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Original Article

Irinotecan Hydrochloride (CPT-11) in Dialysis Patients with Gastrointestinal Cancer

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We investigated changes in drug disposition and toxicities with CPT-11 in 15 dialysis patients with gastrointestinal cancers to clarify whether CPT-11 could be administered safely in such patients. For comparison, the same parameters were also investigated in 10 cancer patients not undergoing dialysis. Items investigated included (1) plasma concentrations of SN-38, SN-38G and CPT-11 at 0, 1, 12, 24, 36, 48 and 72 h after administration, together with a comparison of mean AUC values for 3 dose levels of CPT-11 (50, 60 and 70 mg/m^2) in dialysis patients and controls; and (2) occurrence of adverse events. Several findings emerged from this study: (1) No significant difference was observed in the AUC for SN-38 or CPT-11 between the dialysis and control groups; (2) The AUC for SN-38G at each dose was significantly higher in dialysis patients; and (3) Grade 1-4 leucopenia was observed in 11 of the dialysis patients. One patient developed grade 4 leucopenia and died due to sepsis. Anorexia, diarrhea, nausea, alopecia and interstitial pneumonia occurred in 6 dialysis patients. We found changes in drug dispositions of CPT-11, SN-38 and SN-38G in dialysis patients, suggesting that hepatic excretion, especially that of SN-38G, was increased. No significant difference in occurrence of adverse events was observed between the 2 groups. This indicates that CPT-11 can be administered safely in patients on dialysis.

Key words: irinotecan hydrochloride (CPT-11), chronic kidney disease (CKD), end-stage renal disease (ESRD), dialysis, colorectal cancer

As the most effective curative treatment currently available, surgery is the option of choice for gastrointestinal cancers, while chemotherapy is the main option for both limited-stage and inoperative metastatic cancers. In patients on dialysis, the incidence and mortality of cancer have been shown to be higher than the predicted rates in the general population due to variable immunodeficiency [1–3]. One of the routes that anticancer drugs take as they are discharged from the body is through the kidneys, which are easily impaired. Therefore, chemotherapy is not performed aggressively in patients on dialysis, as its safety has yet to be established in patients with chronic renal failure. Irinotecan hydrochloride (CPT-

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11) was first approved in the United States in 1996, and was the standard of care for second-line therapy in 5-FU-refractory colorectal cancer (CRC) at the inception of the current trial [4, 5]. The incorporation of CPT-11 has proved a promising strategy in improving survival in patients with CRC [4–6]. However, no consensus has been established on the safety of CPT-11 in patients on dialysis.

In this study, we investigated changes in drug disposition and toxicities with CPT-11 in patients with gastrointestinal cancers who were on dialysis to clarify whether CPT-11 could be administered safely in such patients. This study was approved by the institutional review board of this facility. Written informed consent was obtained from all patients prior to enrollment.

Patients and Methods

A total of 15 patients with gastrointestinal cancers who were on dialysis were enrolled in this study between March, 2005 and April, 2008 at the Hachioji Medical Center of Tokyo Medical University. These 15 patients consisted of 10 men and 5 women, with a median age of 71.1 years (range 63–84 years) and median performance status of 1 (range 0–2). The results of the liver function tests for the 15 patients were as follows: median AST, 20.7 IU/L (range, 6–41 IU/L); median ALT, 13.5 IU/L (range, 3–25 IU/L); and median total bilirubin, 0.42 mg/dL (range, 0.2–0.8 mg/dL). Histologically, 11 of the 15 patients were diagnosed with colorectal cancer and 4 with gastric cancer. The patients had been on hemodialysis for 1–168 months, and none had received pre-treatment. Thirteen patients underwent surgical therapy at our department (Table 1). Ten non-dialysis patients with cancers (4 with colorectal, 2 with stomach, 2 with biliary tract and 2 with lung cancer) donated sera for comparison as controls. They included 7 men and 3 women; median age, 61.4 years (range, 35–79 years); median eGFR, 76.3 mL/min/1.73 m^2 (range, 61.5–91.7 mL/min/1.73 m^2); and median serum creatinine, 0.6 mg/dL (range, 0.5–1.0 mg/dL).

