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Clinical studies of irinotecan alone and in combination with cisplatin

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Abstract. Irinotecan (CPT-11), a new derivative of camptothecin, showed schedule-dependent antitumor activity and toxicity in preclinical animal studies. We carried out a phase I study of weekly CPT-11 infusion, which indicated that the recommended dose for phase II studies was 100 mg/m^2. In a phase II trial, CPT-11 achieved a response rate of 32% for non-small cell lung cancer (NSCLC). In two phase II trials, CPT-11 achieved objective response rates of 37% and 47% for small cell lung cancer (SCLC). The high activity of CPT-11 in these phase II studies suggested that the next rational step was to investigate combination chemotherapy. The first phase I trial of CPT-11 combined with cisplatin achieved an encouraging response rate of 54% in 27 patients with previously untreated NSCLC, and the recommended schedule for phase II studies was 60 mg/m^2 of CPT-11 (days 1, 8, and 15) plus 80 mg/m^2 of cisplatin (day 1) given at 4-week intervals. Given the high single-agent activity of CPT-11 against SCLC and NSCLC, a regimen with a higher dose of this agent and a lower dose of cisplatin seemed likely to be more effective. In the second trial, the cisplatin dose was accordingly reduced from 80 to 60 mg/m^2, and the recommended dose of CPT-11 was concluded to be 80 mg/m^2. Thus, reduction of the cisplatin dose to 60 mg/m^2 allowed the safe administration of CPT-11 at 80 mg/m^2 (33.3% dose intensification compared with the original regimen). The most recent trial of this combination with recombinant human granulocyte colony-stimulating factor (rhG-CSF) support demonstrated that the recommended dose is 80 mg/m^2 of CPT-11 and 80 mg/m^2 of cisplatin. Thus, we could raise the CPT-11 dose 33% above that given in the original regimen while maintaining the original cisplatin dose by the use of rhG-CSF support. Further trials are needed to evaluate the effect of CPT-11 given in combination with other active agents for the treatment of lung cancer.

Key words: Irinotecan – Lung cancer – Clinical studies

Introduction

Camptothecin is a plant alkaloid isolated by Wall and colleagues [40] in 1966 from the Chinese plant *Camptotheca acuminata*. It is a potent inhibitor of DNA topoisomerase I [1, 13] and has shown strong antitumor activity both in vitro [6, 18] and in experimental animal tumor systems [9]. Camptothecin was tested in clinical trials in the late 1960s and early 1970s, but further clinical development was halted because of the low response rate and high toxicity demonstrated in clinical trials [5, 11, 12, 23, 25]. In attempts to reinforce the antitumor activity and decrease the toxicity of camptothecin, many derivatives have been synthesized [4, 17, 27, 42]. One of these derivatives is irinotecan (CPT-11), a water-soluble compound synthesized by Yokokura and co-workers at Yakult Honsha Co., Ltd. (Tokyo, Japan). CPT-11 is active against a broad spectrum of experimental tumors, including pancreatic adenocarcinoma 03, P388 leukemia, mammary adenocarcinoma 16/C, Ehrlich ascites carcinoma, NH134 hepatoma, sarcoma 180, Lewis lung carcinoma, Meth A fibrosarcoma, L1210 leukemia, and colon carcinoma C38 [2, 16, 33, 39]. CPT-11 is transformed to an active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38) by carboxylesterase, an enzyme that is found mainly in the liver, bowel mucosa, and tumor tissue [38]. SN-38 has 1000 times more antitumor activity than CPT-11 itself in vitro and plays an essential role in the cytocidal activity and toxicity of the parent compound, suggesting that CPT-11 is a prodrug [14]. An initial phase I study of CPT-11 given as a single in-

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Table 1. Patients' characteristics

