

## Pharmacokinetic Assessment of Irinotecan, SN-38, and SN-38-Glucuronide: A Substudy of the FIRIS Study

TAROH SATOH<sup>1</sup>, HIROFUMI YASUI<sup>2</sup>, KEI MURO<sup>3</sup>, YOSHITO KOMATSU<sup>4</sup>, SHINICHI SAMESHIMA<sup>5</sup>, KENSEI YAMAGUCHI<sup>6</sup> and KENICHI SUGIHARA<sup>7</sup>

<sup>1</sup>Osaka University Graduate School of Medicine, Suita, Japan;

<sup>2</sup>Shizuoka Cancer Center, Shizuoka, Japan;

<sup>3</sup>Aichi Cancer Center Hospital, Nagoya, Japan;

<sup>4</sup>Hokkaido University Hospital Cancer Center, Sapporo, Japan;

<sup>5</sup>Dokkyo Medical University Koshigaya Hospital, Saitama, Japan;

<sup>6</sup>Saitama Cancer Center, Saitama, Japan;

<sup>7</sup>Tokyo Medical and Dental University, Tokyo, Japan

**Abstract.** *Background:* We evaluated the pharmacokinetics of irinotecan (CPT-11) and its metabolites in patients with metastatic colorectal cancer receiving the combination of CPT-11/S-1 (IRIS) or 5-fluorouracil (5-FU)/l-leucovorin (LV)/CPT-11 (FOLFIRI) regimens in the FIRIS trial. *Patients and Methods:* Serum CPT-11, SN-38 (an active metabolite of CPT-11), and SN-38-glucuronide concentrations were compared between the IRIS and FOLFIRI regimens, and between days 1 and 15 of administration. *Correlations* between pharmacokinetic data and incidence of neutropenia and diarrhea were also assessed. *Results:* There were no significant differences in the pharmacokinetics of CPT-11 or its metabolites between days 1 and 15. SN-38 concentrations were correlated with the occurrence of neutropenia, which was significantly more frequent in the FOLFIRI group than in the IRIS group. *Conclusion:* No alterations in CPT-11 pharmacokinetics after repeated IRIS or FOLFIRI administration were observed. Neutropenia was more frequent in the FOLFIRI group than in the IRIS group because exposure to SN-38 was greater in the former group.

The combination of 5-fluorouracil (5-FU)/l-leucovorin (LV) with either irinotecan (CPT-11) (FOLFIRI) or oxaliplatin

(FOLFOX) is established as first-line chemotherapy for metastatic colorectal cancer (mCRC). Initial treatment with FOLFOX followed by secondary FOLFIRI treatment, or *vice versa*, is currently recommended as the standard therapy (1, 2). However, neither long-term continuous intravenous infusion of 5-FU nor implantation of an intravenous port system for 5-FU infusion with FOLFOX or FOLFIRI is convenient. Therefore, some clinical trials have tested the viability of replacing 5-FU infusion with oral 5-FU derivatives.

S-1 is an oral 5-FU derivative anticancer agent, consisting of tegafur, 5-chloro-2,4-dihydropyrimidine (CDHP), and potassium oxonate. In this formulation, tegafur is a pro-drug of 5-FU; CDHP inhibits the 5-FU-degrading enzyme, dihydropyrimidine dehydrogenase, and maintains the blood concentration of 5-FU; and potassium oxonate is an orotate phosphoribosyltransferase inhibitor that reduces gastrointestinal toxicity. In Japan, phase II studies, consisting of CPT-11 plus S-1, combination therapy as first-line treatment for mCRC, achieved a response rate of 52.5-60% and median progression-free survival of 7.8-8.6 months (3-5). Based on these results, the FIRIS study was conducted to verify the non-inferiority of CPT-11/S-1 (IRIS) to FOLFIRI in patients with mCRC who failed first-line chemotherapy (6).

CPT-11 is an extremely important anticancer agent in the treatment of gastrointestinal cancer (7). Because CPT-11 and 5-FU have different mechanisms of action, several clinical trials have assessed the feasibility and safety profile of different combination therapies of CPT-11 and 5-FU (8, 9). However, the pharmacokinetics of CPT-11 show a high degree of interpatient variability, and some reports suggest that this variability may be due to genetic background or drug interactions (10, 11). In one study of weekly administration of CPT-11 in patients with mCRC, decreased

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*Correspondence to:* Taroh Satoh, MD, Department of Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan. Tel: +81 668792641, Fax: +81 668792639, e-mail: taroh@cfs.med.osaka-u.ac.jp

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mean maximum concentrations ( $C_{max}$ ) and areas under the curve (AUC) for SN-38 were observed in the plasma (12). In a case report, daily oral administration of S-1 markedly reduced the AUC of SN-38 (13). Finally, there is some indication that exposure to CPT-11 or SN-38 is related to the occurrence of neutropenia and diarrhea. Indeed, although the FIRIS trial verified that IRIS is not inferior to FOLFIRI as second-line chemotherapy for mCRC, the trial revealed differences in the adverse event profiles of the two regimens (6). Therefore, better understanding of the pharmacokinetics of these treatments is critical for optimal CPT-11-based chemotherapy.

