

Phase I study of intraperitoneal irinotecan in patients with gastric adenocarcinoma with peritoneal seeding

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Abstract

Purpose The objectives of this phase I study were to determine the maximum-tolerated dose (MTD), dose-limiting toxicities (DLTs), and preliminary efficacy of intraperitoneally administered irinotecan (CPT-11) in gastric cancer patients with peritoneal seeding.

Experimental design Gastric adenocarcinoma patients with surgical biopsy proven peritoneal seeding were enrolled at the time of surgery. Prior to IP chemotherapy, patients underwent palliative gastrectomy and CAPD catheter insertion in which CPT-11 was administered on post-operative day 1. The IP CPT-11 was initiated at 50 mg/m², which was escalated to 100, 150, 200, 250, and 300 mg/m². IP CPT-11 chemotherapy was repeated every 3 weeks.

Results Seventeen patients received a total of 56 cycles at five different CPT-11 dose levels. The DLTs were neutropenic fever, neutropenia, and diarrhea. At the dose level 2

(100 mg/m²), there were one DLTs in one of the first cohort of three patients, but no DLTs at the second cohort of this level. At the dose level 5 (250 mg/m²), two DLTs were detected in the first two patients; thus, the accrual was stopped resulting in the recommended dose of IP CPT-11 of 200 mg/m². Median progression-free survival was 8.6 months (95% CI, 5.9,11.2), and median overall survival was 15.6 months (95% CI, 8.4,22.8). Pharmacokinetic results of the study showed that the $C_{\max}$ of peritoneal SN-38 was achieved earlier than that of plasma SN-38.

Conclusions Intraperitoneally administered CPT-11 was feasible and tolerable. Further, phase II study of IP CPT-11 in gastric cancer patients with peritoneal seeding is warranted.

Keywords Gastric adenocarcinoma · Peritoneal seeding · Irinotecan · Intraperitoneal administration

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Introduction

The peritoneal cavity is a common site of tumor dissemination for gastrointestinal malignancies. Over the past decade, the potential role of intraperitoneal (IP) administration of antineoplastic drugs in the treatment of intraabdominal malignancies has been investigated. The major aim of this strategy was to expose tumor within peritoneal cavity to greater concentrations of cytotoxic agents for longer period than can be accomplished with intravenous (IV) drug administration. For most agents, IP drug administration significantly increases drug exposure in the peritoneal cavity, while at the same time produces systemic concentrations comparable to those obtained following IV drug administration. Peritoneal fluids to plasma concentration gradients of 10–2,000 have been observed depending on the drug used and the details of administration.

In support of the hypothesis, survival benefit of IP chemotherapy has been documented in ovarian cancer in which a large randomized trial showed significant survival advantage for women with ovarian cancer receiving IP chemotherapy [2, 3, 14]. Drugs such as 5-fluorouracil, cisplatin, mitomycin-C, paclitaxel, and docetaxel are used for IP chemotherapy in patients with gastric cancer [12, 18, 19, 21]. Even the small number of phase III trials reported, some studies showed improvement in survival for patients randomized to IP therapy compared to those receiving no postoperative treatment [9].

Irinotecan (CPT-11, Camptostar, 7-ethyl-10-[4]-1-piperidino)-1-piperidino] carbonyloxy camptothecin) is converted by carboxyl esterase in the liver and other tissues to its active metabolite, SN-38. SN-38 is a potent inhibitor of the nuclear enzyme topoisomerase I (Topo I). Topo I normally functions by causing a single-stranded, protein-bridged DNA break, which allows the intact DNA strands to pass through the break and thereby relieve torsional strain ahead of a replication fork and then reseal the break. Several clinical studies of irinotecan alone or in combination with other chemotherapeutic agents have documented promising activity in colorectal, lung, uterine cervix, and gastric cancer.

In a mouse model, IP administration of CPT-11 was significantly more effective than IV administration in terms of antitumor activity against both peritoneal seeding and liver metastases. The pharmacokinetic (PK) study of IP CPT-11 in mice bearing P3888 leukemic ascites demonstrated higher IP CPT-11 and SN-38 AUC values when compared with those after IV injections [15]. Moreover, the clearance rate of IP CPT-11 was 10-fold lower than the IV administration of CPT-11. Accordingly, a preclinical PK study in a rat model also demonstrated higher concentrations of SN-38 and SN-38G were observed after IP administration of CPT-11 [8].