	Monotherapy				Combination chemotherapy		
	Phase I [28]	Phase II [7]	Phase II [29]	Phase II [19]	Phase I [20]	Phase I [21]	Phase I [22]
Total number of patients entered	17	73	41	15[a]	27	14	20
Sex: M/F	13/4	53/20	33/8	12/3	17/10	8/6	15/5
Age: Median years (range)	64 (45–78)	67 (34–75)	62 (40–74)	63 (38–76)	63 (38–75)	61 (43–74)	59 (43–72)
Performance status (ECOG): 0–1/2	10/7	54/19	28/13	6/9	18/9	10/4	18/2
Stage: IIIA/IIIB/IV	3/2/12	20/13/40	4/8/29	4/1/10	0/6/21	0/7/7	0/5/15
Histology:							
Adenocarcinoma	9	47	0	0	15	8	10
Squamous-cell carcinoma	5	22	0	0	9	3	7
Large-cell carcinoma	3	3	0	0	3	1	2
Adenosquamous carcinoma	0	1	0	0	0	0	1
Small-cell carcinoma	0	0	41	15	0	2	0
Prior therapy: yes/no	2/15	0/73	33/8	15/0	0/27	0/14	0/20

ECOG, Eastern Cooperative Oncology Group
[a] Number of eligible patients

travenous dose every 3–4 weeks showed that the dose-limiting toxicity was myelosuppression and that the maximum tolerated dose was 250 mg/m^2 [34].

Camptothecin and its derivatives show schedule-dependent antitumor activity and toxicity [25, 26]. In preclinical studies, the antitumor effect of CPT-11 increased when it was given by repeated administration instead of on a single day at the same total dose [8]. Accordingly, weekly administration of CPT-11 seems likely to be superior to a monthly schedule for achieving an objective response. On this basis, we carried out one phase I trial and three phase II trials of CPT-11 given as a single weekly intravenous infusion to patients with advanced lung cancer.

Significant activity of CPT-11 has previously been observed against leukemia, lymphoma [31, 37], small-cell lung cancer (SCLC) [19, 29], non-small-cell lung cancer (NSCLC) [7], colorectal cancer [32], ovarian cancer, and cervical cancer [36], tumors for which cisplatin is also among the most active agents, excluding colorectal carcinoma [3]. Successful chemotherapy generally requires the use of a combination of drugs. The synergism between CPT-11 and cisplatin in preclinical studies [15, 35], the lack of cross-resistance with CPT-11 [19, 30], the different mechanisms of action of the two drugs [1, 43], and the relatively different toxicity profiles of these agents [10, 28] provide a rationale for considering their use in combination chemotherapy. A trial of this combination was performed to determine the maximum tolerated dose of CPT-11 given with a fixed dose of cisplatin and to define and quantify the dose-limiting toxicities of the combination.

In view of the high single-agent activity of CPT-11 against SCLC [19, 29] and NSCLC [7], a regimen with a higher dose of this agent and a lower dose of cisplatin seemed likely to be more active. In the next phase I trial of combination therapy with CPT-11 and cisplatin, we reduced the cisplatin dose from 80 to 60 mg/m^2 and increased the dose of CPT-11 in an attempt to maximize the potential cytocidal effect of this drug.

Since leukopenia was one of the dose-limiting toxicities of CPT-11 and cisplatin combination therapy [20], we also conducted a phase I trial of this combination with recombinant human granulocyte colony-stimulating factor (rhG-CSF) support. The primary goal of this trial was to evaluate the feasibility of increasing the dose of CPT-11 given in combination with cisplatin by using rhG-CSF, with the hope that a high-dose regimen would increase the response rate and survival of patients with NSCLC. This article summarizes our experience with weekly intravenous CPT-11 given alone or in combination with cisplatin.

Patients and methods

Patients' characteristics. Between 1988 and 1992, a total of 207 patients with histologically or cytologically proven lung cancer were entered into seven trials of CPT-11 given alone or in combination with cisplatin. The clinical profiles of the patient populations studied are summarized in Table 1.

Treatment schedule. The patients were treated with CPT-11 monotherapy or combination therapy according to one of five regimens (Table 2). CPT-11 was obtained in 5-ml vials containing 100 mg of the drug (Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan, and Yakult Honsha Co., Ltd., Tokyo) and was dissolved in 500 ml of normal saline for administration as a 90-min intravenous infusion. On the basis of experience obtained in a phase I trial of weekly CPT-11 [28], the dose was modified according to the leukocyte count obtained on the day when the next dose was scheduled (Table 3).

