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A phase I study of irinotecan and infusional cisplatin for advanced non-small-cell lung cancer

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Abstract A phase I study was performed to establish the optimum dose for combination therapy with infusional cisplatin and irinotecan (CPT-11) in non-small-cell lung cancer (NSCLC). The subjects were 20 patients with a performance score of 0–2 with untreated advanced NSCLC. Cisplatin was administered by 5-day continuous intravenous infusion at 20–25 mg/m^2 per day. CPT-11 was administered by bolus infusion at a starting dose of 20 mg/m^2 on days 1 and 8 or 60 mg/m^2 per day on day 1 alone, followed by serial increments of 20 mg/m^2. Since grade 4 granulocytopenia was observed in two of the five patients receiving 20 mg/m^2 per day cisplatin (days 1–5) and 100 mg/m^2 CPT-11 (day 1), and since one of them developed severe pneumonia and sepsis associated with the granulocytopenia, the regimen was considered to be intolerable. In the same patient, grade 4 thrombocytopenia and grade 3 diarrhea were observed. Therefore, the optimum dose appeared to be 20 mg/m^2 per day (days 1–5) for cisplatin and 80 mg/m^2 (day 1) for CPT-11. The side effects were grade 2 diarrhea in one of three patients, and grade 2 vomiting in three patients, but grade ≥ 2 hemotoxicity was not observed. This combined regimen resulted in a partial response in 9 out of 19 assessable patients. The dose-limiting factor in this combination therapy was granulocytopenia, and a high efficacy rate was obtained.

Key words Non-small-cell lung cancer · Cisplatin · Irinotecan · Continuous infusion · Phase I study

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Introduction

Cisplatin-based chemotherapy can be used against advanced non-small-cell lung cancer (NSCLC), and a response rate of 25–50% has been reported for a variety of combination chemotherapy regimens such as cisplatin plus vindesine/vinblastine or etoposide and cisplatin plus vindesine plus mitomycin C [1, 8]. However, complete responses are rarely attained, and the effects on survival have not been clarified in advanced NSCLC. Advances in the treatment of this disease will be made only by discovering more active agents and successfully including such drugs in rational combination chemotherapy regimens.

Irinotecan hydrochloride (CPT-11), a semisynthetic derivative of camptothecin, has shown strong antitumor activity against a wide range of tumors in vitro [9, 14]. CPT-11 has also been found to be active against NSCLC [4, 16], small-cell lung cancer (SCLC) [10], leukemia, lymphoma [17] and colorectal cancer [18, 21]. A response rate of 32% to CPT-11 for NSCLC is encouraging [4].

Cisplatin is the most effective active agent for chemotherapy in advanced NSCLC. In addition, cisplatin is gaining widespread acceptance as one of two or three agents used in combination chemotherapy [2, 19]. There are several methods of administering cisplatin, and some institutes including our hospital use a 5-day continuous infusion (CI) [3, 20]. In previous study at our institute, cisplatin CI was given as a single agent to 30 previously untreated patients with NSCLC, and a high response rate, 40%, was obtained. Good clinical results have been obtained for cisplatin CI, and although the total dose is larger than for bolus administration, CI is associated with less severe emesis and renal toxicity [20], making cisplatin CI an effective and safe treatment for NSCLC.

In preclinical studies, CPT-11 has shown no cross-resistance and marked synergism with cisplatin [5–7].

To evaluate the potential therapeutic benefit of adding CPT-11 to cisplatin and to further assess the toxicity of CPT-11 in combination chemotherapy, we performed a phase I clinical study in patients with advanced NSCLC who had received no prior therapy. The purposes of this study were (a) to determine the optimal dose of CPT-11 in combination with a fixed dose of cisplatin, (b) to further assess the toxicity of CPT-11 in combination chemotherapy, and (c) to obtain preliminary evidence of the therapeutic activity in patients with advanced NSCLC.