CPT-11 was provided by Yakult Honsha Co. Ltd. (Tokyo, Japan) as a solution ready for use in 2- or 5-ml vials containing 40 and 100 mg of the drug, respectively. CPT-11 was diluted with 500 mL sodium chloride and administered by intravenous infusion over 90 min within 2 h of completion of hemodialysis. Three dose levels of CPT-11 were studied: 50, 60 and 70 mg/m^2. Dosage was increased in 10-mg/m^2 increments from 50 to 70 mg/m^2.

Analysis of CPT-11 in plasma and data evaluation. To assess changes in drug disposition of CPT-11 (the unchanged compound), its active metabolite, 7-ethyl-10-hydroxycampothecin (SN-38), and SN-38G (the glucuronide), serial blood samples were collected into 6.0-ml tubes at the following

Table 1 Disease characteristics of enrolled patients

No.	Sex	Age	PS	HD duration (m)	Origin	Procedure	Stage
1	M	69	2	50	A/C	–	Ⅳ(H3)
2	F	66	1	5	Rectum	–	–
3	M	75	2	110	Rectum	Hartmann	Ⅲ
4	F	63	2	48	S/C	Hartmann	Ⅲ
5	M	68	0	1	Rectum	Hartmann	Ⅱ
6	F	81	1	1	S/C	HAR	Ⅱ
7	M	75	0	66	T/C	Rt.-hemi	Ⅲ
8	M	67	1	8	A/C	Rt.-hemi	Ⅰ
9	M	67	0	2	S/C	HAR	Ⅱ
10	F	68	1	168	A/C	Rt.-hemi	Ⅲb
11	F	66	1	144	S/C	HAR	Ⅳ(H3)
12	M	67	1	6	Stomach	Total	Ⅱ
13	M	72	1	3	Stomach	Distal	Ⅱ
14	M	84	1	1	Stomach	Distal	ⅠA
15	M	78	1	76	Stomach	Total	ⅠB

times: t = 0 (immediately after completion of CPT-11 infusion) and at 1, 12, 24, 36, 48 and 72 h after administration. Blood samples were centrifuged at 3,500 g for 5 min, and the plasma was transferred into polypropylene tubes, followed by addition of 0.146 $M$$H_3PO_4$. The standard samples were stored at −20℃. Plasma samples were analyzed for SN-38, SN-38G and CPT-11 using a validated high-performance liquid chromatography (HPLC) method and the PROSPECT fully automated on-line solid-phase extraction system [7]. The areas under the plasma concentration vs. time curves (AUCs) for SN-38, SN-38G and CPT-11 were calculated for each dose. The AUC value was determined using the trapezoidal method with MOMENT (EXCEL) [8].

Items investigated.

1) Mean AUC values for each dose were compared between dialysis patients and controls.

2) Occurrence of adverse events.

Toxicity was evaluated in all patients receiving 1–3 cycles of CPT-11. Toxicities (hematological and non-hematological) were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), revised version 2.0. Hematological toxicity was assessed based on blood cell count and blood chemistry data obtained twice weekly, with worst toxicity being reported. Hemoglobin, blood urea nitrogen (BUN), creatinine and electrolyte levels were excluded from the assessment as all 15 patients on dialysis had developed anemia and renal dysfunction. All patients in both groups were given G-CSF when they developed grade 3 febrile leucopenia (white blood cell count < 1,500 cells/mm^3) or grade 4 non-febrile leucopenia (white blood cell count < 1,000 cells/mm^3).

Statistical analysis. Differences in AUCs between dialysis patients and controls were compared using an unpaired t-test. All p values reported are two-tailed, and all tests were performed at a 0.05 significance level. Statistical analysis of the data was conducted using the GraphPad software (San Diego, CA, USA).

Results

AUC values. Figs. 1, 2 and 3 show the blood concentration curves after CPT-11 administration for SN-38, SN-38G and CPT-11 in the dialysis patients and the controls. There appeared to be no increase in the AUC for SN-38, SN-38G or CPT-11 among the successive dose levels (50, 60 and 70 mg/m^2). No significant difference between the 2 groups was observed in mean AUC values and standard errors for SN-38 or CPT-11 obtained at each dose (50, 60 and 70 mg/m^2; Table 2). On the other hand, the mean and standard error of the AUC values for SN-38G at each dose (50, 60 and 70 mg/m^2) were significantly higher in the dialysis patients than in the controls (Table 2).

Intensity of adverse events.