Evaluation. Tumor staging was done on the basis of a complete medical history and physical examination; routine chest radiography; whole-lung tomography; bone scintiscanning; computed tomography of the head, chest, and abdomen; and fiber-optic bronchoscopy. Staging was performed according to the tumor-node-metastasis system [24]. The eligibility, evaluability, and response of each patient were assessed by extramural review. Tumor response was classified in accordance with the World Health Organization (WHO) criteria [41]. The duration of response was defined as the number of days from the documentation of a response to tumor progression. The WHO or Eastern Cooperative Oncology Group (ECOG) common toxicity criteria were used to assess organ damage. The maximum tolerated dose

Table 2. Treatment schedules

CPT-11 monotherapy:	
Phase I trial:	CPT-11 given at 50, 100, 125, and 150 mg/m^2 by 90-min weekly intravenous infusion
Phase II trials:	CPT-11 given at 100 mg/m^2 by 90-min weekly intravenous infusion
CPT-11 plus cisplatin:	
Trial I:	Fixed dose of cisplatin (80 mg/m^2) given on day 1 plus CPT-11 (30, 40, 50, 60, and 70 mg/m^2) given on days 1, 8, and 15
Trial II:	Fixed dose of cisplatin (60 mg/m^2) given on day 1 plus CPT-11 (60, 80, and 90 mg/m^2) given on days 1, 8, and 15
Trial III:	Fixed dose of cisplatin (80 mg/m^2) given on day 1 plus CPT-11 (70, 80, and 90 mg/m^2) given on days 1, 8, and 15 with rhG-CSF (2 μg/kg) being given by daily subcutaneous injection from day 4 to day 21 of each treatment cycle (except on the days of CPT-11 administration)

Table 3. Dose modification

CPT-11 monotherapy:	
Phase I trial:	None
Phase II trials:	When the WBC count was ≥3,000/μl, treatment was continued at the full dose. When the WBC count was 2,000–3,000/μl, treatment was postponed until recovery from leukopenia and then restarted at the full dose. When the WBC count was 1,000–2,000/μl, treatment was postponed and restarted at 80 mg/m^2. When the WBC count was <1,000/μl or other grade 4 toxicities occurred, treatment was discontinued
CPT-11 plus cisplatin:	
Trial I:	CPT-11 was ceased if leukopenia more severe than grade 1 (leukocyte count, <3,000/μl) was noted on the day when the dose was due
Trial II:	Same as trial I
Trial III:	CPT-11 treatment was ceased if grade 3 or worse leukopenia (leukocyte count, <2,000/μl) was noted on the day when the dose was due

was usually defined as the dose producing grade 3–4 nonhematologic toxicity (except nausea and vomiting) in one-third or more of the patients and/or grade 3–4 hematologic toxicity in two-thirds or more of the patients after the first course.

Results

Phase I study of CPT-11 monotherapy

In this study [28], gastrointestinal toxicity was the most prominent nonhematologic toxicity (Table 4) and included nausea and vomiting, anorexia, diarrhea, and paralytic ileus. Nausea and vomiting occurred in 9 of 17 patients, whereas diarrhea occurred in 7. Grade 4 diarrhea associated with paralytic ileus was observed in one patient at a dose of 150 mg/m^2, and it coincided with grade 4 leukopenia and thrombocytopenia. This patient died on day 32 of the treatment schedule. After this lethal toxicity occurred, three other patients were entered at a dose of 125 mg/m^2. Despite this dose reduction, one patient died on day 25 of treatment due to sepsis and severe diarrhea. After receiving eight doses of CPT-11, another patient developed drug-induced pneumonitis, which responded well to steroid therapy. No cystitis occurred during this study. Myelosuppression was another major dose-limiting toxicity of this schedule (Table 4). The median leukocyte nadir was 4,300/μl at 50 mg/m^2, 2,500/μl at 100 mg/m^2, 3,000/μl at 125 mg/m^2, and 1,800/μl at 150 mg/m^2. Thrombocytopenia occurred much less frequently than leukopenia, whereas mild to moderate anemia was noted at each dose level.

Among the 11 assessable patients, a partial response (PR) was observed in two previously untreated patients (18%) who received doses of 100 and 125 mg/m^2, respectively (Table 4).