Conversely, the PK of IP CPT-11 in human subjects has not been extensively studied. The PK study of IP CPT-11 40–60 mg in four patients with peritoneal seeding (two gastric cancer cases, two colon cancer cases) showed an equivalent serum and peritoneal fluid levels of CPT-11, SN-38, and SN-38G at 30 min after IP administration of CPT-11 [16]. Consequently, high concentration of CPT-11 was noted following IP administration, which may lead to a more effective therapy in patients with peritoneal seeding.

Based on these data, we undertook a phase I study to determine the maximum-tolerated dose of IP CPT-11 in gastric cancer patients with peritoneal seeding and to evaluate PK profile.

Methods

Patients

Eligible patients were at least 18 years of age with histologically proven gastric adenocarcinoma and received no

previous chemotherapy, immunotherapy, or radiotherapy. All patients had performance status of ECOG 0–1, adequate hematologic (WBC count $\geq 4,000/\text{mm}^3$, platelet count $\geq 150,000/\text{mm}^3$), hepatic (bilirubin level $\leq 1.5 \text{ mg/dL}$), and renal (creatinine concentration $\leq 1.5 \text{ mg/dL}$) functions. Childbearing potentials were controlled, if female, either by surgery, radiation, or menopause, or attenuated by use of an approved contraceptive method (intrauterine device [IUD], birth control pills, or barrier device) and if male, by use of an approved contraceptive method during the study and 3 months afterward. Patients were required to have resectable disease during preoperative evaluation such as endoscopic findings suggestive of advanced gastric cancer, radiologic finding of T3 or T4 disease with or without suspicious peritoneal seeding. The surgical finding and biopsy of suspected peritoneum must have demonstrated peritoneal involvement of adenocarcinoma. Exclusion criteria included patients with myocardial infarction within 6 months or symptomatic heart disease, including unstable angina, congestive heart failure or uncontrolled arrhythmia, serious concomitant infection, second primary malignancy (except in situ carcinoma of the cervix or adequately treated basal cell carcinoma of the skin or prior malignancy treated more than 5 years ago without recurrence), and history of significant neurologic or psychiatric disorders. Pregnant or lactating women were also excluded. All patients provided written informed consent. The study was approved by the institutional review board at Samsung Medical Center.

Treatment

Once the patient provided an informed consent form to participate in the trial, patients underwent palliative resection of the primary tumor and concomitant CAPD (continuous ambulatory peritoneal dialysis) catheter insertion for IP chemotherapy administration. The first IP CPT-11 chemotherapy was administered via CAPD catheter on postoperative day 1. The initial dose in the first cohort was CPT-11 50 mg/m^2 which was mixed in 1 L of prewarmed normal saline at 37°C . Prophylactic atropine (0.3 mg of atropine subcutaneously just before IP CPT-11 administration) was given to all patients, and all concomitant medications were recorded.

Three patients were accrued to each dose level. If none of the three patients experienced DLT, the dose was increased in a subsequent group of three patients to 100 mg/m^2 . If one of the first three patients experienced DLT, three more patients were accrued to that dose level. If none of these additional three patients experienced DLT, then the dose was escalated to 150 mg/m^2 . If one of the additional three patients experienced DLT, then either an additional cohort of patients was added or dose escalation was terminated. If two or more of the second group of three

patients experienced DLT, then accrual was stopped. If two of the first three patients experienced DLT, then an additional three patients could be accrued at that dose level, but dose escalation was continued only if none of the additional cohort experienced DLT. The last planned dose escalation was 300 mg/m². Cohorts of at least three patients were entered at each dose level and monitored for at least 4 weeks after treatment before dose escalation. Inpatient dose escalation was not permitted.