1. Hematologic Toxicities. The main adverse reaction was myelotoxicity, with leucopenia occurring 75.0% (24/32 cycles) in 11 (73.3%) patients: 4 patients with grade 1, 3 patients with grade 2, 3 patients with grade 3, and 1 patient with grade 4 after administration of 50–70 mg/m^2 CPT-11. Four patients (26.7%) showed grade 3 or 4 leucopenia. Although one patient with grade 4 leucopenia after administration of 70 mg/m^2 was treated with G-CSF, he died due to sepsis and pneumonia (Table 3). No thrombocytopenia was observed, and no patient required a blood transfusion in any cycle.

2. Non-hematologic Toxicities. Anorexia, diarrhea, nausea, alopecia and interstitial pneumonia occurred in 6 patients (Table 4).

Discussion

Camptothecin (CPT), a plant alkaloid extract from the Chinese tree *Camptotheca acuminate*, has strong antitumor activity due to its inhibition of the nuclear enzyme DNA topoisomerase-1 (Topo-1) [9–11]. Irinotecan hydrochloride, a water-soluble derivative of camptothecin developed to improve its antitumor activity and decrease its toxicity in mice and rats [12, 13], has been shown to be highly effective in the treatment of metastatic colorectal cancer [4–6]; and CPT-11 with 5-fluorouracil (5-FU) and leucovorin (LV) has been shown to be effective for metastatic colorectal cancer in large randomized phase three trials [14, 15]. These studies [4–6, 14, 15] formed the basis for the selection of CPT-11 for investigation in the present study.

Only a small fraction of the administered CPT-11 is metabolized by carboxylesterase enzymes [16, 17] to SN-38, which is a significantly more potent inhibitor of tumor activity [18]. In addition, SN-38 is