Phase II trials of CPT-11 monotherapy for lung cancer

Phase II study in previously untreated NSCLC. In this study [7], 23 of 72 patients (32%) showed a PR, but none of the patients showed a complete response (CR; 95% confidence limits for the overall response rate, 20%–44%; Table 4). In all, 10 of the 32 patients with locoregional disease and 13 of the 40 patients with metastatic disease showed a re-

Table 4. Results of trials

	CPT-11 alone				CPT-11 plus cisplatin		
	Phase I [28]	Phase II [7]	Phase II [29]	Phase II [19]	Phase I [20]	Phase I [21]	Phase I [22]
Dose-limiting toxicities	Diarrhea/ leukopenia	–	–	–	Diarrhea/ leukopenia	Diarrhea	Diarrhea/ leukopenia
Maximum tolerated dose (mg/m^2)	100				70	90	90
Number of patients assessable	11	72	35	15	26	14	20
Response (%):							
Complete response	0	0	2 (6)	0	0	1 (7)	0
Partial response	2 (18)	23 (32)	11 (31)	7 (47)	14 (54)	5 (36)	10 (50)
No change	5 (45)	47 (65)	15 (43)	7 (47)	11 (42)	8 (57)	9 (45)
Disease progression	4 (36)	6 (8)	7 (20)	1 (6)	1 (4)	0	1 (5)

sponse. The response rates for adenocarcinoma and squamous-cell carcinoma were 30% and 24%, respectively. The median duration of response for all responders was 15 weeks, and the median duration of survival for all patients was 42 weeks.

Leukopenia of grade 2 or worse occurred in 40 patients, and grade 3 or 4 leukopenia was observed in 18 patients. Anemia of grade 3 or 4 occurred in 11 patients, but no grade 3 or 4 thrombocytopenia was experienced.

Nausea and/or vomiting occurred in 56 patients, and diarrhea was observed in 48 patients (67%). The diarrhea was so severe that it was very difficult to control in three patients. Mucositis and skin rash were observed in three patients and one patient, respectively, but hemorrhagic cystitis did not occur. Pulmonary toxicity affected six patients (8%). Five of these six patients were treated with corticosteroids: one died of respiratory failure, four responded to treatment, and one improved spontaneously within 1 week.

Phase II study in SCLC conducted by a multicenter lung cancer study group. In this study [29], among 35 evaluable patients, 2 achieved a CR and 11 attained a PR, resulting in an overall response rate of 37% (95% confidence interval for the response rate; 19%–55%; Table 4). The response rate was 33% in 27 previously treated patients and 50% in 8 previously untreated patients. The median duration of survival was 35 weeks for all patients and 28 weeks for those with extensive disease. The median duration of survival for patients with limited disease has not yet been reached.

A total of 39 patients were assessable for toxicity. The major toxicities were leukopenia and diarrhea. Grade 3–4 leukopenia affected 31% of the patients and grade 3 or 4 diarrhea occurred in 15%, being persistent in some patients. Marked interpatient variation in the severity of diarrhea was observed during this trial.

Phase II study in previously treated patients with SCLC. In this study [19], the most frequent toxicity was myelosuppression, and 33% of the patients developed severe leukopenia (WHO grade 3 or 4), whereas 20% had WHO grade 3 anemia. Gastrointestinal toxicity was another prominent problem with this treatment; nausea and vomiting of worse than grade 2 occurred in two patients (13%), and diarrhea was observed in one patient (7%). Furthermore, one patient (7%) experienced grade 4 paralytic ileus after receiving four weekly doses of CPT-11. No bladder, kidney, or liver toxicity was observed. Grade 3 or 4 pulmonary toxicity occurred in two patients (13%) after the administration of five and seven doses of CPT-11, respectively, and one of them subsequently died of progressive respiratory insufficiency.

Although there was no CR among the 15 assessable patients, a PR was obtained in seven patients (47%; 95% confidence limits for the overall response rate; 21%–72%). The median duration of response was 58 days (range; 28–156 days; Table 4). A PR was achieved in three of the five patients with limited disease and four of the ten patients with extensive disease. The median duration of survival for the 15 eligible patients was 187 days from the start of CPT-11 therapy.

