Cisplatin in Combination with Irinotecan in the Treatment of Patients with Malignant Pleural Mesothelioma

A Pilot Phase II Clinical Trial and Pharmacokinetic Profile

Takashi Nakano, M.D.[1]
A. Philippe Chahinian, M.D.[2]
Miho Shinjo, M.D.[1]
Naoki Togawa, M.D.[1]
Atsushi Tonomura, M.D.[1]
Mitsutomi Miyake, M.D.[1]
Koji Ninomiya, M.D.[1]
Tetsuya Yamamoto, M.D.[1]
Kazuya Higashino, M.D.[1]

[1] Third Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan.

[2] Department of Neoplastic Diseases, Mount Sinai Medical Center, New York, New York.

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Address for reprints: Takashi Nakano, M.D., Third Department of Internal Medicine, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan.

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BACKGROUND. The purpose of this study was to assess the efficacy and toxicity of a combination of cisplatin and irinotecan (CPT-11) in the treatment of patients with malignant pleural mesothelioma and to characterize the pharmacokinetic profiles of CPT-11 and its active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38).

METHODS. Fifteen previously untreated patients with malignant pleural mesothelioma were treated with cisplatin (60 mg/m^2 on Day 1) and CPT-11 (60 mg/m^2 on Days 1, 8, and 15) administered intravenously and followed by a 1-week rest period. The course of treatment was repeated every 28 days. After intravenous administration, the levels of CPT-11 and SN-38 in the plasma and pleural fluid were determined for each histologic subtype of mesothelioma.

RESULTS. All patients were evaluable for response and toxicity. Four partial responses (response rate of 26.7%) with a median response duration of 25.9 weeks and 2 regressions of evaluable disease (overall response rate of 40%) were observed. The median survival time after chemotherapy was 28.3 weeks, and the median time to treatment failure was 22.1 weeks. The 1-year survival rate for all patients was 38.5%. Toxicity was well tolerated, and there were no treatment-related deaths. World Health Organization Grade 3 leukopenia occurred in 3 patients (20%), and Grade 1 or 2 diarrhea occurred in 3 patients (20%). There was no excess toxicity in patients with large pleural effusions compared with those with no pleural effusions. CPT-11 and SN-38 were detected in the pleural fluid 1 hour after intravenous administration. The maximum concentrations of CPT-11 and SN-38 in the pleural fluid were 36.5% and 75.8%, respectively, of the corresponding plasma values.

CONCLUSIONS. The combination of cisplatin and CPT-11 had definite activity against malignant pleural mesothelioma and was well tolerated. The intravenous administration of CPT-11 produced adequate distribution of CPT-11 and its active metabolite SN-38 into the pleural fluid and allowed a higher concentration of the more active SN-38 to make contact with mesothelioma cells in the thoracic cavity. These results warrant further clinical evaluation of this combination chemotherapy for the treatment of malignant pleural mesothelioma in a confirmatory Phase II trial. ***Cancer* 1999;85:2375–84.** © *1999 American Cancer Society.*

KEYWORDS: irinotecan, cisplatin, phamacokinetics, mesothelioma, chemotherapy, SN-38.

The incidence of malignant mesothelioma is rising and is expected to continue to increase into the next decade.[1,2] Malignant mesothelioma is a highly lethal and particularly refractory tumor for

which chemotherapeutic regimens have been far from satisfactory in achieving clinical responses. At diagnosis, the majority of patients have clinical Stage Ib or more locally advanced disease,[3] as defined by the International Mesothelioma Interest Group (IMIG).[4]. These patients do not benefit from surgery and rapidly succumb to their disease.[5]

Antineoplastic drugs, including doxorubicin (ADR), detorubicin, epirubicin, cyclophosphamide, ifosfamide, mitomycin (MMC), methotrexate, edatrexate, carboplatin, and cisplatin, have demonstrated some activity against malignant mesothelioma,[6,7], although their single-agent response rates are disappointingly low. Several combinations of these agents have been tested in many Phase II studies, but the role of drug combinations in the treatment of malignant mesothelioma remains unclear. A response rate of 13–14% can be achieved by using cisplatin as a single agent against malignant mesothelioma.[8,9] Treatment regimens in which one further active agent has been added to cisplatin have been used in attempts to enhance antimesothelioma activity. The most widely tested combination had been cisplatin and ADR, first tested by Zidar et al.[10], with which response rates of 15–25% have been achieved.[6,7,11] The Cancer and Leukemia Group B (CALGB) tested the combinations of cisplatin plus ADR and cisplatin plus MMC in a randomized clinical trial.[12] The results were not encouraging: A 14% response rate was achieved using cisplatin plus ADR, and a 26% response rate was achieved using cisplatin plus MMC. Therefore, there is a critical need for newer and more effective chemotherapy regimens as the incidence of malignant mesothelioma continues to increase internationally.[13,14]

Irinotecan (CPT-11) is a semisynthetic derivative of camptothecin and a promising new agent. It is a potent inhibitor of topoisomerase I activity and has demonstrated pronounced activity against various experimental tumors,[15,16] including those that show pleiotrophic drug resistance.[17] In Phase II trials evaluating single-agent CPT-11 therapy, significant activity has been shown against nonsmall cell lung cancer (NSCLC), achieving response rates of 31.9–34.3%;[18,19] against small cell lung cancer, achieving a response rate of 47%;[20] and against colorectal cancer, achieving response rates of 20.5–32%.[21] Recently, CPT-11 has been combined with other cytotoxic agents in an attempt to identify a potentially additive or synergistic combination chemotherapy regimen. In experimental models, CPT-11 reacted synergistically[22,23] and additively with cisplatin.[24] In a preclinical study, CPT-11 also demonstrated cytotoxic activity against mesothelioma using a colony-forming assay.[25] These reports encouraged us to perform a pilot Phase II study of cisplatin in combination with CPT-11 against malignant pleural mesothelioma. The immediate objectives were 1) to determine the objective response rate to this combination, 2) to define the toxicities involved, and 3) to evaluate the distribution of CPT-11 and its more active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), in pleural fluid after intravenous administration. The activity of cisplatin and CPT-11 against mesothelioma has not been studied previously.