The current study was undertaken as an additional component of the FIRIS study (6) to evaluate the pharmacokinetics of CPT-11, SN-38, and SN-38 glucuronide (SN-38G) on days 1 and 15. We evaluated the changes in the pharmacokinetics of CPT-11 and its metabolites during the IRIS and FOLFIRI treatment cycles, and we compared the relative exposure of patients in each group to these agents. We also attempted to re-confirm any correlation between drug exposure and the occurrence of neutropenia and diarrhea. This study is registered with ClinicalTrials.gov, number NCT00284258.

## Patients and Methods

**Patients.** The FIRIS study was an open-label, multicenter, randomized, phase II/III study of patients with second-line mCRC receiving either the IRIS or FOLFIRI treatment regimen (6). Of the 40 institutions participating in the FIRIS study, six participated in the present additional study. The inclusion and exclusion criteria were identical to those in the full FIRIS study (6).

The patients provided informed consent to participate in the main FIRIS study and to participate in the pharmacokinetic study before randomization. The protocol was approved by the Institutional Review Board and/or Ethics Committee of each institution.

**Treatments.** In accordance with the FIRIS study protocol, patients were centrally randomized to receive either the FOLFIRI or IRIS regimens using a minimization method, with stratification by institution, prior therapy (with or without oxaliplatin), and PS (0 or 1). The IRIS group received CPT-11 (125 mg/m<sup>2</sup>) intravenously on days 1 and 15, and S-1 (40-60 mg, based on body surface area) twice daily for two weeks from days 1 to 14, followed by two weeks of rest. This dosing regimen was selected on the basis of results from previous phase II studies (14, 15).

In the FOLFIRI group, patients received concurrent administration of LV (200 mg/m<sup>2</sup> over 120 min) and CPT-11 (150 mg/m<sup>2</sup>) followed by a bolus injection of 5-FU (400 mg/m<sup>2</sup>) on day 1 and subsequent continuous infusion of 5-FU (2,400 mg/m<sup>2</sup>) over 46 h, every two weeks (each 4-week cycle was considered a single course). The dose of CPT-11 used in the FOLFIRI group (150 mg/m<sup>2</sup>) is an approved clinical dose in Japan (16).

**Sample collection.** For the pharmacokinetic studies, blood samples (3 ml) were collected on days 1 and 15 in tubes containing sodium

heparin anticoagulant. Samples were obtained before CPT-11 administration and at specific intervals (1, 1.5, 2, 2.5, 3.5, 5.5, 8.5, and 24 h) after starting CPT-11 infusion. All blood samples were stored in an ice bath until the plasma was prepared, and they were centrifuged within 30 min of sample collection. The supernatant was collected as the plasma sample and stored at -20°C until analysis.

**Analytical methods.** Plasma samples for CPT-11 and its metabolites were analyzed at Sekisui Medical Co., Ltd. (Naka-gun, Ibaraki, Japan), using liquid chromatography with fluorescence detection. Plasma concentrations of CPT-11, SN-38, and SN-38G were determined as previously described, with some minor modifications (17). This method was fully validated by Sekisui Medical Co., with quality-control procedures and acceptance criteria based on requirements described by Shah *et al.* (18) and the FDA Guidance for Industry (19). Camptothecin was used as the internal standard.

**Pharmacokinetic analyses.** Profiles of plasma concentration *versus* time for CPT-11, SN-38, and SN-38G were obtained for each patient, and standard pharmacokinetic parameters were calculated using non-compartmental methods with WinNonlin v5.2 software (Pharsight Corporation, Mountain View, CA, USA). Total AUC was calculated by adding the AUC<sub>0-24</sub> values on days 1 and 15 for each compound to evaluate the correlation between total AUC values of CPT-11, SN-38, or SN-38G and the occurrence of neutropenia or diarrhoea.

**Efficacy and safety assessment.** In accordance with the FIRIS study protocol, physical examinations, electrocardiography, performance status (PS), and laboratory tests were performed at baseline and repeated at least every two weeks during treatment. Tumours were assessed at baseline (within one month before enrolment); at two, three, and four months after enrolment; and every two months thereafter until progression. Progression was defined as the occurrence of any of the following three events: (i) progressive disease based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 (20); (ii) clinical progression as judged by the investigator; or (iii) death from any cause without progression. Toxicity was evaluated based on the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) (21).