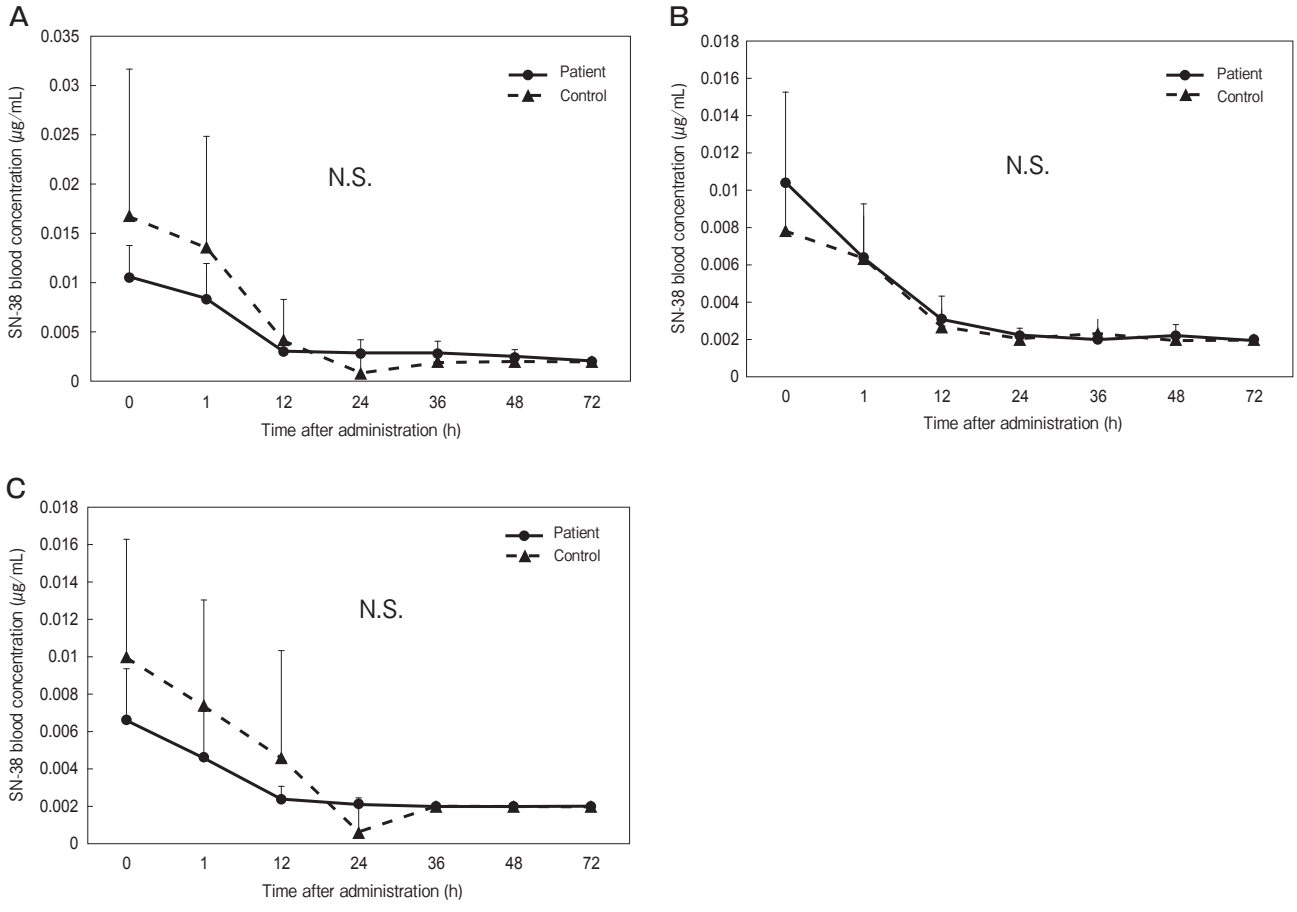

Fig. 1 SN-38 blood concentration curves after administration of CPT-11 at 50 mg/m^2 (**A**), 60 mg/m^2 (**B**) and 70 mg/m^2 (**C**) in dialysis patients and controls.

conjugated by the polymorphic enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) to SN-38 glucuronide (SN-38G) [16, 19–21], which is excreted in the bile, urine and feces [21]. Slatter *et al.* noted that CPT-11 was the major excretory product in bile, urine and feces, and that fecal excretion accounted for $63.7 \pm 6.8\%$ of the dose, whereas urine excretion accounted for $32.2 \pm 6.9\%$ after intravenous infusion of CPT-11 in 7 patients with solid tumors [22]. SN-38 was shown to be a significant metabolite in feces ($8.24 \pm 2.51\%$) and urine ($0.43 \pm 0.12\%$) [22]. These data may explain why no significant difference was observed in the mean AUC values for CPT-11 and SN-38 between the dialysis patients and the controls in this study. On the other hand, SN-38G was also shown to be a significant metabolite in urine ($3.02 \pm 0.77\%$) and feces ($0.27 \pm 0.17\%$) [22]. This may explain why the mean AUC values for SN-38G were significantly higher in the dialysis patients than in the controls here. In other words, the absence of renal clearance of SN-38G in the dialysis patients led to a significant increase in their AUC value for SN-38G.

Furthermore, these results suggest that SN-38G was exclusively excreted in the feces in dialysis patients, and that enterohepatic circulation of SN-38 was slight or absent. If enterohepatic circulation of SN-38 was present, the mean plasma AUC value for SN-38 would have been higher in the dialysis patients than in the controls. However, no significant difference was observed in the mean AUC values for SN-38 between the 2 groups. Asai *et al.* reported the accurate estimation of the AUC of carboplatin following irinotecan using a limited sampling model [23]. They