PATIENTS AND METHODS

Patient Eligibility

Our criteria for eligibility were histologically confirmed malignant mesothelioma; measurable or assessable disease; no prior chemotherapy; a predicted life expectancy of at least 12 weeks; age younger than 75 years; performance status (PS) score of 2 or less; no evidence of central nervous system metastases; adequate bone marrow function (white blood cells $> 4 \times 10^9$/L, platelets $> 100 \times 10^9$/L), hepatic function (serum bilirubin <1.5 mg/dL, serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase values less than twice the norm for the institution), and renal function (serum creatinine <1.5 mg/dL, blood urea nitrogen <25 mg/dL); absence of other concurrent, active malignancies; and written informed consent to participate in this study.

Pathology

Pathologic diagnosis was performed by two independent pathologists (Dr. Takashi Nishigami and Dr. Kunio Uematsu) using the published criteria of the CALGB.[26]

Pretreatment and Follow-Up Studies

Pretreatment evaluation involved taking the patient's medical history, with emphasis on asbestos exposure, a physical examination, complete blood cell counts, a blood chemistry profile, an electrocardiogram, complete urinalysis, a bone marrow examination, bone scintigraphy, a chest X-ray and computed tomography (CT) scan of the chest and brain, magnetic resonance imaging of the chest, and an ultrasonic study of the abdomen. A clinical assessment was performed each week. CT of the chest was performed on completion of each cycle of chemotherapy. Patients were staged according to the TNM classification system proposed by the IMIG.[4]

Drug Administration

CPT-11 (Irinotecan), 60 mg/m^2 in 500 mL of normal saline, was administered intravenously on 3 consecutive weeks: as a 90-minute infusion on Days 1, 8, and 15 followed by a 1-week rest. Cisplatin 60 mg/m^2 was

administered intravenously in 500 mL of normal saline over 1 hour, two hours after the end of the CPT-11 infusion on Day 1 of each course of treatment. When the cisplatin infusion had been completed, adequate intravenous hydration was given. Prior to administering the chemotherapy, patients with a large pleural effusion were required to have the pleural fluid drained. This treatment was repeated every 4 weeks for at least two cycles. A 25% reduction in drug dosage was required in subsequent cycles for those patients who experienced World Health Organization (WHO) Grade 4 myelotoxicity, Grade 2 diarrhea, Grade 2 nephrotoxicity, and/or another severe treatment-related toxicity. Once the dose was reduced, the patient received that reduced dose for the remaining weeks of that treatment course. For patients who achieved a response, the treatment was continued for an additional two cycles or until disease progression or intolerable toxicity was observed.

As concurrent therapy, patients were instructed to begin treatment with 1 mg of intravenous atropine for diarrhea during or within 24 hours of the CPT-11 infusion and to take loperamide 2 mg and Kampo (Chinese herb medicine in granule form) at the earliest signs of diarrhea occurring more than 24 hours after receiving CPT-11. Antiemetics (ondansetron or granisetron) were used routinely. The severity of drug toxicity was graded according to the WHO toxicity scales.

Response Criteria

Response was assessed according to the standard criteria for tumor shrinkage by repeating the thoracic CT scan after two treatment cycles. In addition to the standard criteria, the category of "regression" of evaluable disease, which CALGB used in their malignant mesothelioma study,[12] also was included in the response criteria for our study. A complete response (CR) was defined as the complete disappearance of all measurable or assessable disease for more than 4 weeks without appearance of any new lesions. A partial response (PR; for measurable disease only) was defined as a 50% or greater reduction in the sum of the products of two longest perpendicular dimensions of measurable lesions for more than 4 weeks. Regression of evaluable disease was defined as a definite decrease in tumor size agreed on by two independent investigators without the appearance of any new lesion for more than 8 weeks. Stable disease (SD) for measurable disease was defined as a reduction of less than 50% to an increase of less than 25% without the appearance of any new lesions. For evaluable disease, SD was defined as the absence of a clear-cut change in tumor size or any new lesions for more than 8 weeks. Progressive disease (PD) was defined as an increase of more than 25% in the size of any measurable lesion, or as a definite increase in tumor size for assessable disease, or as the appearance of new lesions. Durations of response and survival were estimated from the start of chemotherapy.

Pharmacokinetics

Pharmacokinetic studies on CPT-11 and its metabolite SN-38 were performed on plasma and pleural fluid samples from three patients, each with a different histologic subtype of malignant mesothelioma (epithelial, biphasic, or fibrosarcomatous), to evaluate the distribution of the agents in the pleural fluid after intravenous administration. Prior to the intravenous administration of CPT-11, a thoracic catheter was inserted and any effusion drained. Blood and pleural fluid samples were collected before the initiation of the 90-minute intravenous infusion of CPT-11 on the Day 1 of the first course of the treatment, every hour thereafter for 12 hours, and also after 24 hours and 48 hours. The samples were immediately placed on ice, centrifuged, and stored at −60°C until assay. Concentrations of CPT-11 and SN-38 were quantitated by using high-performance liquid chromatography.[27] The area under the concentration versus time curve (AUC) was calculated according to the limited-sampling models of a 90-minute intravenous infusion of CPT-11 proposed by Sasaki et al.[28]

Statistical Analysis

Survival was calculated from the start of treatment to death by using the Kaplan–Meier method. The exact confidence intervals for the response rates were calculated according to the formula proposed by Ghosh.[29]

RESULTS

Patient Characteristics

The characteristics of the 15 patients entered into this study between January, 1995 and January, 1998 are summarized in Table 1. All patients were evaluable for response and toxicity and gave written informed consent to participate in this study after being informed of the investigational nature of this study. Ten patients had epithelial subtype, four had biphasic subtype, and one had fibrosarcomatous subtype. Prior asbestos exposure was documented in 4 of 15 patients. One patient had Stage II disease (T2N1M0), seven had Stage III disease, and seven had Stage IV disease. None had had a prior surgical excision. Eight patients had a significant pleural effusion on admission. The median PS score was 1, and the median number of treatment courses administered was 2.6 (range, 2–4 courses).