**Statistical analysis.** Summary statistics, such as mean and standard deviation calculations, were performed for all pharmacokinetic parameters for both treatment groups on days 1 and 15. The time-dependent alterations in the pharmacokinetics of CPT-11 and its metabolites after repeated administration were evaluated by applying paired *t*-tests to log-transformed means for each pharmacokinetic parameter (excluding  $t_{max}$ ) in each treatment group (CPT-11, SN-38, and SN-38G) to compare data between days 1 and 15. Differences in  $t_{max}$  between days 1 and 15 were evaluated using the Wilcoxon rank test for paired data. Exposure to CPT-11, SN-38, and SN-38G were compared between the two treatments using Student's *t*-test with log-transformed total AUC values for each compound. To evaluate the correlation between total AUC of CPT-11, SN-38, or SN-38G and the occurrence of neutropenia or diarrhea, log-transformed total AUCs for each compound for patients with and without adverse events were compared using Student's *t*-test. A *p*-value of  $\leq 0.05$  was considered statistically significant. Data storage and statistical analyses were carried out using SAS v8.02 software (Cary, NC, USA).

Table I. Pharmacokinetic profiles of irinotecan (CPT-11), SN-38, and SN-38 glucuronide (SN-38G) on days 1 and 15 in the IRIS and FOLFIRI treatment groups.

	CPT-11		SN-38		SN-38G	
	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15
<b>IRIS</b>						
C <sub>max</sub> (ng/ml)	1844±584	1631±246	17.96±4.78	19.09±9.36	87.25±46.12	103.39±71
AUC <sub>0-24</sub> (ng h/ml)	9813±2528	9940±1440	145.7±33.4	159±53.8	1031.1±646.3	1273.1±884.2
t <sub>1/2</sub> (h)	6.63±0.83	6.74±1.03	13.7±1.95	13.69±3.42	13.18±2.72	13.1±3.55
t <sub>max</sub> (h)	1.4±0.2	1.5±0	1.7±0.5	1.8±0.4	2.5±0.5	3.2±0.5
MRT (h)	6.98±1.1	7.37±1.22	16.56±3.07	17.3±4.6	18.02±3.94	18.41±5.09
CL (l/h/m <sup>2</sup> )	12.5±2.9	11.9±1.8	–	–	–	–
VD <sub>ss</sub> (l/m <sup>2</sup> )	86.2±20.4	86.8±16.4	–	–	–	–
<b>FOLFIRI</b>						
C <sub>max</sub> (ng/ml)	2079±461	2175±488	36.03±11.59	33.61±13.79	99.14±30.74	94.44±29.67
AUC <sub>0-24</sub> (ng h/ml)	11037±1775	11239±1912	269.4±102.5	249±86.8	982.9±304.6	974.2±264.2
t <sub>1/2</sub> (h)	6.2±0.72	5.96±0.47	11.02±1.74	12.24±2.2	10.93±2.13	11.79±3.19
t <sub>max</sub> (h)	1.6±0.3	1.5±0	2.3±0.5	2.1±0.7	2.5±0.5	2.5±0.5
MRT (h)	6.44±0.89	6.31±0.53	13.05±1.68	14.98±2.78	14.58±3.07	16.07±4.48
CL (l/h/m <sup>2</sup> )	13.3±3	13.1±2.6	–	–	–	–
VD <sub>ss</sub> (l/m <sup>2</sup> )	84±14.1	81.8±14	–	–	–	–

IRIS, Irinotecan/S-1; FOLFIRI, 5-fluorouracil/l-leucovorin/irinotecan; C<sub>max</sub>, maximum concentration; AUC, area under the curve; t<sub>1/2</sub>, half-time; t<sub>max</sub>, time taken to reach maximum concentration; MRT, mean residence time from 0 to infinity; CL, plasma clearance; VD<sub>ss</sub>, apparent volume of distribution at steady state.

## Results

**Patients' characteristics.** Among the 426 patients enrolled in the FIRIS study, 18 patients were enrolled in this pharmacokinetic study from May 2007 to January 2008. Six patients (five males and one female) were enrolled into the IRIS group and 12 patients (five males and seven females) to the FOLFIRI group. The median age was 59 years (range=46-72 years) and 57 years (range=41-73 years), respectively. Four and 2 patients in the IRIS group and 10 and two patients in the FOLFIRI group had an Eastern Cooperative Oncology Group (ECOG) PS of 0 and 1, respectively. Four patients in the IRIS group and 6 in the FOLFIRI group had received previous chemotherapy with oxaliplatin. There were no obvious differences in patient characteristics between the patients enrolled in the FIRIS study (6) and those enrolled in this pharmacokinetic study. All of the patients enrolled in the present study were treated in accordance with the FIRIS study protocol (6).