Table 1 Dose escalation schedule

Dose level	Dose (mg/m^2)		No. of patients	Total no. of courses
	CPT-11	Cisplatin		
1	20×2	25×5	3	5
2	20×2	20×5	3	7
3	40×2	20×5	3	6
4	60	20×5	3	7
5	80	20×5	3	7
6	100	20×5	5	8

Materials and methods

Patient population

All patients with histologically or cytologically confirmed advanced NSCLC were eligible for this phase I trial. None of the patients had received prior therapy. Other eligibility criteria included expected survival of ≥ 12 weeks, age < 75 years, Eastern Cooperative Oncology Group performance score of 0–2, measurable lesions, and adequate hematological function (WBC $\geq 4000/mm^3$, platelet count $\geq 100\,000/mm^3$, hemoglobin ≥ 10 g/dl), renal function (serum, creatinine ≤ 1.5 mg/dl, creatinine clearance > 60 ml/min), and hepatic function (total serum bilirubin < 1.5 mg/dl, glutamic oxaloacetic transaminase and glutamic pyruvic transaminase less than twice the normal range). The protocols used were approved by the ethical committee of the Tochigi Cancer Center (Tochigi). Written informed consent was obtained in every case stating that the patient was aware of the investigational nature of this treatment regimen. Pretreatment evaluation included medical history, physical examination, complete blood count, bone marrow examination, serum biochemical analyses, chest radiograph, electrocardiogram, and urinalysis. All patients underwent a radionuclide bone scan, computerized tomography of the brain and thorax, and ultrasonography or computerized tomography of the abdomen. All patients were admitted to the Tochigi Cancer Center Hospital during this trial. Complete blood count, biochemical tests, serum electrolytes, urinalysis, and chest radiographs were obtained weekly during this phase I trial. Tests of measurable disease parameters such as computerized tomography were repeated every 4 weeks.

Study design and treatment plan

All patients were hospitalized for the combined treatment with CPT-11 plus cisplatin.

In the first part (level 1), the starting CPT-11 dose was 20 mg/m^2 on days 1 and 8 (40 mg/m^2 per course), and the dosage was increased in subsequent increments of 20 mg/m^2 (Table 1). The starting dose (40 mg/m^2 per course) was based on 1/10 (26.4 mg/m^2) of the dose which was lethal to 10% of mice tested or 1/3 (69.3 mg/m^2) of the low toxic dose in dogs on a single-dose schedule (data on file at Daiichi Pharmaceutical Co. and Yakult Honsha Co.). CPT-11 was kindly provided by Yakult Honsha (Tokyo, Japan), and Daiichi (Tokyo, Japan). Three patients were entered. The dose of CPT-11 in 500 ml normal saline or 5% glucose was infused intravenously (i.v.) over 90 min. Cisplatin (25 or 20 mg/m^2) was given daily for 5 days by i.v. CI. One-third of the daily dose was administered every 8 h dissolved in 800 ml physiological saline [20]. Antiemetic drugs used were metoclopramide (3 mg/kg per day, CI for 5 days), methylprednisolone (125 mg bolus infusion every 8 h, days 1–5), diphenhydramine (30 mg orally, days 1–7) and alprazolam (1.2 mg orally, days 1–7). The course was repeated every 4 weeks.

In the second part (levels 2, 3), we studied dose escalation of CPT-11 (days 1 and 8) with a fixed dose of cisplatin (20 mg/m^2 per day, CI, on 5 days) given every 4 weeks. The starting CPT-11 dose was 20 mg/m^2 and the dosage was then increased in increments of 20 mg/m^2. Three patients each were entered at the first level and second level (Table 1).