CPT-11 combination chemotherapy

CPT-11 in combination with cisplatin for advanced NSCLC. In this study [20], remarkably little toxicity was observed in general at the first four dose levels during the first course of therapy. At 30 and 40 mg/m^2 of CPT-11, none of the patients exhibited grade 3 or worse leukopenia, but one patient exhibited grade 3 leukopenia at 50 mg/m^2. At 60 mg/m^2, grade 3 or 4 leukopenia occurred in three of ten patients. At 70 mg/m^2, the myelosuppression was more severe and dose-limiting, with two of six patients developing grade 3 leukopenia. The leukocyte nadir usually occurred around day 21, with recovery by day 29 being seen in most patients. Grade 3 or worse thrombocytopenia was observed on only 1 occasion in 72 courses and grade 3–4 anemia was observed in 17 courses.

Diarrhea did not become a significant problem until dose level 5 (70 mg/m^2). At dose levels 1–4 (30–60 mg/m^2), grade 3 or worse diarrhea was noted in only 2 of 58 courses, but 2 of 6 patients experienced grade 4 diarrhea during the first course at 70 mg/m^2. Maximal grade 4 diarrhea was observed on day 18 in these patients and was refractory to the usual antidiarrheal drugs and even to codeine phosphate. The grade 4 diarrhea coincided with grade 2 or 3 leukopenia, but recovery occurred by days 24–25 with extensive supportive care. Grade 3 nausea and vomiting was observed in 17 of 72 courses. However, none of the patients developed hepatic, renal, or pulmonary toxicity related to drug administration.

Although the intrapatient variability in toxicity was small, the interpatient variability was considerable. On the basis of the results obtained during the first course of treatment, we concluded that the maximum tolerated dose for this schedule was 70 mg/m^2 (Table 4). No further dose escalation was carried out during this trial.

Among the 26 evaluable patients, objective responses were observed in 14 (54%; 95% confidence limits for the overall response rate; 35%–73%; Table 4). All the responses were PRs and the duration ranged from 38 to 175 days (median, 82 days). In all, 11 patients showed no change, and 1 patient suffered disease progression.

Phase I and pharmacology study of CPT-11 in combination with cisplatin for advanced lung cancer. In this study [21], leukopenia was the most common hematologic side effect, but none of the patients exhibited grade 4 leukopenia. Grade 3 leukopenia occurred in five patients during six cycles, and it occurred in 33%, 15%, and none of the courses given at doses of 60, 80, and 90 mg/m^2, respectively. No grade 2 or worse thrombocytopenia was observed in any of the 33 courses, and grade 3 anemia was observed in only 2 of 33 courses (6%).

Gastrointestinal toxicity was the most prominent adverse effect and included nausea and vomiting, anorexia, and diarrhea. Diarrhea was the principal dose-limiting toxicity of this combination regimen. It was observed in the early and middle parts of the 28-day treatment cycle and generally ceased between days 15 and 35. No diarrhea of worse than grade 2 occurred at the 60-mg/m^2 dose level. At 80 mg/m^2, grade 3 diarrhea affected 2 of 8 patients during 3 of 20 cycles, but no grade 4 diarrhea was observed. Diar-

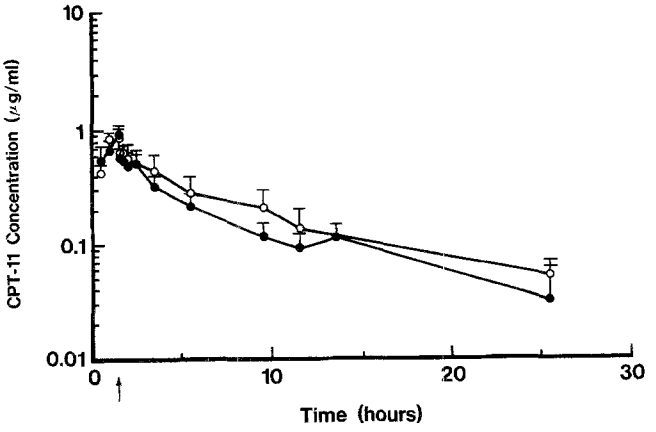

Fig. 1. Plasma disposition curves of CPT-11 in patients treated at 80 (●) and 90 mg/m² (○). Data points represent mean values ± SD for 7 (●) and 3 patients (○). *Arrows* indicate the completion of infusion. From Masuda et al. [21]