**Pharmacokinetic analysis of CPT-11, SN-38, and SN-38G in the IRIS regimen.** Following treatment with the IRIS regimen, we recorded the mean plasma concentration–time profiles of CPT-11, SN-38, and SN-38G on days 1 and 15 (Figure 1) and the pharmacokinetic parameters of CPT-11, SN-38, and SN-38G every day (Table I). No statistically significant differences were detected in any of the

pharmacokinetic parameters for CPT-11, SN-38 and SN-38G between days 1 and 15. These results suggest that the extent of plasma exposure of CPT-11, SN-38, and SN-38G was not affected by repeated administration of S-1 and CPT-11 in patients with mCRC.

**Pharmacokinetic analysis of CPT-11, SN-38, and SN-38G in the FOLFIRI regimen.** Following treatment with the FOLFIRI regimen, we recorded the mean plasma concentration–time profiles of CPT-11, SN-38, and SN-38G on days 1 and 15 (Figure 2) and the pharmacokinetic parameters of CPT-11, SN-38, and SN-38G every day (Table I). No statistically significant differences were detected in any of the pharmacokinetic parameters for CPT-11, SN-38, and SN-38G between days 1 and 15. These results suggest that the plasma exposure of CPT-11, SN-38, and SN-38G was unchanged during the course of the study.

**Comparison of exposure to CPT-11, SN-38, and SN-38G between the IRIS and FOLFIRI regimens.** Figure 3 shows the total AUCs (*i.e.* the total exposure to each compound during one treatment cycle) for CPT-11, SN-38, and SN-38G following the IRIS and FOLFIRI regimens. Although there were no significant differences in the total AUC values for CPT-11 and SN-38G between the two treatment regimens, the total AUC value for SN-38 (an active metabolite of CPT-11) was significantly greater in the FOLFIRI regimen than in the IRIS regimen.

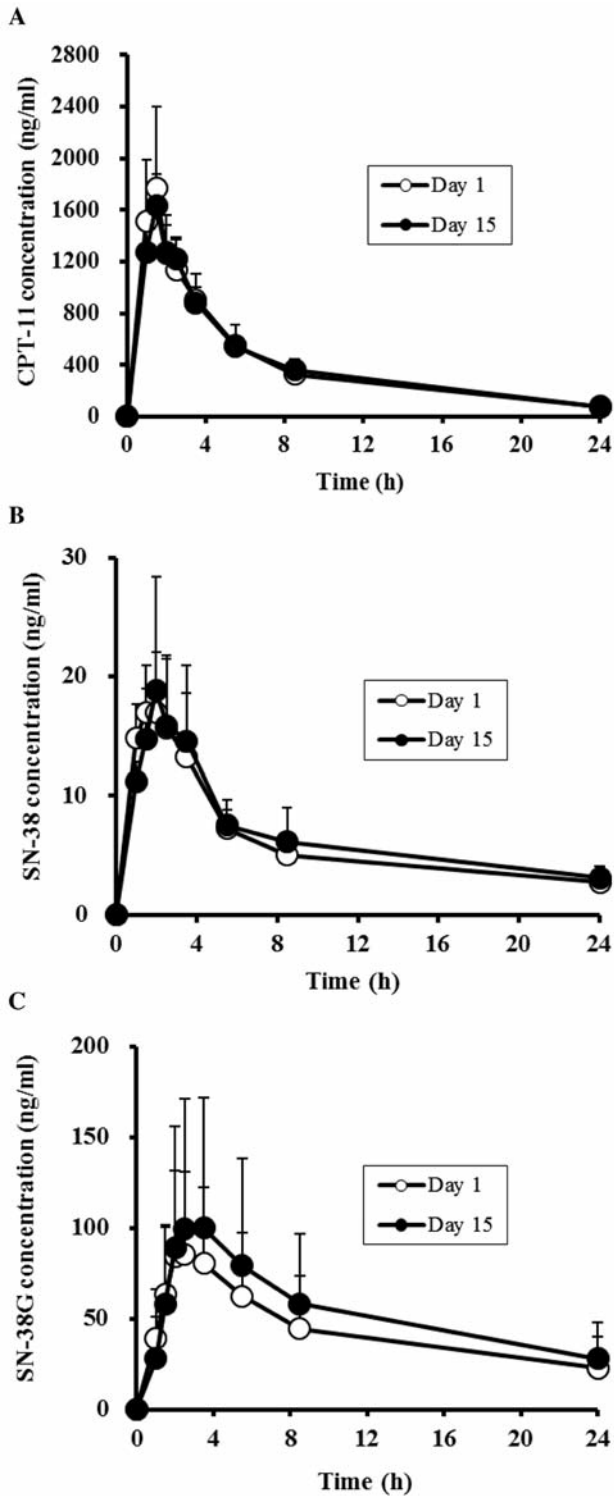


Figure 1. Mean plasma concentration–time profiles of irinotecan (CPT-11) (A), SN-38 (B), and SN-38G (C) after a 2-h intravenous infusion of CPT-11 on days 1 and 15 in the CPT-11/S-1 (IRIS) treatment group. Day 1: S-1 was orally administered 7 h after starting CPT-11 infusion. Day 15: S-1 was administered twice daily from day 1 and simultaneously administered at the start of CPT-11 infusion on day 15. Each point represents the mean±SD of six patients.