TABLE 1
Patient Characteristics

Characteristic	No. of patients
Patients	
Entered/evaluable	15 of 15
Male/Female	3 of 12
Median age in yrs (range)	61 (31–74)
Histologic subtype	
Epithelial	10
Biphasic	4
Fibrosarcomatous	1
Performance status	
0–1	8
2	7
IMIG clinical stage	
II and III	8
IV	7

IMIG: International Mesothelioma Interest Group.

TABLE 2
Response to Treatment

Characteristic	No. of patients	Response			Response rate (overall RR%)
		CR	PR	Regression	
IMIG clinical stage					
II and III	8	—	3	—	37.5
IV	7	—	1	2	14.3 (42.9)
Total	15	—	4	2	26.7 (40.0)
Histologic subtype					
Epithelial	10	—	3	2	30 (50)
Biphasic	4	—	1	—	25
Fibrosarcomatous	1	—	—	—	0
PS score					
0–1	8		3	2	37.5 (62.5)
2	7		1	—	14.3

CR: complete response; PR: partial response; RR: response rate; IMIG: International Mesothelioma Interest Group; PS: performance status.

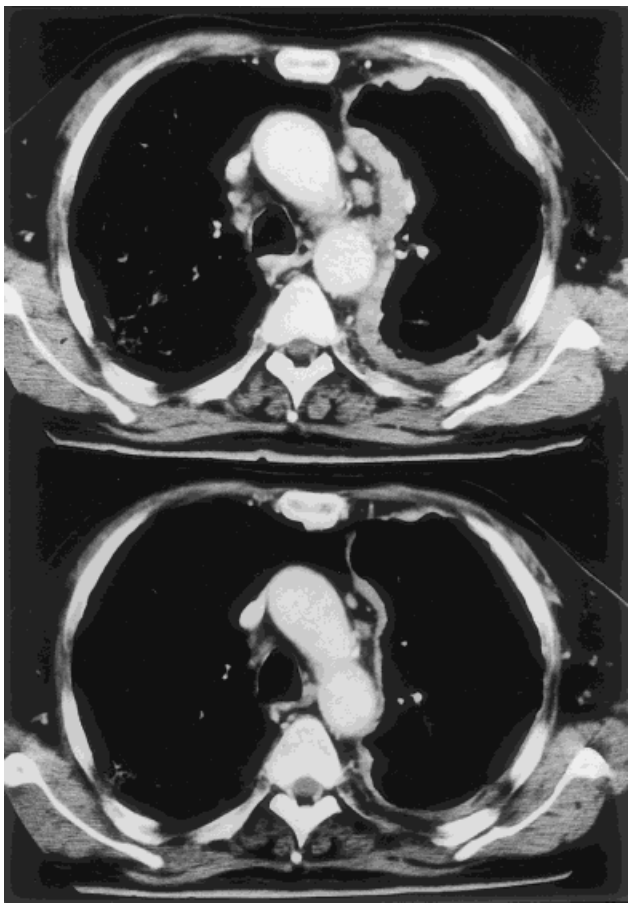

FIGURE 1. Thoracic computed tomography (CT) scans of the patient with epithelial malignant mesothelioma who responded to combination chemotherapy using cisplatin 60 mg/m^2 and irinotecan (CPT-11) 60 mg/m^2. (Top) Contrast-enhanced CT scan taken before chemotherapy shows the typical appearance of a circumferential rind of thickened pleura and metastases in the para-aortic and right lower paratracheal lymph nodes. (Bottom) After two cycles of the treatment, a marked reduction in tumor volume and in lymph node metastases of >50% are noted, which lasted more than 4 weeks.

After completing the chemotherapy, two responding patients with Stage III disease underwent thoracic irradiation (50 grays [Gy]) and extrapleural pneumonectomy. Dose reduction was required for 5% of the courses because of diarrhea and hematotoxicity.

Response

The objective responses to treatment are shown in Table 2. Of the 15 evaluable patients, 4 patients achieved PR, with a major response rate of 26.7% (95% confidence interval, 7.8–55.1%) and a median response duration of 25.9 weeks. In addition, two evaluable patients achieved a regression, bringing the overall response rate to 40.0% (95% confidence interval, 16.3–67.7%). SD was observed in eight patients (53.3%), whereas one patient suffered from PD (6.7%). Median time to treatment failure was 22.1 weeks. Of the four responding patients, three had tumors with epithelial histology, and one had a tumor with biphasic histology. Their PS scores were 1. The CT scans of one of the patients who achieved a PR are shown in Figure 1. The rate of pleural fluid accumulation was clearly diminished in all patients with effusion after the chemotherapy, so that palliative thoracentesis could be discontinued.

Ten of the 15 patients had died by the time of analysis. The overall median survival after chemotherapy was 28.3 weeks (range, 18.9–94 weeks). The median survival for patients with IMIG Stage II and III disease was 28.3 weeks compared with 27.3 weeks for

TABLE 3
Toxicity (n = 15)

Toxicity/presence of pleural fluid	WHO grade 1	2	3	4
Leukopenia				
Fluid (+)	1	3	2	—
Fluid (−)	1	4	1	—
Total (%)	2 (13.3)	7 (46.7)	3 (20)	—
Thrombocytopenia				
Fluid (+)	1	—	—	—
Fluid (−)	1	—	—	—
Total (%)	2 (13.3)	—	—	—
Anemia				
Fluid (+)	2	4	1	—
Fluid (−)	2	3	1	—
Total (%)	4 (26.7)	7 (46.7)	2 (13.3)	—
Nephrotoxicity				
Fluid (+)	2	—	—	—
Fluid (−)	1	—	—	—
Total (%)	3 (20)	—	—	—
Hepatotoxicity				
Fluid (+)	—	1	—	—
Fluid (−)	1	—	—	—
Total (%)	1 (6.7)	1 (6.7)	—	—
Vomiting/nausea				
Fluid (+)	3	3	—	—
Fluid (−)	2	3	—	—
Total (%)	5 (33.3)	6 (40)	—	—
Diarrhea				
Fluid (+)	—	1	—	—
Fluid (−)	2	—	—	—
Total (%)	2 (13.3)	1 (13.3)	—	—

WHO: World Health Organization.

those with Stage IV disease. The 1-year survival rate for all patients was 38.5%. There were too few patients to determine any difference in survival according to tumor histology.