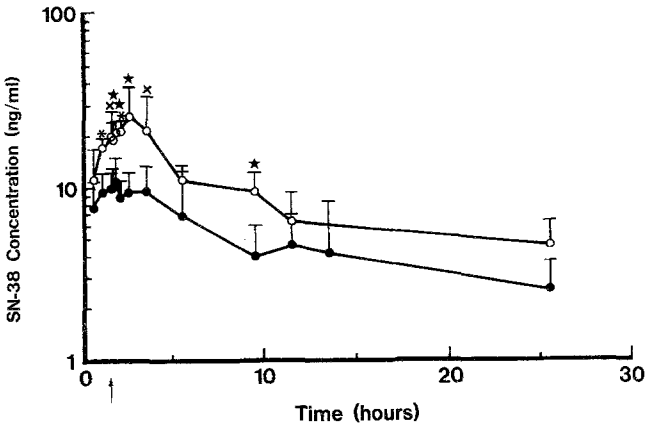

Fig. 2. Pharmacokinetic profile of SN-38 in the same patients shown in Fig. 1 who received CPT-11 at 80 (●) and 90 mg/m² (○). The difference between the two dose levels was statistically significant (*P <0.005; *P <0.01 and ×P <0.05). From Masuda et al. [21]

rhea became ubiquitous at the highest dose level of 90 mg/m², with all three patients suffering grade 3 diarrhea during all four treatment cycles. This diarrhea was refractory to the usual antidiarrheal agents and was also resistant to codeine phosphate. A somatostatin analog (sandostatin) was given to three of the five patients with grade 3 diarrhea, but subcutaneous administration of a dose of 50–100 μg three times daily for at least 2 days did not improve any of the patients. We concluded that the maximum tolerated dose for this schedule was 90 mg/m² of CPT-11 given on days 1, 8, and 15 plus 60 mg/m² of cisplatin given on day 1 (Table 4).

Grade 3 nausea and vomiting was observed in 10 of 33 courses. A grade 1 skin rash was observed in only one patient, and there was no evidence of hepatic, renal, or pulmonary toxicity.

All 14 patients were assessed for their response to treatment (Table 4). There were five PRs and one CR. In addition, eight patients showed no change, and none of them showed disease progression. The response rates for NSCLC and SCLC were 33% (4/12 patients) and 100% (2/2 patients), respectively.

Phase I study of CPT-11 and cisplatin with granulocyte colony-stimulating factor support for advanced NSCLC. In this study [22], leukopenia was the principal hematologic side effect. During the first cycle of chemotherapy, only 1 of the 14 patients treated at the first 2 dose levels (70 and 80 mg/m² of CPT-11) exhibited grade 4 toxicity. However, myelosuppression was more pronounced at the highest CPT-11 dose (90 mg/m²), and grade 3–4 leukopenia occurred in two of the six patients treated. During all cycles of chemotherapy, the leukocyte nadir usually occurred around day 15 (range, days 8–29), with recovery to ≥ 3,000/μl usually being noted by day 20. Grade 2 or 3 thrombocytopenia was observed on 2 occasions each in 52 courses, and no grade 4 thrombocytopenia was noted during this trial. Grade 3 anemia was observed on 5 occasions in the 52 courses.

Diarrhea was the most prominent nonhematologic adverse reaction. After administration of the first course of therapy, there was no severe diarrhea (greater than grade 2) at the 70-mg/m² dose level. Grade 3–4 diarrhea was observed in 1 of the 11 patients treated at 80 mg/m². However, at the 90-mg/m² dose level, two of the six patients treated developed grade 3–4 diarrhea (Table 4). Thus, 90 mg/m² was considered to be the maximum tolerated dose and no further escalation of the CPT-11 dose was carried out. Maximal grade 3–4 diarrhea occurred on a median of day 12 (range, days 1–15) in six (12%) cycles of treatment, and recovery was observed by day 24 (range, days 8–36).