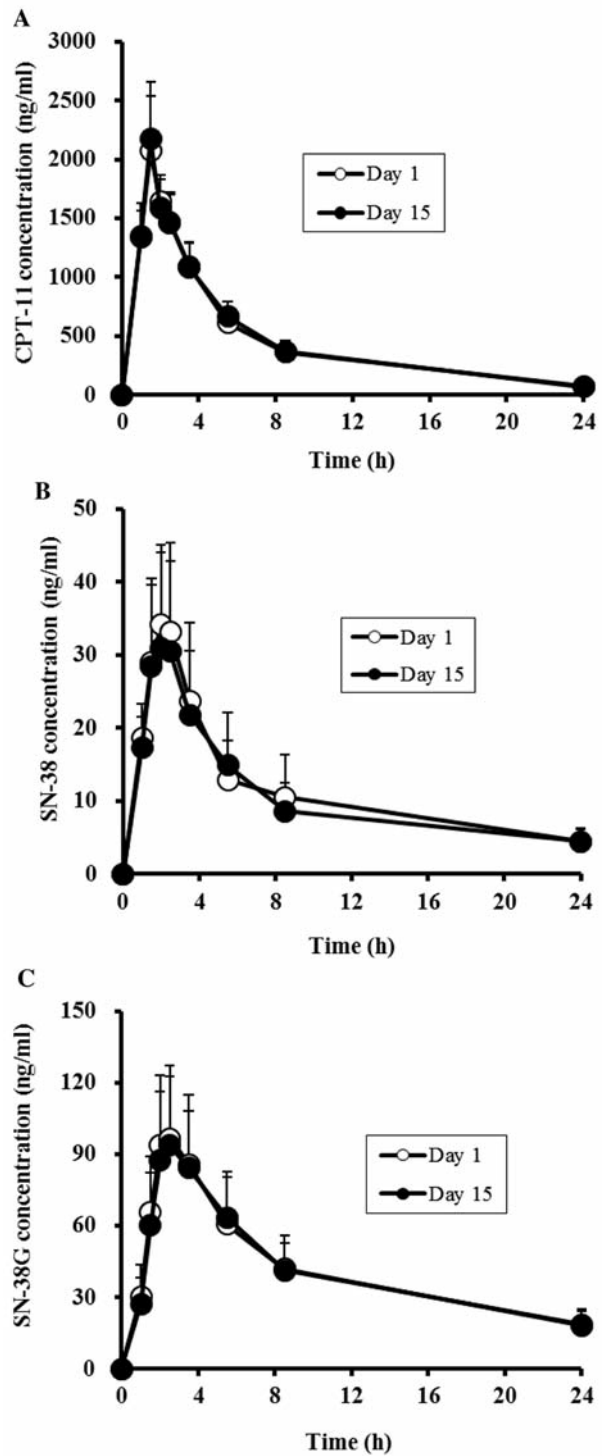


Figure 2. Mean plasma concentration–time profiles of irinotecan (CPT-11) (A), SN-38 (B), and SN-38G (C) after a 2-h intravenous infusion of CPT-11 on days 1 and 15 in the 5-fluorouracil (FU)/l-leucovorin (LV)/CPT-11 (FOLFIRI) treatment group. The patients received concurrent administration of CPT-11 (150 mg/m<sup>2</sup>) and LV (2,000 mg/m<sup>2</sup>) over 90 and 120 min, respectively, followed by a bolus injection of 5-FU (400 mg/m<sup>2</sup>) and continuous infusion of 5-FU (2,400 mg/m<sup>2</sup>) over 46 h on days 1 and 15.