In the third part (levels 4–6), a successive cohort was used to study the dose escalation of CPT-11 (day 1) with a fixed dose of cisplatin (20 mg/m^2 per day, CI, on 5 days), given every 4 weeks. The starting CPT-11 dose was 60 mg/m^2 and the dosage was then increased in increments of 20 mg/m^2. The starting dose of CPT-11 was determined at 60 mg/m^2, because this dose, which was between 40 mg/m^2, the total dose at the first level of the second part, and 80 mg/m^2, the total dose at the second level, was considered to be reasonable with regard to safety. The goal was to focus primarily on the dose escalation of CPT-11. The hydration and antiemetics were administered in the same way as in the first part.

We initially planned to treat three patients at each dose level. No dose escalation was permitted in the same patient. The maximally tolerated dose (MTD) was that at which either of the following was produced in at least 50% of the patients treated: (a) nonhematological toxicity of grade ≥ 3 or nausea and vomiting of grade 4, or (b) the persistence of a nadir with an absolute granulocyte count of $< 500/mm^3$ for ≥ 7 days. This was determined by carrying out a complete blood count every other day when the leukocyte and platelet count decreased to $< 2000/mm^3$ and $50\,000/mm^3$, respectively. The reason we decided to use granulocytopenia lasting ≥ 7 days as a dose-limiting factor was that we expected this regimen to induce severe granulocytopenia, but that this would be manageable under the careful supervision made possible by the hospital setting. Recombinant human granulocyte colony-stimulating factor (rhG-CSF) was not used in this trial. In addition, no prophylactic measures such as antibiotic administration were taken prior to the occurrence of fever associated with the granulocytopenia.

Toxicity was graded according to the common toxicity criteria [23]. Patients were treated for at least two cycles of therapy unless disease progression or unacceptable toxicity was encountered or the patient's wishes intervened. No dosage modification was made on the basis of bone marrow toxicity. In the case of stable or progressive disease after two courses of treatment, subsequent therapy was left to the discretion of the physician in charge of the patient. The criteria for response were as follows. Complete response was defined as the complete disappearance of all evidence of tumor for at least 4 weeks. Partial response was defined as a $> 50\%$ reduction in the sum of the product of the two greatest perpendicular diameters of all indicator lesions for at least 4 weeks and no appearance of new lesions or progression of any lesion. Disease progression was defined as a $\geq 25\%$ increase in tumor area or the appearance of new lesions. All other circumstances were classified as stable disease.

Results

A group of 20 patients participated in this study between September 1992 and July 1993 and received 40 courses of the regimen. Table 2 shows the patient characteristics. There were 8 women and 12 men, with a median age of 63 years (range 43 to 74 years). Three patients had stage IIIB disease and 17 stage IV disease. A total of 40 courses of therapy were given, and all were assessable for toxicity. The mean number of cycles administered per patient was two, ranging from one to three (one cycle in 3 patients, two in 14 patients, and three in 3 patients). Table 1 shows the number of patients and courses per dose level.

Toxicity

Tables 3 and 4 show the side effects. In level 1, granulocytopenia of grade 4 lasting for ≥ 7 days was noted in two of three patients, but they had no infectious complications. The regimen was considered to be intolerable. In the second part, the dosage of cisplatin was fixed at 20 mg/m^2, and that of CPT-11 was increased, but grade 4 granulocytopenia lasting for ≥ 7 days was observed in two of three patients at level 3. They had no infectious complications. The regimen was considered to be intolerable. In the third part, CPT-11 was administered only on day 1, and the dosage of CPT-11 was increased. Grade 4 granulocytopenia lasting for ≥ 7 days was noted in two of five patients at level 6, and one of them developed severe pneumonia and sepsis associated with the granulocytopenia, so that the regimen was considered to be intolerable. Grade 4 thrombocytopenia and grade 3 diarrhea were observed in the same patient.

At level 3, grade 4 diarrhea was observed in one of three patients, and grade 3 vomiting and liver dysfunction associated with increases in transaminases were noted in the same patient.