Toxicity

The toxicities encountered are summarized in Table 3. The chemotherapy regimen generally was well tolerated, and there were no treatment-related deaths. Hematotoxicity was mild. Grade 3 leukopenia and anemia were observed in three patients (20%) and two patients (13.3%), respectively. Nonhematologic toxicity also was generally mild. Eleven patients suffered nausea or vomiting, but this never exceeded Grade 2. Grade 1 or 2 diarrhea was observed in three patients (20%), who responded well to loperamide and Kampo. There was no excess toxicity in patients with pleural effusion compared to those with no pleural effusion. No patients developed clinical signs or symptoms of pulmonary toxicity. We observed no incidents of nephrotoxicity greater than Grade 1.

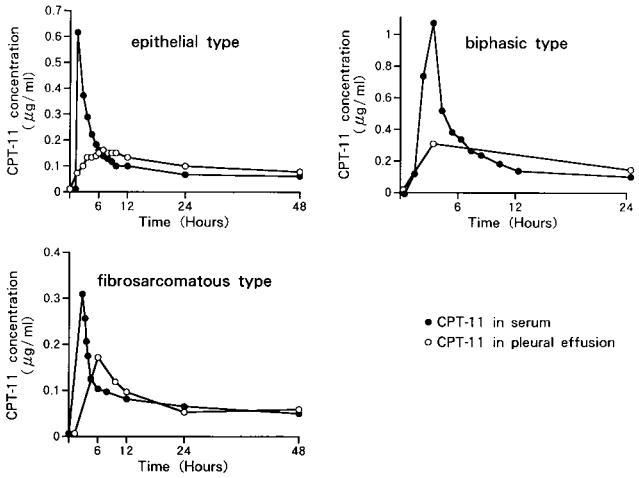

FIGURE 2. The simultaneous changes in plasma and pleural fluid concentrations of cisplatin and irinotecan (CPT-11) after a 90-minute intravenous infusion at a dose of 60 mg/m^2 in patients with epithelial, biphasic, and fibrosarcomatous malignant pleural mesothelioma. Open circles show the levels in plasma, and solid circles show those in pleural fluid.

Pharmacokinetics

Figure 2 shows the pharmacokinetic profiles of CPT-11 after a 90-minute intravenous infusion at a dose of 60 mg/m^2 in three patients, each with a different histologic subtype of malignant pleural mesothelioma. The maximum concentration (Cmax) of CPT-11 in plasma was reached between 1 hour and 3 hours from the onset of infusion (0.31–1.07 μg/mL). After the intravenous infusion, the CPT-11 concentration in the pleural fluid was measured serially, although fluid samples could not always be obtained because of the small amount of fluid flowing from the chest drainage tube. CPT-11 was seen in the pleural fluid 1 hour after the infusion. The level then increased, to peak between 3 hours and 6 hours from the onset of infusion. Thereafter, the level of CPT-11 in the pleural fluid was equivalent to that in the plasma and declined in parallel with the plasma level.

Figure 3 shows the pharmacokinetic profiles of the active metabolite SN-38 according to histologic subtype. Rapid increases in the plasma levels of SN-38 were observed, and the Cmax of SN-38 was reached within 3 hours of the infusion and then decreased. SN-38 was seen in the pleural fluid 1 hour after the intravenous infusion and achieved levels equivalent to those in plasma after 4 hours. Cmax was reached 6 hours after the infusion. Thereafter, the SN-38 level in the pleural fluid of the patient with epithelial mesothelioma remained higher than that in the plasma, but the SN-38 level in the pleural fluid of the patient with fibrosarcomatous mesothelioma decreased in parallel with the plasma level. The Cmax of CPT-11

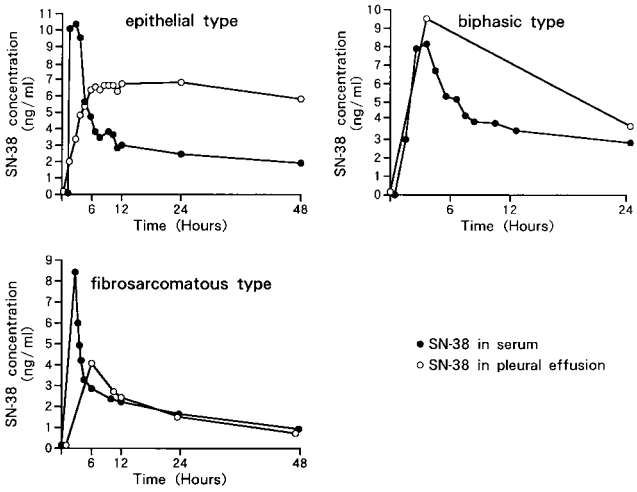

FIGURE 3. The changes in the level of SN-38 in three patients with different histologic subtypes of malignant pleural mesothelioma after a 90-minute intravenous infusion of cisplatin and irinotecan (CPT-11) at a dose of 60 mg/m^2. Open circles show the levels in serum, and solid circles show those in pleural fluid.

and that of SN-38 in pleural fluid were 36.5% (range, 25.8–54.8%) and 75.8% (range, 46.5–117.3%), respectively, of the corresponding plasma values.

The AUCs of CPT-11 in plasma were 4.20 μg H/mL, 6.92 μg H/mL, and 3.58 μg H/mL in the patients with epithelial, biphasic, and fibrosarcomatous mesothelioma, respectively. The AUCs of SN-38 in plasma were 135.5 ng H/mL, 144.0 ng H/mL, and 120.2 ng H/mL, respectively. The AUC of SN-38 in the pleural fluid of the patient with epithelial mesothelioma (203.2 ng H/mL) was higher than the corresponding AUC in plasma (135.5 ng H/mL), which was in turn higher than that in the pleural fluid of the patient with fibrosarcomatous mesothelioma. The AUC of SN-38 in the patient with biphasic mesothelioma could not be calculated because of the limited number of fluid samples available; however, the AUCs of SN-38 were higher in the pleural fluid than in the plasma in the available samples (taken 3 hours and 24 hours after the infusion).