The CTCAE (Common Terminology Criteria for Adverse Events) ver. 3.0 was used to assess toxicity in this study. DLTs were defined as follows: any grade 4 non-hematologic toxicity or as noted below; $\geq$ grade 3 diarrhea or stomatitis lasting ≥ 7 days despite optimal supportive care; hematologic DLTs were defined grade 4 neutropenia complicated by fever $\geq 38^{\circ}\text{C}$; grade 4 hemorrhage or thrombocytopenia; failure to recover neutrophils ($\geq 1,500/\text{mm}^3$) or platelets ($\geq 100,000/\text{mm}^3$) by day 28. No prophylactic colony stimulating factors were allowed in this study unless a life-threatening event occurred. The MTD was defined as the dose level that produced dose-limiting toxicity in $\geq 50\%$ of patients and the recommended dose was defined as one level below that. Patients were treated up to 4 cycles of IP chemotherapy at a 3-week interval.

Close monitoring including physical examination, complete blood count, blood chemistry, and serum electrolytes were done daily up to postchemotherapy 5 days and then weekly thereafter during the treatment course.

Pharmacokinetics samples and analytical methods

Plasma samples were collected prior to IP chemotherapy and at 0.5, 1.5, 2, 3.5, 8, 12, 25.5, 49, and 56 h following chemotherapy. At each time point, 5 mL of blood was drawn into heparinized tubes and stored on ice until centrifuged at 1,258 *g* for ~ 10 min at room temperature. The resulting plasma was removed and placed into a 17 $\times$ 100 mm polypropylene, snap-cap tube that is appropriately labeled. Samples were frozen and stored at -80°C until analysis. Samples of peritoneal fluid and urine were obtained at 0.5, 1.5, 2, 3.5, 8, 12, 25.5, 49, and 56 h following chemotherapy, and all samples were handled and stored with the same method. All samples were analyzed by a validated reverse-phase high-performance liquid chromatography except for changes in the percentage of acetonitrile in mobile phase from 30 to 35% and the reconstitution of samples in the mobile phase rather than in acidified methanol.

Pharmacokinetic analysis

Pharmacokinetic parameters for irinotecan (CPT-11) and its metabolite (SN-38) were estimated by non-compartmental analysis using WinNonlin (Ver 5.2, Pharsight Co,

Mountain View, CA). The Area under the drug concentration–time curve from 0 to infinity ($\text{AUC}_{0-\infty}$) was calculated with the linear trapezoidal method and extrapolation through infinite time according to the terminal elimination rate constant (λ_z), which was obtained by log-linear regression of concentration–time curve. The peak peritoneal or plasma concentration ($C_{\max}$) and the time to $C_{\max}$ ($T_{\max}$) were determined by direct inspection of concentration–time data. The terminal elimination half-life [$t_{1/2}(\lambda_z)$] was calculated from the relationship $(0.693/\lambda_z)$. The apparent systemic clearance (CL/F) and the apparent volume of distribution during the terminal phase (V_z/F) were obtained from the relationship: $\text{Dose}/\text{AUC}_{0-\infty}$ and $\text{CL}/F/\lambda_z$, respectively. Moreover, Kruskal–Wallis test which is the non-parametric counterpart of one-way ANOVA test was performed to assess the differences in the pharmacokinetic parameters with respect to dose level using SAS enterprise guide (Ver 3.0, SAS Institute Inc, Cary, NC).

Results

Patient characteristics

From October 2004 to August 2007, 17 patients were enrolled onto this study. All 17 patients received more than 1 cycle of IP CPT-11 and a total of 56 cycles. The median age was 50 years (range, 37–64). Histologic subtypes included tubular adenocarcinoma ($n = 12$), signet-ring cell carcinoma ($n = 4$), and mucinous adenocarcinoma ($n = 1$). Postoperative TNM stage was T2N0 ($n = 1$), T2N3 ($n = 2$), T3N0 ($n = 1$), T3N1 ($n = 1$), T3N2 ($n = 6$), T3N3 ($n = 5$), and T4N0 ($n = 1$). Nine patients received total gastrectomy and eight patients received subtotal gastrectomy (Billroth I, $n = 3$; Billroth II, $n = 5$).