Table 4 shows granulocytopenia and diarrhea as side effects. In the first course, the granulocyte count was maintained at $2.0 \times 10^3/\text{mm}^3$ at median nadir at level 5. The median day until nadir and the median day of recovery were slightly delayed in the levels 1–3 groups, in which CPT-11 was administered on days 1 and 8, than in the levels 4–6 groups, in which it was administered on day 1 alone. In a total of 40 courses, grade ≥ 3 diarrhea was observed in only 2 courses. Grade ≥ 3 diarrhea developed on median day 10 (day 8, 12), and recovery was observed on median day 16 (day 14, 18). Diarrhea could be managed with loperamide HC1 in addition to i.v. fluid and electrolyte replacement.

No patients experienced tarry stool or grossly bloody diarrhea. Finally, there were no treatment-related deaths. The maximum tolerated dose (MTD) in this study was 100 mg/m^2 CPT-11 on day 1 combined with cisplatin (20 mg/m^2 per day, CI, on 5 days).

Response to treatment

Table 5 shows the therapeutic responses. One patient was nonassessable for response. This patient was

Table 2 Patient characteristics

No. of patients	
Sex	20
Male	12
Female	8
Age (years)	
Median	63
Range	43–74
Performance status	
0–1	12
2	8
Stage	
IIIB	3
IV	17
Histology	
Adenocarcinoma	13
Squamous	6
Adenosquamous	1

Table 3 Toxicity of CPT-11 and infusional cisplatin (*DLT* dose limitng toxicity, *numbers in parentheses* numbers of patients with grade 4 granulocytopenia lasting ≥ 7 days)

Dose level	No. of patients/no. of patients with DLT	WBC (grade)			Granulocytes (grade)			Platelets (grade)			Liver (grade)		Diarrhea (grade)		Nausea/vomiting (grade)		Alopecia (grade)	
		2	3	4	2	3	4	2	3	4	2	3	2	≥ 3	2	3	1	2
1	3/2	0	2	0	0	0	2(2)	1	0	0	0	0	0	0	0	1	0	1
2	3/0	1	0	0	0	1	0	1	1	0	0	0	1	0	2	0	0	1
3	3/2	2	1	0	0	1	2(2)	1	0	0	0	1	0	1	1	1	1	2
4	3/0	0	1	0	0	1	0	0	0	0	0	0	1	0	2	0	0	3
5	3/0	0	0	0	0	0	0	0	0	0	0	0	1	0	3	0	2	1
6	5/2	1	1	1	0	1	2(2)	0	0	1	1	0	1	1	2	0	1	1

Table 4 Granulocytopenia and diarrhea as major toxic effect at each dose level

	Dose level					
	1	2	3	4	5	6
No. of patients	3	3	3	3	3	5
No. of courses	5	7	6	7	7	8
Granulocyte counts in first course						
No. of patients[a]	2	1	3	1	0	3
Nadir ($\times 10^3/mm^3$)						
Median	0.37	0.64	0.56	0.52		0.27
Range	0.25, 0.50		0.35–0.87			0–0.52
Day of Nadir						
Median	18	21	19	15		17
Range	17, 19		17–22			12–22
Day of recovery[b]						
Median	32	28	32	17		29
Range	26, 39		29–33			24–36
Diarrhea[c]	0	0	1	0	0	1

[a]Only patients suffering grade 2 or worse toxicity
[b]Granulocyte counts $\geq 2 \times 10^3/mm^3$
[c]Number of courses which exhibited grade 3 or 4 diarrhea in all courses

Table 5 Therapeutic response at each dose level (*CR* complete response, *PR* partial response, *SD* stable disease)

Dose level	No. of assessable patients	No. of patients responding			Responders		Response duration (days)	
		CR	PR	SD	No.	%	Median	Range
1	3	0	2	1	2	66	68	68
2	3	0	1	2	1	33	66	
3	3	0	1	2	1	33	129	
4	3	0	1	2	1	33	102	
5	3	0	3	0	3	100	84	44–100
6	4	0	1	1	1	25	60	
Overall	19	0	9	8	9	47	83	44–129

removed from the study after one cycle of treatment for granulocytopenia of grade 4 lasting 4 days and grade 3 diarrhea.