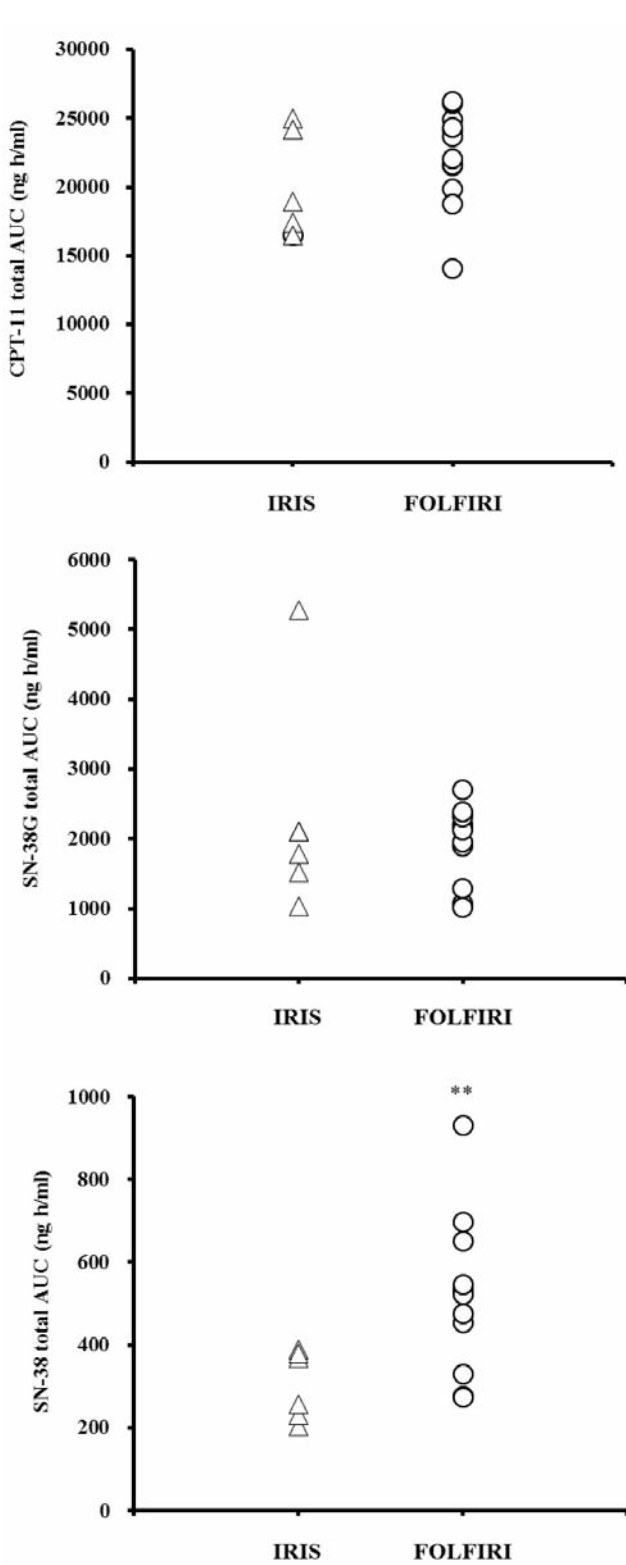


Figure 3. Comparison of the total area under the curve (AUC) values of irinotecan (CPT-11), SN-38, and SN-38G (sum of the AUCs on days 1 and 15) between CPT-11/S-1 (IRIS) and 5-fluorouracil/l-leucovorin/CPT-11 (FOLFIRI) regimens. \*\* $p < 0.01$ , IRIS vs. FOLFIRI.