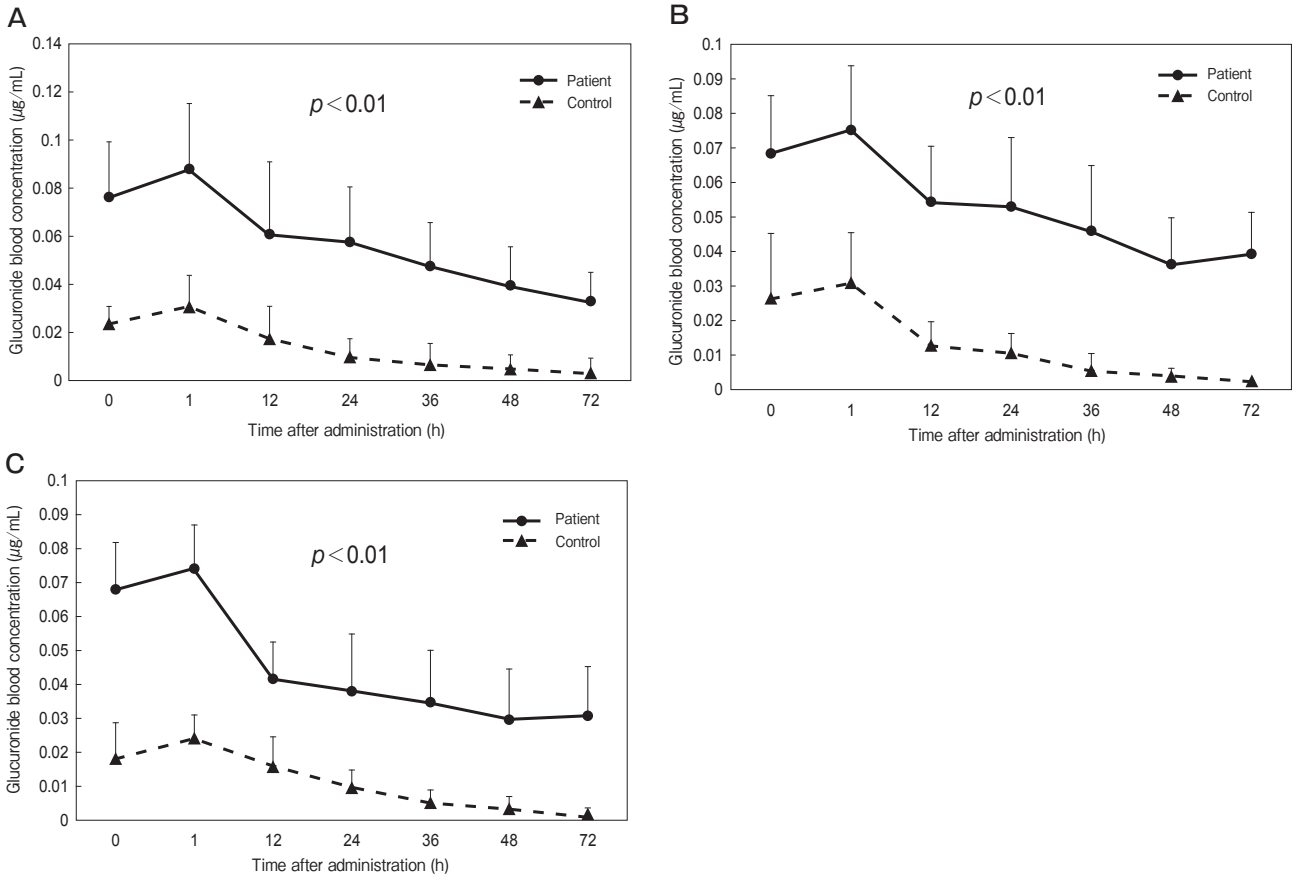

Fig. 2 SN-38G blood concentration curve after administration of CPT-11 at 50 mg/m^2 (**A**), 60 mg/m^2 (**B**) and 70 mg/m^2 (**C**) in dialysis patients and controls.

noted that the dispersion of the AUC value was greater in the limited sampling model and that drug-drug interactions might alter the pharmacokinetics of carboplatin [23]. However, as no 5-FU or LV was administered along with CPT-11 to the patients in our study, the influence of such interactions on the pharmacokinetics of CPT-11 was not investigated.

Although CPT-11 shows marked anti-cancer activity, this drug also shows certain side effects. These include a decrease in blood cells, especially neutrophils, alopecia, nausea and gastrointestinal toxicities such as diarrhea [24, 25]. Rothenberg noted that diarrhea and myelosuppression remained the most clinically significant and common toxicities of irinotecan (CPT-11) [26]. In the present study, no significant difference was observed in the occurrence of leucopenia between our results (73.3%) and those of previous clinical reports (75.8～91%) [4, 6, 25]. Eleven patients developed grade 1–4 leucopenia and 4 patients (26.7%) developed grade 3/4 leucopenia. In 10 out of these 11 patients, leucopenia was resolved by conservative treatment including G-CSF, while the remaining patient with grade 4 leucopenia died due to sepsis. Although this latter patient received G-CSF when he developed grade 3 leucopenia, the white blood cell count showed no improvement, and the leucopenia progressed to grade 4. In dialysis patients, it is necessary to investigate the timing of G-CSF administrations, as the reactivity of G-CSF differs in such patients. Kurita *et al.* noted that one pharmacokinetic parameter (Cmax) of CPT-11 was closely related to the incidence and severity of myelosuppression [27]. However, the pharmacodynamic relationship between the AUCs for SN-38, SN-38G (glucuronate) and CPT-11 showed no correlation with the severity of leucopenia in this study.