A complete response was not achieved in any patient. A partial response was achieved in 9 of the 19 assessable patients. There was no clear relationship between the dose of CPT-11 and the response to treatment. The median duration of response was 11.5 weeks (range 6–18 weeks).

Discussion

CPT-11 is clearly effective against SCLC [10] and advanced NSCLC [4, 16]. Cisplatin is also a most effective active agent. In in vitro studies, combinations of CPT-11 and cisplatin have been shown to be synergistic [5]. The two drugs have different action mechanisms, and the principal toxicities do not overlap. Combination therapy with CPT-11 and cisplatin has also been used against advanced lung cancer [11, 12, 22].

The current phase I study of CPT-11 in combination with a fixed dose of cisplatin (CI) was conducted to determine the toxicity and morbidity associated with this regimen in the treatment of patients with advanced NSCLC who had received no prior therapy.

The toxicities of this regimen were leukopenia, especially granulocytopenia. In this study, we regarded an absolute granulocyte count of $< 500/mm^3$ for ≥ 7 days as unacceptable toxicity. The duration of granulocytopenia may be reduced by the use of rhG-CSF. Since rhG-CSF was not used in this study, delay of treatment due to granulocytopenia was noted in level 3 although no treatment-related deaths due to granulocytopenia were observed. Concerning the diarrhea as a toxicity of CPT-11 [4, 16, 18], grade ≥ 3 diarrhea appeared in only two courses of a total of 40 courses coincidentally with grade 4 granulocytopenia. Diarrhea of grade ≥ 3 was infrequent, probably because the dose of CPT-11 was 10–25% of that used in the phase I study, in which CPT-11 was administered weekly at

100 mg/m^2 [16]. Grade ≥ 3 diarrhea could be managed by administration of 2–4 mg loperamide HCl daily in addition to i.v. fluid and electrolyte replacement.

There are several methods of administering cisplatin, and some institutes including our hospital have used a 5-day continuous infusion [3, 20]. Good clinical results have been obtained with cisplatin CI, and although the total dose is larger than with bolus administration, CI is associated with less severe emesis and renal toxicity [19, 20], making cisplatin CI an effective and safe treatment for NSCLC.

In a phase I trial of a combination of CPT-11 and cisplatin reported by Masuda et al. [11, 12], cisplatin was administered at 60 and 80 mg/m^2 every 4 weeks. Since it was administered at 20 mg/m^2 per day on 5 consecutive days every 4 weeks in this study, the dosage of cisplatin in this regimen was 1.67 and 1.25 times higher than that in the study of Masuda et al.

On the other hand, based on the assumption of dose-efficiency relationship, CPT-11 could be combined with high-dose cisplatin (25 mg/m$^2 \times 5$) at only 10% (20 mg/m^2 on days 1 and 8) of the dose intensity of 100 mg/m^2 per week achieved as a single agent [16]. Therefore, we conducted the second and third parts of the study on this regimen to focus primarily on the dose escalation of CPT-11. The dose of CPT-11 combined with cisplatin (20 mg/m$^2 \times 5$) was able to be increased to 20% (80 mg/m^2 on days 1) of the dose intensity of the drug when given alone. This dose intensity of CPT-11 (20%) was lower than that reported by Masuda et al. (45%, 60%) [11, 12]. The low dose intensity of CPT-11 is considered to be at least partly due to an additive myelosuppressive effect of the concomitant use of cisplatin [11].