Grade 3 nausea and vomiting was observed in 11 of 52 courses. Skin rash (grade 2) occurred in only one patient, and there was no evidence of hepatic, renal, or pulmonary toxicity. Few side effects attributable to rhG-CSF were detected in this trial.

All the patients were assessed for response (Table 4). There were ten PRs (50%), nine patients showed no change, and one patient suffered disease progression.

Clinical pharmacology

A pharmacokinetics study of CPT-11 and SN-38 was carried out in ten patients entered into the second trial of combination chemotherapy. Figure 1 shows the CPT-11 concentration-time profiles obtained after doses of 80 and 90 mg/m². A modest increase in the delivered dose from 80 to 90 mg/m² resulted in an extraordinary increase in the mean peak plasma concentration of SN-38 from 13.23 ± 4.18 (SD) to 29.03 ± 10.88 (SD) ng/ml (Fig. 2). In the last trial, another pharmacokinetics study was carried out in 13 patients. A modest increase in the CPT-11 dose also resulted in a marked increase in the mean (±SD) peak plasma concentration of SN-38 from 18.17 ± 7.10 to 27.17 ± 13.27 ng/ml. In addition, the correlation between dose-limiting toxicity and pharmacokinetics was much better for SN-38 than for CPT-11. Diarrhea was clearly influenced by the maximal concentration (Cmax) of SN-38, since three of five patients with SN-38 levels of > 24.0 ng/ml developed grade 3 or worse diarrhea, whereas none of

the patients with an SN-38 level of ≤ 24.0 ng/ml developed severe diarrhea ($P = 0.035$).

Discussion

The phase I study of CPT-11 monotherapy showed that severe toxicity occurred only at doses of ≥125 mg/m². The dose-limiting toxicities of CPT-11 given as a short-term weekly intravenous infusion included myelosuppression and diarrhea (Table 4). Although it was infrequent and sporadic, pulmonary toxicity may also be dose-limiting. We observed two (18%) PRs in previously untreated patients given weekly doses of ≥100 mg/m². On the basis of these results, we recommend that phase II studies use a weekly CPT-11 dose of 100 mg/m² given intravenously with very careful monitoring of the hematologic and gastrointestinal toxicities. Since lethal toxicity occurred very precipitously and was unpredictable, CPT-11 should be ceased if leukopenia more severe than grade 1 (leukocyte count, <3,000/μl) is noted on the day when the dose is due.

It has become evident from the results of three phase II trials of CPT-11 monotherapy that a dose of 100 mg/m² given according to this schedule achieves a response rate of 32% in patients with previously untreated NSCLC (Table 4). Additionally, in a multicenter phase II trial [29], CRs and PRs were observed in 6% and 31%, respectively, of 35 patients with SCLC, 8 of whom had received no prior therapy. Furthermore, in a single-institution study performed at the Osaka Prefectural Habikino Hospital, a very high response rate of 47% was obtained in patients with refractory or recurrent SCLC. Therefore, CPT-11 deserves to be studied more closely in combination with other drugs for the treatment of lung cancer.

In an attempt to establish a combination regimen with a synergistic cytotoxic effect, CPT-11 was combined with cisplatin. In three phase I trials of the combination, the major dose-limiting toxicities were leukopenia and diarrhea. Marked interpatient variability in these toxicities, which is a well-known feature of CPT-11, was also observed during these trials. The toxicity of the combination chemotherapy was more pronounced than that of CPT-11 alone, suggesting that a pharmacodynamic interaction exists between CPT-11 and cisplatin.

It is noteworthy that the severity of diarrhea was related to the peak plasma concentrations of SN-38 measured on day 8, and levels above 24.0 ng/ml resulted in severe clinical toxicity in three of five patients. Therefore, monitoring of the SN-38 level may enable the prediction of severe diarrhea. However, further pharmacology studies of this regimen are needed to improve the therapeutic index of treatment.

We are now planning to carry out a randomized trial to evaluate the effect of CPT-11 given in this combination regimen. This new study will determine whether an improved outcome can be obtained with combination therapy. In addition, studies of CPT-11 given in combination with 5-fluorouracil and topoisomerase II inhibitors are needed to achieve significant advances in the treatment of lung cancer.

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