities. One possible schedule is to give the paclitaxel and CPT-11 administrations on separate days. This might reduce the drug–drug interactions. However, the exact mechanisms of the increase of CPT-11 and SN-38 remains undetermined. Therefore, other schedules need to be examined regarding their toxicities and pharmacokinetic parameters in phase I studies.

8 (31%; 95%CI, 14–52%) of 26 patients achieved a PR. Recent studies have shown response rates in advanced NSCLC to platinum-based chemotherapeutic regimens of approximately 30% [1–3]. Although the present study was a phase I study, the combination of paclitaxel and CPT-11 seems a promising strategy for NSCLC, compared with these platinum-based regimens.

In conclusion, we conducted a phase I study of paclitaxel (day 1) combined with weekly CPT-11 (days 1, 8 and 15) in NSCLC patients. The recommended dose using this regimen was 180 mg/m^2 for paclitaxel and 50 mg/m^2 for CPT-11. Although the preceding paclitaxel administration increased the AUCs of CPT-11 and SN-38, this regimen was well tolerated and active against NSCLC. The toxicities, except for neutropenia, were mild. Therefore, this regimen warrants additional phase II studies in NSCLC patients.

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