DLT and recommended dose

The starting dose was 50 mg/m², and the dose was escalated sequentially to 100, 150, 200, and 250 mg/m². The number and types of DLTs are listed in Table 1. In summary, a total of four DLTs occurred in three patients. No patient treated at dose level 1 (50 mg/m²) had DLT. Two DLTs, grade 4 neutropenia with fever and failure to recover neutropenia by day 28, occurred in one of the first three patients at dose level 2 (100 mg/m²). Three additional patients were enrolled at this dose level, and no further DLT was observed. There were no DLTs detected at levels 3 and 4. Two DLTs (grade 3 diarrhea lasting more than 7 days and grade 4 neutropenic fever) were detected in the first two patients at the dose level 5 (250 mg/m²). Thus, the accrual was stopped resulting in the recommended dose of IP CPT-11 of 200 mg/m². Other non-dose-limiting toxicities

Table 1 Dose escalation and DLT

Dose level	Dose	No. pts treated	No. cycles	No. DLTs	Responses
1	50	3	7	0	2 SD, 1 PD
2	100	6	23	2	5 SD, 1 PD
3	150	3	12	0	1 SD, 2 PD
4	200	3	9	0	3 SD
5	250	2	8	2	2 PD

DLT dose-limiting toxicities, SD stable disease, PD progressive disease

Grade 4 neutropenia + fever, failure to recover neutrophils by day 28; Grade 3 diarrhea lasting ≥ 7 days, Grade 4 neutropenia + fever

Table 2 Non-DLT related to IP CPT-11 (NCI-CTC 3.0 ≥ 3)

Dose (No. pt)	50 (3)	100 (6)	150 (3)	200 (3)	250 (2)
Anemia	1	1	1	1	1
Neutropenia	0	0	1	1	0
Thrombocytopenia	0	0	0	0	0
Diarrhea	0	2	0	0	0
Nausea	0	1	1	0	0
Vomiting	0	1	1	0	0

included grade 3 diarrhea ($n = 2$) and grade 3 nausea ($n = 2$) (Table 2).

Antitumor efficacy

All 17 patients were assessed for treatment response. Although no objective responses were noted in our study, eleven patients had stable disease. The median follow-up time was 29 months (range, 11–46 months). Median progression-free survival was 8.6 months (95% CI, 5.9, 11.2), and median overall survival was 15.6 months (95% CI, 8.4, 22.8) (Fig. 1). At the time of analysis, five patients were alive.

Pharmacokinetic parameters and urinary excretion

Pharmacokinetic parameters for CPT-11 and SN-38 after intraperitoneal CPT-11 infusion for 60 min at a dose level of 200 mg/m² are summarized in Table 3. Figure 2 shows the peritoneal and plasma concentration–time profiles for CPT-11 and SN-38. The time courses of cumulative urinary recovery of CPT-11 and SN-38 are illustrated in Fig. 3. The T_{max} of peritoneal SN-38 (1.5 h) was identical to that of peritoneal CPT-11 (1.5 h) and shorter than those of plasma SN-38 (4.2 h). The $t_{1/2}(\lambda_z)$ of peritoneal SN-38 (26.24 h) was similar to that of plasma SN-38 (26.91 h). Up to 56 h