DISCUSSION

Most patients with earlier stage malignant mesothelioma present with a pleural effusion, which allows chemotherapeutic agents to be administered intrapleurally. This therapeutic approach has the pharmacologic advantage of exposing pleural tumors to higher concentrations of the agents than the intravenous route. However, with advancing clinical stage, the parietal and visceral pleural surfaces begin to fuse, and then the pleural space is obliterated by bulky confluent tumor and eventually disappears.[4] This lack of free pleural space prevents the intrapleural administration of drugs. Mesothelioma can also metastasize widely despite its pronounced tendency to remain localized in the pleural cavity. Intrapleural therapy should be limited to patients with earlier stage disease and to those patients with small volume disease for whom adequate diffusion into the tumor is possible. In addition, the topoisomerase I inhibitor CPT-11 used in our regimen first must be converted into its considerably more active metabolite, SN-38.[27,30] CPT-11 is converted by the enzyme endogeneous carboxylesterase, which is found in the plasma, the intestinal mucosa, and the liver.[27,30,31] This was one reason for administering the chemotherapy intravenously rather than intrapleurally in this trial.

Clinical studies of CPT-11 have been conducted in the United States, Japan, and France for most types of solid tumors. The antineoplastic effect of CPT-11 was shown to be schedule dependent. Three different administration schedules have been evaluated: once every 3 weeks; daily for 3 (or 5) consecutive days every 3 weeks; and once weekly for 3 (or 4) consecutive weeks followed by a 1-week (or 2-week) rest period. The best results in NSCLC were obtained by using a weekly schedule and a dose of 100 mg/m^2.[19] We chose the weekly schedule, whereby CPT-11 60 mg/m^2 was given intravenously for 3 consecutive weeks (on Days 1, 8, and 15), followed by a 1-week rest, in combination with cisplatin at a dose of 60 mg/m^2 on Day 1 of each course of the treatment. The doses used in this study were based on those used by Fukuoka and Masuda[32] in Phase I/II studies in lung cancer. In Phase I studies of weekly schedules of CPT-11 plus cisplatin and CPT-11 plus etoposide against NSCLC, the response rates were 54%[33] and 22%,[34] respectively.

Much of the chemotherapeutic data for mesothelioma involves cisplatin alone and in combinations. ADR in combination with cisplatin yields response rates of 15–20%.[6,7,11] In the past few years, new antitumor agents with novel mechanisms of action have also been tested against mesothelioma. Paclitaxel achieves a single-agent response rate of 0–13%,[35,36] and its use in combination with cisplatin has modest activity (6%).[37] A new antifolate trimetrexate has a single-agent response rate of 12%.[38] Topotecan, a semisynthetic analogue of camptothecin, achieved no objective responses against mesothelioma when used as a single agent in a North Central Cancer Treatment Group trial.[39] In our trial, we employed another semisynthetic camptothecin derivative, CPT-11, in combination with cisplatin. Unlike topotecan, CPT-11 is converted to its more active metabolite, SN-38, which has 1000 times the potency of the parent com-

pound.[31,40] We expected a combination regimen of CPT-11 and cisplatin to have an activity superior to the individual agents alone against mesothelioma. We achieved a major objective response rate of 26.7% and an overall response rate of 40% when two regressions in evaluable disease were also included. Recently, Herndon reported that the median survival for the ten treatment regimens evaluated by CALGB ranged from 3.9 to 9.8 months (overall survival, 7.8 months), and the 1-year survival ranged between 14% and 50% (overall, 27%).[41] In our trial, the overall median survival was 28.3 weeks (6.6 months), and the 1-year survival rate was 38.5%.

Many Phase I and II trials have efficiently explored the pharmacokinetics of CPT-11 and SN-38 in the patients receiving CPT-11 therapy.[42–49] However, no information is available on the pharmacokinetics of CPT-11 in pleural fluid after intravenous administration. In this trial, we evaluated the distribution of CPT-11 and its active metabolite SN-38 in the pleural fluid after intravenous administration in patients with different histologic subtypes of malignant mesothelioma. CPT-11 has been detected previously in pleural fluid, bile, sweat, and saliva after intravenous infusion.[42] We found CPT-11 in the pleural fluid 1 hour after intravenous infusion, and the level peaked after 6 hours. The metabolite SN-38 was also seen in the pleural fluid 1 hour after infusion, and a concentration equivalent to that in plasma was achieved after 4 hours. The mean AUCs of CPT-11 and SN-38 in plasma at a dose of 60 mg/m^2 were 4.9 μg H/mL and 133 ng H/mL, respectively, which are approximately equivalent to the defined therapeutic AUCs for advanced lung cancer achieved by using a dose of 70 mg/m^2 on a weekly schedule.[34] In vitro models have demonstrated that a 1-hour exposure to CPT-11 at a concentration of $>$1.5 μg/mL is active against mesothelioma cells.[25] In this study, the Cmax values of CPT-11 in plasma were 0.31–1.07 μg/mL. The Cmax values of CPT-11 and SN-38 in pleural fluid were 36.5% and 75.8%, respectively, of the corresponding plasma values. It has been demonstrated that SN-38 plays a major role in the antitumor activity of CPT-11 and that its inhibitory effect is time dependent.[30] Topoisomerase I inhibitors are highly S-phase specific, and cytotoxicity in vitro is a function of exposure time to the drug above a certain critical concentration.[50,51] Although we have only limited data on the pharmacokinetic of CPT-11 in patients with malignant mesothelioma and an accumulation of pleural fluid, our results suggest that intravenous administration of CPT-11 at a dose of 60 mg/m^2 can produce adequate distribution of CPT-11 and SN-38 into the pleural fluid and allows the more active SN-38 to come into contact with mesothelioma cells in the thoracic cavity for a longer time and at a higher concentration than CPT-11.