It is not clear which is more important, the dose intensity of cisplatin or the dose intensity of CPT-11, in the combination of cisplatin and CPT-11 in the management of the patients with advanced NSCLC [22]. Based on the assumption of a dose-efficacy relationship, it is preferable for CPT-11 to be given in combination with cisplatin at a dose closer to the MTD of CPT-11 when it is used as a single agent. Therefore, we are currently conducting a further trial to determine whether the use of rhG-CSF offers adequate protection against leukopenia to allow further augmentation of the dose intensity of CPT-11 combined with cisplatin [13].

Partial responses were observed in 9 of 19 assessable patients. There was no clear relationship between the dose of CPT-11 and the response to treatment [11]. Although a complete response was not achieved, a response rate of 47% for this regimen is encouraging [4, 11, 12].

In conclusion, CPT-11 combined with 100 mg/m^2 cisplatin could be given at 20% of the dose intensity of the drug when given alone. In this phase I study of 19 assessable patients with previously untreated NSCLC, a partial response was achieved in 9 patients. The major dose-limiting toxicity of this regimen was granulocytopenia. We are conducting a further phase I trial to investigate whether support with rhG-CSF would permit further intensification of the CPT-11 dose in combination with a fixed cisplatin dose.

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References

1. Bonomi P (1986) Brief overview of combination chemotherapy on non-small cell lung cancer. Semin Oncol 13:89
2. Bunn PA Jr (1989) The expanding role of cisplatin in the treatment of non-small-cell lung cancer. Semin Oncol 16 [Suppl. 6]: 10
3. Forastiere AA, Belliveau JF, Goren MP, Vogel WC, Posner MR, O'Leary GP Jr (1988) Pharmacokinetic and toxicity evaluation of five-day continuous infusion versus intermittent bolus cis-diamminedichloroplatinum (II) in head and neck cancer patients. Cancer Res 48:3869
4. Fukuoka M, Niitani H, Suzuki A, Motomiya M, Hasegawa K, Nishiwaki Y, Kuriyama T, Ariyoshi Y, Negoro S, Masuda N, Nakajima S, Taguchi T (1992) A phase II study of CPT-11, a new derivative of camptothecin, for previously untreated non-small-cell lung cancer. J Clin Oncol 10:16
5. Kano Y, Suzuki K, Akutsu M, Suda K, Inoue Y, Yoshida M, Sakamoto S, Miura Y (1992) Effects of CPT-11 in combination with other anti-cancer agents in culture. Int J Cancer 50:604
6. Kanazawa F, Sugimoto Y, Minato K, Kasahara K, Bungo M, Nakagawa K, Fujiwara Y, Liu LF, Saijo N (1990) Establishment of a camptothecin analogue (CPT-11)-resistant cell line of human non-small-cell lung cancer: characterization and mechanism of resistance. Cancer Res 50:5919
7. Kasahara K, Fujiwara Y, Nishio K, Ohmori T, Sugimoto Y, Komiya K, Matsuda T, Saijo N (1991) Metallothionein content correlates with the sensitivity of human small-cell lung cancer cell lines to cisplatin. Cancer Res 51:3237
8. Klastersky J (1986) Therapy with cisplatin and etoposide for non-small-cell lung cancer. Semin Oncol 13:104
9. Kunimoto T, Nitta K, Tanaka T, Uehara N, Baba H, Takeuchi M, Yokokura T, Sawada S, Miyasaka T, Mutai M (1987) Antitumor activity of 7-ethyl-10-[4-(1-piperi-dino)-1-piperidino] carbonyloxy-camptothecin, a novel water-soluble derivative of camptothecin, against murine tumors. Cancer Res 47:5944
10. Masuda N, Fukuoka M, Kusunoki Y, Matsui K, Takifuji N, Kudoh S, Negoro S, Nishioka M, Nakagawa K, Takada M (1992) CPT-11: a new derivative of camptothecin, for the treatment of refractory or relapsed small-cell lung cancer. J Clin Oncol 10:1225
11. Masuda N, Fukuoka M, Takada M, Kusunoki Y, Negoro S, Matsui K, Kudoh S, Takifuji N, Nakagawa K, Kishimoto S (1992) CPT-11 in combination with cisplatin for advanced non-small-cell lung cancer. J Clin Oncol 10:1775
12. Masuda N, Fukuoka M, Kudoh S, Kusunoki Y, Matsui K, Takifuji N, Nakagawa K, Tamanoi M, Nitta T, Hirashima T, Negoro S, Takada M (1993) Phase I trial and pharmacologic study of irinotecan with cisplatin for advanced lung cancer. Br J Cancer 68:777
13. Masuda N, Fukuoka M, Kudoh S, Kusunoki Y, Matsui K, Nakagawa K, Hirashima T, Tamanoi M, Nitta T, Yana T, Negoro S, Takifuji N, Takada M (1994) Phase I study of irinotecan and cisplatin with granulocyte colony-stimulating factor support for advanced non-small-cell lung cancer. J Clin Oncol 12:90