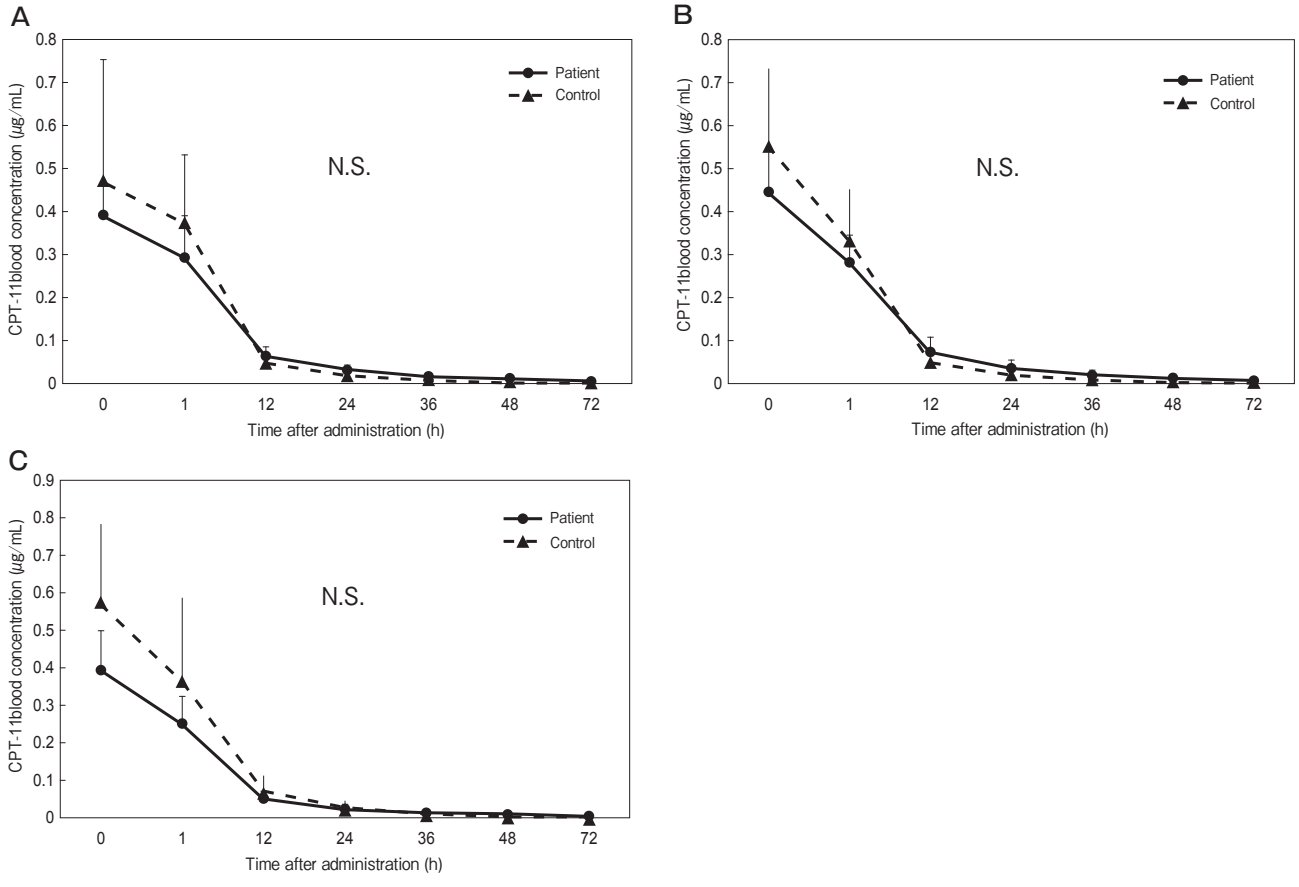

Fig. 3 CPT-11 blood concentration curve after administration of CPT-11 at 50 mg/m^2 (**A**), 60 mg/m^2 (**B**) and 70 mg/m^2 (**C**) in dialysis patients and controls.