The effect of the coadministration of cisplatin and CPT-11 on the pharmacokinetic properties of CPT-11 is unclear. One study has been demonstrated a 28% reduction in the AUC of SN-38 when CPT-11 was administered in combination with infusional 5-fluorouacil (5-FU) compared with the data obtained from a single-agent trial of CPT-11.[52] On the contrary, other investigators have demonstrated that coadministration of 5-FU and CPT-11 had no substantial effect on the pharmacokinetic properties of CPT-11 and SN-38.[43]

The major dose-limiting toxicities of CPT-11 in previous Phase I/II studies that explored different schedules were diarrhea and myelosuppression. Two different types of diarrhea have been reported: acute and delayed onset diarrhea.[53] Acute diarrhea is a acute cholinergic-like syndrome and begins during or immediately after the infusion of CPT-11. Delayed onset diarrhea occurs between the Day 2 and Day 14 after the infusion. We recommended that atropine, loperamide, and the Chinese herb medicine Kampo be used to treat diarrhea from the onset of the earliest symptoms. Three patients (20%) suffered Grade 1 or 2 delayed onset diarrhea and were treated with loperamide and Kampo, to which they responded well. No patient suffered from acute diarrhea. We found that diarrhea was quite manageable if loperamide and Kampo were initiated at the first loose stool. Hematotoxicity was relatively mild. Other common but nondose limiting toxicities were nausea and vomiting, which never exceeded Grade 2.

There is some cautionary information that patients with large pleural effusions or ascites are at an increased risk of severe diarrhea or neutropenia when treated with CPT-11.[54] Several patients reported to have suffered life-threatening toxic effects from anticancer agents had clinically detectable pleural effusions.[55] Therefore, previous clinical studies using CPT-11 to treat lung cancer have not enrolled patients with large pleural effusions. From the chemotherapeutic aspect, the accumulation of pleural fluid often seen in malignant pleural mesothelioma may provide a site for the accumulation of CPT-11 and its more active metabolite SN-38 after intravenous administration. This might offer a chemotherapeutic advantage by exposing tumor cells in the thoracic cavity to higher concentrations of the agents for a prolonged period. A disadvantage could be that the slow release of the agents back into the systemic circulation might increase toxicity in these patients. We found, however, that there was no excess toxicity in patients with pleu-

ral effusions compared with those who had no pleural effusions.

The patients in most of the earlier Phase I and II clinical trials of CPT-11 for advanced lung cancer were required by protocol to be younger than 75 years.[18,19,33,34] We were not able to obtain any information about predictors of severe life-threatening toxicities using CPT-11-based chemotherapy before the initiation of this study. Although there was no evidence that the incidence and severity of toxicity in older patients were different from those in younger patients, we included "age less than 75 years" into eligibility criteria in our study in according with the previous clinical trials using CPT-11.

The relationship between prior occupational or environmental exposure to asbestos and the later development of malignant mesothelioma has been documented extensively and is accepted as one of cause and effect.[2] A history of asbestos exposure often is used as a guide to the diagnosis of this neoplasm. In our study, only 4 of 15 patients had documented asbestos exposure. It is important, and sometimes difficult, to distinguish epithelial mesothelioma from pseudomesotheliomatous adenocarcinoma. In this study, two independent pathologists had made the histological diagnoses (Dr. Takashi Nishigami and Dr. Kunio Uematsu of Hyogo College of Medicine). In about half of the patients, the diagnosis was reconfirmed by autopsy. Epithelial histology and a good PS score have been associated with a favorable prognosis for treated or untreated mesothelioma patients.[3,13,41,56–59] In our results, three out of four responding patients had tumors with epithelial histology and good PS scores (PS = 1).

In conclusion, CPT-11 in combination with cisplatin has definite activity against malignant pleural mesothelioma and is well tolerated. These results warrant further clinical evaluation of this combination for malignant pleural mesothelioma in a confirmatory Phase II trial.

REFERENCES

1. Peto J, Hodgson JT, Matthews FE, Jones JR. Continuing increase in mesothelioma mortality in Britain. *Lancet* 1995; 345:535–9.
2. de Klerk NH, Armstrong BK. The epidemiology of asbestos and mesothelioma. Henderson DW, Shelkin KB, Langlois SLP, Whitaker D, editors. Malignant mesothelioma. New York: Hemisphere, Inc., 1992:223–43.
3. Boutin C, Rey F, Gouvernet J, Viallat JR, Astoul P, Ledoray V. Thoracoscopy in pleural malignant mesothelioma: a prospective study of 188 consecutive patients. Part 2: prognosis and staging. *Cancer* 1993;72:394–404.
4. International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. *Chest* 1995;108:1122–8.
5. Rush VW, Piantadosi S, Holmes EC. The role of extrapleural pneumonectomy in malignant pleural mesothelioma. *J Thorac Cardiovasc Surg* 1991;102:1–9.
6. Aisner J. Current approach to malignant mesothelioma of the pleura. *Chest* 1995;107:332S–44S.
7. Ong ST, Vogelzang NJ. Chemotherapy in malignant pleural mesothelioma: a review. *J Clin Oncol* 1996;14:1007–17.
8. Mintzer DM, Kelsen D, Frimmer D, Heelan R, Gralla R. Phase II trial of high dose cisplatin in patients with malignant mesothelioma. *Cancer Treat Rep* 1985;69: 711–2.
9. Zidar BL, Green S, Pierce HI, Roach RW, Balcerzak SP, Militello L. A phase II evaluation of cisplatin in unresectable diffuse malignant mesothelioma: a Southwest Oncology Group study. *Invest New Drugs* 1988;6:223–6.
10. Zidar BL, Pugh RP, Schiffer LM, Raju RN, Vaidya KA, Bloom RL, et al. Treatment of six of mesothelioma with doxorubicin and cisplatin. *Cancer* 1983;52:1788–91.
11. Ardizzoni A, Rosso R, Salvati F, Fusco V, Cinquegrana A, De Palma M, et al. Activity of doxorubicin and cisplatin combination chemotherapy in patients with diffuse malignant mesothelioma. *Cancer* 1991;67:2984–7.
12. Chahinian AP, Antman K, Goutsou M, Corson JM, Suzuki Y, Modeas C, et al. Randomized phase II trial of cisplatin with mitomycin or doxorubicin for malignant mesothelioma by the Cancer and Leukemia Group B. *J Clin Oncol* 1993;11: 1559–65.
13. Kraruf-Hansen A. Phase II trials of malignant mesothelioma: a commentary and update. *Lung Cancer* 1994;11: 305–8.
14. Vogelzang NJ. Malignant mesothelioma: diagnosis and management strategies for 1992. *Semin Oncol* 1992;19(Suppl 11):64–71.
15. Kunimoto T, Nitta K, Tanaka T, Uehara N, Baba H, Takeuchi M, et al. Antitumor activity of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxy-camptothecin, a novel water-soluble derivative of camptothecin, against murine tumors. *Cancer Res* 1987;47:5944–7.
16. Houghton PJ, Cheshire PJ, Hallman JC, Bissery MC, Mathieu-Boue A, Houghton JA. Therapeutic efficacy of the topoisomerase I inhibitor 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxy-camptothecin against human tumor xenografts: lack of cross-resistance in vivo in tumors with acquired resistance to the topoisomerase I inhibitor 9-dimethlyaminomethly-10-hydroxycamptothecin. *Cancer Res* 1993;53:2823–9.
17. Tsuruo T, Matsuzaki T, Matsushita M, Saito H, Yokokura T. Antitumor effect of CPT-11, a new derivative of camptothecin, against pleiotropic drug-resistant tumors in vitro and in vivo. *Cancer Chemother Pharmacol* 1988;21: 71–4.
18. Fukuoka M, Niitani H, Suzuki A, Motomiya M, Hasegawa K, Nishiwaki Y, et al. A phase II study of CPT-11, a new derivative of camtothecin, for previously untreated non-small cell lung cancer. *J Clin Oncol* 1992;10: 16–20.
19. Negoro S, Fukuoka M, Niitani H, Suzuki A, Nakabayashi T, Kimura M, et al. A phase II study of CPT-11, a camptothecin derivative, in patients with primary lung cancer. *Jpn J Cancer Chemother* 1991;18:1013–9.