14. Matsuzaki T, Yokokura T, Mutai M, Tsuruo T (1988) Inhibition of spontaneous and experimental metastasis by a new derivative of camptothecin, CPT-11, in mice. Cancer Chemother Pharmacol 21 : 308
15. Mori K, Saitou Y, Tominaga K (1992) Phase II study of cisplatin continuous infusion plus vindesine in the treatment of non-small-cell lung cancer. Am J Clin Oncol 15 : 344
16. Negoro S, Fukuoka M, Masuda N, Takada M, Kusunoki Y, Matsui K, Takifuji N, Kudoh S, Niitani H, Taguchi T (1991) Phase I study of weekly administration of CPT-11. J Natl Cancer Inst 83 : 1164
17. Ohno R, Okada K, Masaoka T, Kuramoto A, Arima T, Yoshida Y, Ariyoshi H, Ichimaru M, Sakai Y, Oguro M, Ito Y, Morishima Y, Yokomaku S, Ota K (1990) An early phase II study of CPT-11: a new derivative of comptothecin, for the treatment of leukemia and lymphoma. J Clin Oncol 8 : 1907
18. Rothenberg ML, Kuhn JG, Burris III HA, Nelson J, Eckardt JR, Tristan-Morales M, Hilsenbeck SG, Weiss GR, Smith LS, Rodriguez GI, Rock MK, Von Hoff DD (1993) Phase I and phamacokinetic trial of weekly CPT-11. J Clin Oncol 11 : 2194
19. Ruckdeschel JC, Finkelstein DM, Mason BA, Creech RH (1985) Chemotherapy for metastatic non-small-cell bronchogenic carcinoma: EST 2575, generation V-A randomized comparison of four cisplatin-containing regimens. J Clin Oncol 3 : 72
20. Saito Y, Mori K, Tominaga K, Yokoi K, Miyazawa N (1990) Phase II study of 5-day continuous infusion of cis-diammine-dichloroplatinum (II) in the treatment of non-small-cell lung cancer. Cancer Chemother Pharmacol 26 : 389
21. Shimada Y, Yoshino M, Wakui A, Nakao I, Futatsuki K, Sakata Y, Kambe M, Taguchi T, Ogawa N (1993) Phase II study of CPT-11, a new camptothecin derivative, in metastatic colorectal cancer. J Clin Oncol 11 : 909
22. Shinkai T, Arioka H, Kunikane H, Eguchi K, Sasaki Y, Tamura T, Ohe Y, Oshita F, Nishio N, Karato A, Okamoto H, Nakashima H, Ohmatsu H, Shiraishi J, Nomura N, Saijo N (1994) Phase I clinical trial of irinotecan (CPT-11), 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy-camptothecin, and cisplatin in combination with fixed dose of vindesine in advanced non-small-cell lung cancer. Cancer Res 54 : 2636
23. Wittes RE (1989/1990) Grading toxicity. In: Wittes RE (ed) Manual of oncologic therapeutics. Lippincott, Philadelphia, p 628