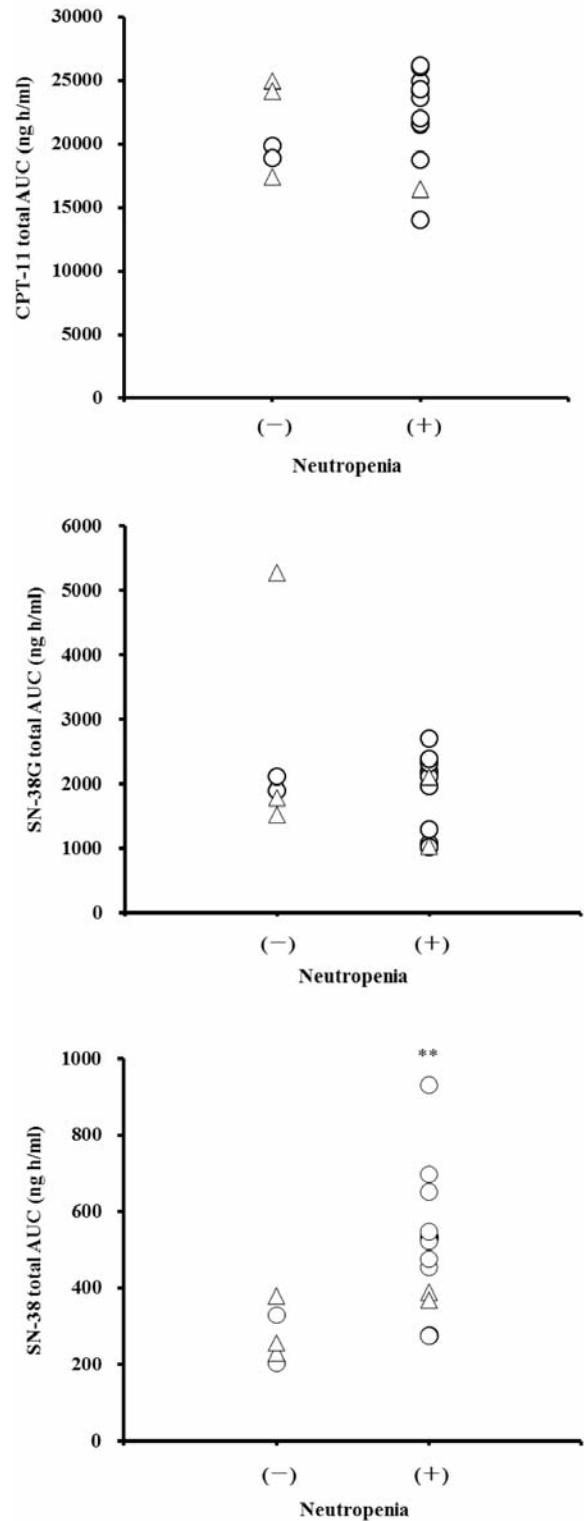


Figure 4. Correlations between the total area under the curve (AUC) values of irinotecan (CPT-11) (A), SN-38 (B), and SN-38G (C) (sum of the AUCs on days 1 and 15) and the occurrence of neutropenia in patients treated with 5-fluorouracil/l-leucovorin/CPT-11 (FOLFIRI) and CPT-11/S-1 (IRIS) regimens. \* $p < 0.01$ , patients without neutropenia (-) vs. with neutropenia (+).

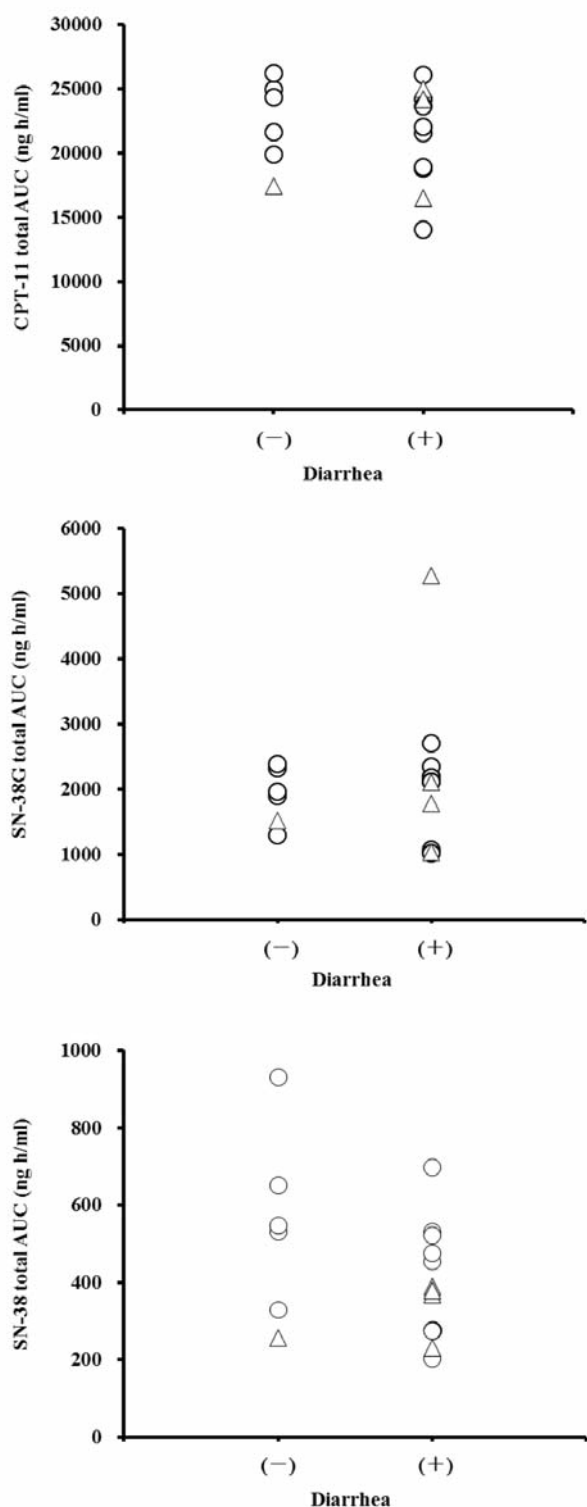


Figure 5. Correlations between the total area under the curve (AUC) values of irinotecan (CPT-11) (A), SN-38 (B), and SN-38G (C) (sum of AUC on days 1 and 15) and the occurrence of diarrhea in the 5-fluorouracil/l-leucovorin/CPT-11 (FOLFIRI) and CPT-11/S-1 (IRIS) regimens. There were no significant differences in the total AUC values between patients without diarrhea (-) or with diarrhea (+).