20. Masuda N, Fukuoka M, Kusunoki Y, Takifuji N, Kudoh S, Negoro S, et al. CPT-11, a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. *J Clin Oncol* 1992;10:1225–9.
21. Wiseman LR, Markham A. Irinotecan, a review of its pharmacological properties and clinical efficacy in the management of advanced colorectal cancer. *Drugs* 1996;52:606–23.
22. Kano Y, Suzuki K, Akutsu M, Suda K, Inoue Y, Yoshida M, et al. Effects of CPT-11 in combination with other anti-cancer agents in culture. *Int J Cancer* 1992;50:604–10.
23. Minagawa Y, Kigawa J, Ishihara H, Itamochi H, Terakawa N. Synergistic enhancement of cisplatin cytotoxicity by SN-38, an active metabolite of CPT-11, for cisplatin-resistant HeLa cells. *Jpn J Cancer Res* 1994;85:966–71.
24. Kudoh S, Takada M, Masuda N, Nakagawa K, Itoh K, Kusunoki Y, et al. Enhanced antitumor efficacy of a combination of CPT-11, a new derivative of camptothecin, and cisplatin against human lung tumor xenografts. *Jpn J Cancer* Res 1993;84:203–7.
25. Shimada Y, Rothenberg M, Hilsenbeck SG, Burris HA III, Degen D, von Hoff DD. Activity of CPT-11 (irinotecan hydrochloride), a topoisomerase I inhibitor, against human tumor colony-forming units. *Anticancer Drugs* 1994; 5:202–6.
26. Vogelzang NJ, Herndon JE, Cirrincione C, Harmon DC, Antman KH, Corson JM, et al. Dihydro-5-azacytidine in malignant mesothelioma. A phase II trial demonstrating activity accompanied by cardiac toxicity. *Cancer* 1997;79:2237–42.
27. Kaneda N, Nagata H, Furuta T, Yokokura T. Metabolism and pharmacokinetics of the camptothecin analogue CPT-11 in the mouse. *Cancer* Res 1990;50:1715–20.
28. Sasaki Y, Mizuno S, Fujii H, Ohtsu T, Wakita H, Igarashi T, et al. A limited sampling model for estimating pharmacokinetics of CPT-11 and its metabolite SN-38. *Jpn J Cancer Res* 1995;86:117–23.
29. Ghosh BK. A comparison of some approximate confidence intervals for binomial parameter. *J Am Stat Assoc* 1979;74: 894–900.
30. Kawato Y, Aonuma M, Hirota Y, Kuga H, Sato K. Intracellular roles of SN-38, a metabolite of the camptothecin derivative CPT-11, in the antitumor effect of CPT-11. *Cancer Res* 1991; 51:4187–91.
31. Tsuji T, Kaneda N, Kado K, Yokokura T, Yoshimoto T, Tsuru D. CPT-11 converting enzyme from rat serum: purification and some properties. *J Pharmacobiodyn* 1991;14:341–9.
32. Fukuoka M, Masuda N. Clinical studies of irinotecan alone and in combination with cisplatin. *Cancer Chemother Pharmacol* 1994;34:S105–11.
33. Masuda N, Fukuoka M, Takada M, Negoro S, Matsui K, Kudoh S, et al. CPT-11 in combination with cisplatin for advanced non-small-cell lung cancer. *J Clin Oncol* 1992;10: 1775–80.
34. Masuda N, Fukuoka M, Kudoh S, Matsui K, Kusunoki Y, Takada M, et al. Phase 1 and pharmacologic study of irinotecan and etoposide with recombinant human granulocyte colony-stimulating factor support for advanced lung cancer. *J Clin Oncol* 1994;12:1833–41.
35. van Meerbeeck J, Debruyne C, van Zandwijk N, Postmus PE, Pennucci MC, van Breukelen F, et al. Paclitaxel for malignant pleural mesothelioma: a phase II study of the EORTC Lung Cancer Cooperative Group. *Br J Cancer* 1996; 74:961–3.
36. Vogelzang NJ, Herndon U, Clamon GH, Mauer AM, Cooper MR, Green MR. Paclitaxel (Taxol) for malignant mesothelioma (MM): a phase II study of the Cancer and Leukemia Group B(CALGB 9234) [abstract]. *Proc Am Soc Clin Oncol* 1994;13:405.
37. Caliandro R, Boutin C, Perol M, Monnet I, Dabouis G, Guerin JC, et al. Phase II study of paclitaxel (Taxol) and cisplatin (CDDP) in advanced pleural malignant mesothelioma [abstract]. Fourth International Mesothelioma Interest Group Meeting, 1997:49.
38. Vogelzang NJ, Weissman LB, Herndon JE, Karen H, Antman KH, Cooper MR, et al. Trimetrexate in malignant mesothelioma: a Cancer and Leukemia Group B phase II study. *J Clin Oncol* 1994;12:1436–42.
39. Maksymiuk AW, Jung S, Marschke RF, Nair S, Jett JR. Phase II trial of topotecan in pleural mesothelioma: a North Central Cancer Treatment Group(NCCTG) trial [abstract]. *Proc Am Soc Clin Oncol* 1995;14:285.
40. O'Reilly S, Rowinsky EK. The clinical status of irinotecan (CPT-11), a novel water soluble camptothecin analogue: 1996. *Crit Rev Oncol Hematol* 1996;24:47–70.
41. Herndon JE, Green MR, Chahinian AP, Corson JM, Suzuki Y, Vogelzang NJ. Factors predictive of survival among 337 patients with mesothelioma treated between 1984 and 1994 by the Cancer and Leukemia Group B. *Chest* 1998; 113:723–31.
42. Abigerges D, Chabot GG, Armand JP, Herait P, Gouyette A, Gandia D. Phase I and pharmacologic studies of the camptothecin analog irinotecan administered every 3 weeks in cancer patients. *J Clin Oncol* 1995;13:210–21.
43. Saltz LB, Kanowitz J, Kemeny NE, Schaaf L, Spriggs D, Staton BA, et al. Phase I clinical and pharmacokinetic study of irinotecan, fluorouracil, and leucovorin in patients with advanced solid tumors. *J Clin Oncol* 1996;14:2959–67.
44. Rothenberg ML, Kuhn JG, Burris HA III, Nelson J, Eckardt JR, Tristan-Marales M, et al. Phase I and pharmacokinetic trial of weekly CPT-11. *J Clin Oncol* 1993;11:2194–204.
45. Negoro S, Fukuoka M, Masuda N, Takada M, Kusunoki Y, Matsui K, et al. Phase I study of weekly intravenous infusions of CPT-11, a new derivative of camptothecin, in the treatment of advanced non-small-cell lung cancer. *J Natl Cancer Inst* 1991;83:1164–8.
46. de Forni M, Bugat R, Chabot GG, Culine S, Extra JM, Gouyette A, et al. Phase I and pharmacokinetic study of the camptothecin derivative irinotecan, administered on a weekly schedule in cancer patients. *Cancer Res* 1994;54: 4347–54.
47. Catimel G, Chabot GG, Guastalla JP, Dumortier A, Cote C, Engel C, et al. Phase I and pharmacokinetic study of irinotecan (CPT-11) administered daily for three consecutive days every three weeks in patients with advanced solid tumors. *Ann Oncol* 1995;6:133–40.
48. Gupta E, Mick R, Ramirez J, Wang X, Lestingi TM, Vokes EE, et al. Pharmacokinetic and pharmacodynamic evaluation of the topoisomerase inhibitor irinotecan in cancer patients. *J Clin Oncol* 1997;15:1502–10.
49. Chabot GG, Abigerges D, Catimel G, Culine S, de Forni M, Extra JM, et al. Population pharmacokinetics and pharmacodynamics of irinotecan(CPT-11) and active metabolite SN-38 during phase I trials. *Ann Oncol* 1995;6:141–51.
50. Burris HA III, Hanauske AR, Johnson RK, Marshall MH, Kuhn JG, Hilsenbeck SG, et al. Activity of topotecan, a new topoisomerase I inhibitor, against human tumor colony-forming units in vitro. *J Natl Cancer Inst* 1992;84:1816–20.