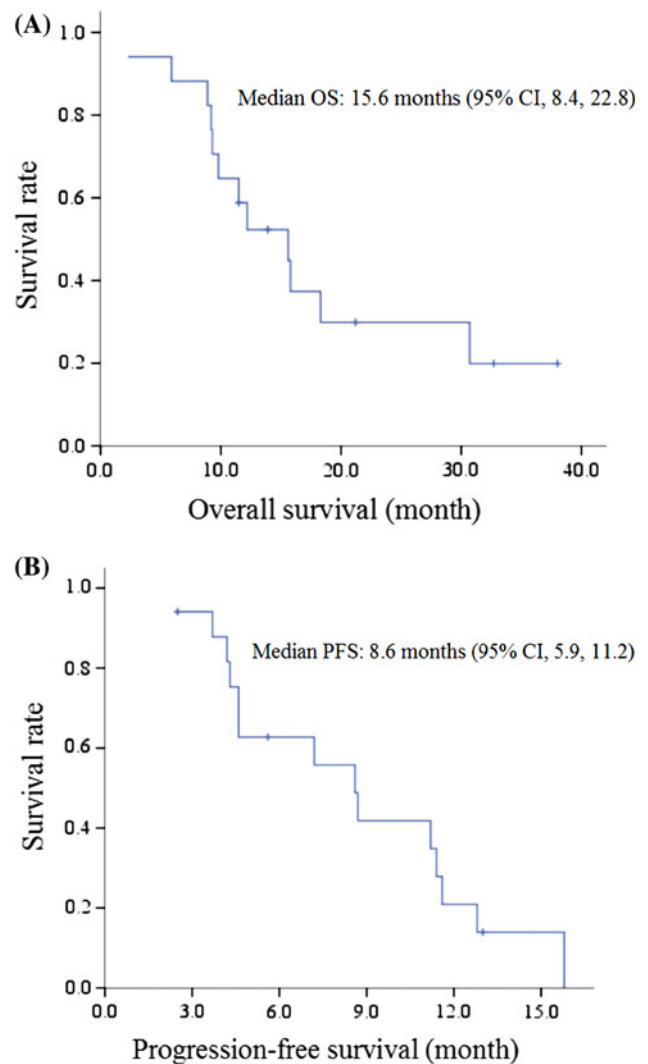


Fig. 1 **a** Overall survival of patients ($n = 17$); **b** Progression-free survival

after intraperitoneal CPT-11 infusion, cumulative amounts of CPT-11 and SN-38 were $8.49 \pm 6.74\%$ (mean $\pm$ SD) and $0.69 \pm 0.81\%$ (mean $\pm$ SD) of the administered dose, respectively. The Kruskal–Wallis test for dose-linearity did not show statistically significant differences of pharmacokinetic parameters with respect to dose level.

Discussion

This phase I trial represents the first to evaluate feasibility of intraperitoneal single irinotecan in gastric cancer patients with surgical biopsy proven gastric adenocarcinoma. The rationale of IP chemotherapy is to expose the major site of disease to high concentration of drug with reduced systemic side effects. Cytoreductive surgery followed by intraperitoneal chemotherapy has evolved into a promising approach for selected patients with peritoneal seeding from gastrointestinal

Table 3 Pharmacokinetic parameters for CPT-11 and SN-38 after intraperitoneal CPT-11 infusion for 60 min

Parameter	IP CPT-11		IP SN-38		PL CPT-11		PL SN-38	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
$AUC_{0-\infty}$ (h mg/L)	450.08	123.19	1.12	0.67	12.77	3.83	0.57	0.35
C_{max} (mg/L)	111.67	30.12	0.08	0.02	1.74	0.59	0.02	0.01
T_{max} (h)	1.50	0.00	1.50	0.00	2.34	0.44	4.22	3.60
$t_{1/2}(\lambda_z)$ (h)	16.57	17.60	26.24	20.17	9.34	3.56	26.91	9.98
V_z/F (L/m ²)	9.99	6.25	7119.02	4057.16	219.59	83.92	16315.75	7414.72
CL/F (L/h/m ²)	0.47	0.11	242.18	135.09	17.14	5.54	453.72	225.17

IP, Intraperitoneal; PL, Plasma; $AUC_{0-\infty}$, Area under the drug concentration–time curve from time 0 to infinity at a normalized dose level of 200 mg/m²; C_{max} , Peak concentration at a normalized dose level 200 mg/m²; T_{max} , Time to peak concentration; $t_{1/2}(\lambda_z)$, terminal elimination half-life; V_z/F ; apparent volume of distribution; CL/F , apparent systemic clearance