Table 2 Comparison of mean AUC value between dialysis patients and controls

Variable	Dose (mg/m^2)	Patients (μg · h/mL)	Controls (μg · h/mL)	*P*-value
SN-38	50	0.22 ± 0.07	0.26 ± 0.11	N.S.
	60	0.19 ± 0.03	0.18 ± 0.02	N.S.
	70	0.17 ± 0.03	0.22 ± 0.08	N.S.
SN-38G	50	3.64 ± 1.21	0.74 ± 0.53	<0.01
	60	3.42 ± 0.98	0.64 ± 0.29	<0.01
	70	2.73 ± 0.88	0.62 ± 0.25	<0.01
CPT-11	50	3.55 ± 1.00	3.47 ± 1.21	N.S.
	60	3.74 ± 1.28	3.28 ± 1.33	N.S.
	70	2.94 ± 1.11	3.86 ± 2.00	N.S.

Table 3 Incidence of leucopenia (per cycle) possibly or probably related to CPT-11 administration

CPT-11 (mg/m^2)	Grade 1 No. (%)	Grade 2 No. (%)	Grade 3 No. (%)	Grade 4 No. (%)
50	6 (60)	1 (10)	2 (20)	0
60	3 (25)	3 (25)	2 (16.7)	1 (8.3)
70	1 (10)	3 (30)	2 (20)	0

CPT-11 and its active metabolite SN-38 induce non-specific gastrointestinal symptoms, especially diarrhea, which has been recognized as a dose-limiting factor [28]. It has been suggested that there are two different mechanisms by which CPT-11 induces acute (functional) and delayed diarrhea [29, 30]. It is assumed that acute diarrhea occurs not only due to inhibition of cholinesterase activity, resulting in cholinergic syndrome [29, 31], but also to activation of the 5-HT$_3$ receptor [32]. In other words, the cholinergic activity of CPT-11 stimulates intestinal contractility, disturbing normal intestinal mucosal absorptive and secretory functions [29, 32, 33]. On the other

Table 4 Incidence of non-hematologic adverse events (per cycle) possibly or probably related to CPT-11 administration

Adverse event	Frequency (%)	Patient No.	Dose of CPT-11 (mg/m^2)	Grade
		2	60, 70	1
Anorexia	18.8	4	50, 60	1
		9	60, 70	1
Diarrhea	3.1	13	60	1
Nausea	3.1	9	50	1
Alopecia	3.1	3	70	1
Interstitial pneumonia	3.1	5	70	2

hand, delayed diarrhea arises as a consequence of direct enteric injury by SN-38 and/or CPT-11 [30, 34].

Previous clinical reports have reported incidence rates of diarrhea due to CPT-11 of 62.9～87% [4, 6, 25]. However, only one patient developed acute diarrhea after administration of 70 mg/kg CPT-11 in our study, and his diarrhea was resolved without loperamide. Generally speaking, constipation occurs frequently in dialysis patients [35, 36], due to a number of possible causes, including restricted fluid intake, insufficient dietary fiber, disturbance of intestinal mucosal absorption and bowel movement, the side effects of drugs, and enforced physical inactivity. Among these, insufficient bowel movement due to disturbance of autonomic nerve function has been suggested to inhibit the mechanism that can lead to the onset of acute diarrhea with CPT-11. As a result, it is believed that diarrhea is unlikely to occur following administration of CPT-11 in dialysis patients. The patient in our study who did develop diarrhea had been on dialysis for only 2 months, and had had no episodes of constipation before administration of CPT-11. Hammer *et al.* noted that the duration of dialysis showed no significant influence on the prevalence of gastrointestinal symptoms, although a trend was found towards a higher prevalence in patients who were on dialysis for more than 8 months [37].

In conclusion, we found changes in drug disposition of CPT-11, SN-38 and SN-38G in patients on dialysis, suggesting that hepatic excretion was increased, especially that of SN-38G. In dialysis patients, there is the concern that anuresis may cause an increase in side effects. However, no increase in side effects was observed with an increase in SN-38G in this study, a finding which is of clinical importance. Moreover, no difference was observed in the incidence of side effects, especially leucopenia, between dialysis patients and non-dialysis patients, which suggests little or no enterohepatic circulation. In 10 out of 11 patients, leucopenia was resolved by conservative treatment. This indicates that CPT-11 can be administered safely in patients on dialysis.

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