51. Houghton PJ, Cheshire PJ, Hallman JD II, Lutz L, Friedman HS, Danks MK, et al. Efficacy of topoisomerase I inhibitors, topotecan and irinotecan, administered at low dose levels in protracted schedules to mice bearing xenografts of human tumors. *Cancer Chemother Pharmacol* 1995;36:393–403.
52. Sasaki Y, Ohtsu A, Shimada Y, Ono K, Saijo N. Simultaneous administration of CPT-11 and fluorouracil: alteration of the pharmacokinetics of CPT-11 and SN-38 in patients with advanced colorectal cancer. *J Natl Cancer Inst* 1994;86: 1096–8.
53. Armand JP, Terret C, Couteau C, Rixe O. CPT-11. the European experience. *Ann NY Acad Sci* 1996;803:282–91.
54. Society of Japanese Pharmacopoeia. Irinothecan hydrochloride, summary basis of approval no.1 (revised edition). Pharmaceuticals and Cosmetics Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, editor. Tokyo: Yakujinippo, Inc., 1996:105.
55. Grem JL, Ellenberg SS, King SA, Shoemaker DD. Correlates of severe or life-threatening toxic effects from trimetrexate. *J Natl Cancer Inst* 1988;80:1313–8.
56. Calavrezos A, Koschel G, Husselmann H, Taylessani A, Heilmann HP, Fabel H, et al. Malignant mesothelioma of the pleura. *Klin Wochenschr* 1988;66;607–13.
57. Pisani RJ. Malignant mesothelioma of the pleura. *Mayo Clin Proc* 1988;63:1234–44.
58. van Meerbeeck JP. Prognostic factors in malignant mesothelioma: where do we go from here? *Eur Respir J* 1994;6:1029–31.
59. Sugarbaker DJ, Strauss GM, Lynch TJ, Richards W, Mentzer SJ, Lee TH, et al. Node status has prognostic significance in the multimodality therapy of diffuse malignant mesothelioma. *J Clin Oncol* 1993;11:1172–8.