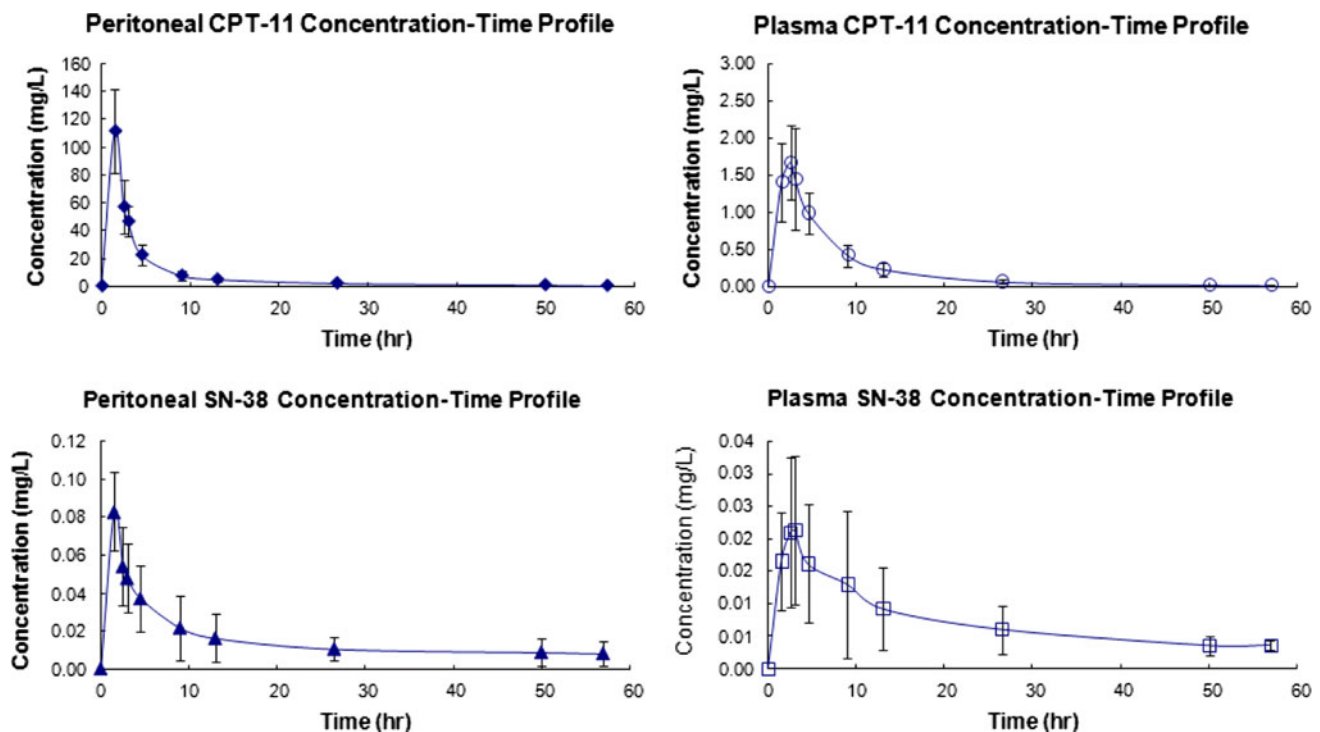


Fig. 2 Peritoneal and plasma CPT-11 and its metabolite SN-38 concentration–time profiles after intraperitoneal CPT-11 infusion for 60 min at a normalized dose level, 200 mg/m². The C_{max} of plasma SN-38 were about 1/80 of the C_{max} of plasma CPT-11

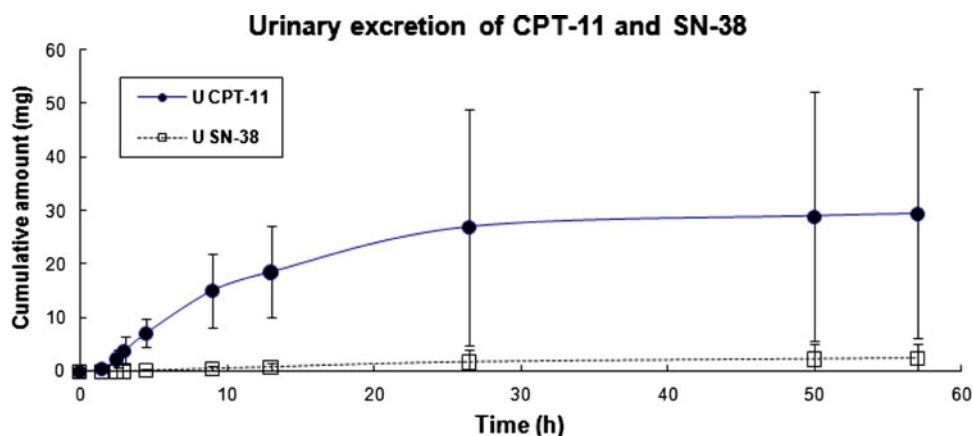
cancer [20]. In addition, one group reported a substantial proportion of 5-year survivors in patients with peritoneal seeding arising from gastric cancer [7]. Although a variety of agents have been investigated for use of intraperitoneal chemotherapy for the treatment of peritoneal seeding of gastrointestinal cancer, the standard regimen for IP chemotherapy has not been established yet.

Recent data have emerged on the use of intravenous irinotecan in advanced gastric cancer, both as a single agent and in diverse combination regimens. These have rendered acceptable response rates and overall survival but have also been associated with significant grade 3–4 neutropenia and

diarrhea [1]. Phase II studies with irinotecan plus 5-FU and leucovorin (FOLFIRI) including ours demonstrated response rates of 21–43% with median survival time between 7.6 and 11.3 months [4, 11, 17].

The IP irinotecan chemotherapy has been rarely studied in human trials. Recently, phase I study on IP irinotecan in combination with oxaliplatin following complete cytoreductive surgery was reported. The starting dose of irinotecan was 300 mg/m², and the recommended dose was 400 mg/m² with fixed dose of 460 mg/m² of oxaliplatin in gastrointestinal malignancies with peritoneal seeding [5, 6]. The regimen was associated with high incidence of $\geq$ grade

Fig. 3 Cumulative urinary excretion-time profiles of CPT-11 and its metabolite SN-38 after a 60 min intraperitoneal CPT-11 infusion at a normalized dose level of 200 mg/m². (U CPT11, Urinary CPT-11; U SN-38, Urinary SN-38)



3 hematologic toxicity rate (58%), grade 4 neutropenia (41%), and grade 3 thrombocytopenia (26%). In contrast, our regimen seems to be more tolerable with lower incidence of $\geq$ grade 3 neutropenia (23%), neutropenic fever (12%), and no incidence of $\geq$ grade 3 thrombocytopenia. Moreover, the median progression-free survival duration of 8.6 months and median survival time of 13.8 months seemed to be more favorable than those reported in the literature. Due to limited number of patients, however, the survival benefit from IP irinotecan chemotherapy should be further investigated in this subset of patients. Of note, the clinical implication of response rate may not be reflective of IP irinotecan in this trial since only one patient had measurable disease at the time of treatment. Thus, the progression-free survival may be more appropriate index of antitumor activity for this trial. The most common site of progression was peritoneum (57%).

There were three patients who experienced postoperative complications. One patient had postoperative bleeding which was completely resolved after second laparotomy. There was one case of intraabdominal abscess due to anastomosis site leakage, which eventually led to death at postoperative day 27 due to sepsis. One Krukenberg tumor patient who had undergone total hysterectomy and bilateral salpingo-oophorectomy developed vaginal stump leakage 28 days following IP chemotherapy. An animal study suggested that IP chemotherapy has a detrimental effect on the healing and strength of intestinal anastomoses, which may explain the relatively high morbidity rates following this procedure [13]. However, the definite causal relationship between these leakage and IP irinotecan has not been established.

Generally, it was known that transformation of CPT-11 to its active metabolite SN-38 occurs mainly by hepatic carboxylesterase. However, previous PK studies using animal model suggested that CPT-11 may be converted to SN-38 in the peritoneum by the carboxylesterase existing in the peritoneal tissue, plasma carboxylesterase which might have been exudated over the peritoneal membrane, or some

carboxylesterase activity existing in the cancer cells [9, 10]. PK results of the present study showed that the $C_{\max}$ of peritoneal SN-38 was achieved earlier than that of plasma SN-38. This finding suggests that in situ conversion of CPT-11 to SN-38 occurs in the peritoneal cavity and intraperitoneal infusion of irinotecan could be an efficient route of administration in patients with peritoneal seeding. The similarity in terminal half-lives of peritoneal SN-38 and plasma SN-38 suggests that the peritoneal SN-38 is eliminated by urinary and biliary excretion after its distribution to the plasma compartment. The mean $C_{\max}$ of plasma SN-38 was about 1/80 of that of plasma CPT-11, which was similar to those reported previously. The plasma concentrations were well above IC_{50} values reported for KB and L1210 cells (0.37 and 3.6 μ g/L, respectively) in preclinical studies [10]. Urinary excretion ratios of CPT-11 (8.49%) and SN-38 (0.69%) in present study were lower than those reported previously [22, 23].

In conclusion, this study demonstrated that intraperitoneal chemotherapy with CPT-11 is feasible and tolerable. The recommended dose of intraperitoneally administered CPT-11 was 200 mg/m². Further, phase II study of IP CPT-11 in gastric cancer patients with peritoneal seeding is planned.

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