**Efficacy and safety.** Overall, 17 patients were included in efficacy evaluations, and 18 patients were included in safety evaluations. Partial responses were seen in 3/6 patients in the IRIS group and in 3/11 patients in the FOLFIRI group. Common non-haematological toxicities in the IRIS and FOLFIRI groups included all-grade diarrhea (83.3% vs. 66.7%), anorexia (83.3% vs. 75.0%), and nausea (50.0% vs. 83.3%), with no grade 4 toxicities in either group. Common haematological toxicities in the IRIS and FOLFIRI groups included all-grade neutropenia (33.3% vs. 100.0%), anaemia (100.0% vs. 66.7%), and thrombocytopenia (66.7% vs. 25.0%). The incidence of adverse events in each group was not markedly different from that in the previous report (6).

**Pharmacokinetic/pharmacodynamic analyses.** Figure 4 shows the total AUC values for CPT-11, SN-38, and SN-38G and the occurrence of neutropenia. The total AUC of SN-38 was significantly higher in patients experiencing neutropenia than in those who did not. However, the total AUC of CPT-11 and SN-38G did not correlate with the occurrence of neutropenia. In contrast, the total AUCs of CPT-11, SN-38, and SN-38G were not correlated with the occurrence of diarrhea (Figure 5).

**Discussion**

Combination chemotherapies based on infused 5-FU are standard first- and second-line treatments for mCRC. Several clinical trials have assessed the feasibility and safety profile of different combinations of CPT-11 and 5-FU (8, 9). FOLFIRI is a standard first- or second-line regimen for advanced colorectal cancer, with published response rates ranging from 40% to 50%, and is widely used for mCRC (2). In Japan, the non-inferiority of IRIS to FOLFIRI as a second-line chemotherapy for mCRC was verified in the FIRIS study, a phase II/III randomized study (6). Thereafter, in the ESMO Consensus Guidelines for management of patients with colon and rectal cancer, IRIS is listed in the table of the treatment options (22)

The pharmacokinetic profiles of CPT-11 and SN-38 are very complex because of the existence of multiple biotransformation and elimination pathways involving various enzymes (23) and transporters (24-26). Genetic factors, such as uridine diphosphate glucuronyltransferase 1A1 (*UGT1A1*) polymorphisms, also affect their profiles (27-30). Patients treated with CPT-11 occasionally experience severe neutropenia and delayed diarrhea. However, there is marked interpatient variability in the degree of toxicity because of pharmacokinetic variations in CPT-11, SN-38, and SN-38G arising from differential biological backgrounds. Furthermore, pharmacokinetic changes of CPT-11 and its metabolites during the treatment cycle have been reported. For example, Rothenberg *et al.* reported that the  $C_{max}$  and  $AUC_{0-24}$  of SN-

38 achieved with a fixed weekly dose of CPT-11 monotherapy were lower in week 3 than in week 1 in colorectal cancer patients in a phase II study, which suggests that weekly administration of CPT-11 affects the pharmacokinetics of SN-38 (12). Furthermore, Yokoo *et al.* reported that repeated administration of S-1 reduced the plasma concentration of SN-38 on day 7 (13). Thus, it is particularly important to evaluate the pharmacokinetic profiles of CPT-11, SN-38, and SN-38G during the treatment cycle because they may be related to the occurrence of adverse events.

To assess the pharmacokinetic profiles of CPT-11, SN-38, and SN-38G within the treatment cycles of the IRIS and FOLFIRI regimens, we performed a pharmacokinetic study of CPT-11 on days 1 and 15. We found no significant differences in the pharmacokinetic parameters of CPT-11, SN-38, and SN-38G between days 1 and 15 with either regimen. Rothenberg *et al.* (12) reported that weekly CPT-11 monotherapy resulted in a decrease in the plasma concentration of SN-38, but we found no differences in the pharmacokinetics of CPT-11, SN-38, and SN-38G after repeated administration of CPT-11 as part of the IRIS or FOLFIRI regimens in this study. Moreover, the results observed in the IRIS group suggest that repeated administration of S-1 did not affect the pharmacokinetics of CPT-11, SN-38, or SN-38G. The conversion of CPT-11 to SN-38 is catalysed by a carboxylesterase and leads to a reduction in the AUC of SN-38. It has also been proposed that the 5-FU metabolite, fluorouracil, inhibits the activity of this enzyme (10). Because S-1 contains CDHP, which inhibits 5-FU degradation, no such inhibition occurs, and the plasma concentrations of CPT-11, SN-38, and SN-38G are unlikely to change after repeated administration of S-1. However, the results of repeated administration in this study differ from those reported by Yokoo *et al.* (13), casting doubt on the validity of this hypothesis.

We also compared the exposure to CPT-11, SN-38, and SN-38G between the IRIS and FOLFIRI regimens. Although there were no significant differences in the total AUC values of CPT-11 and SN-38G between the IRIS and FOLFIRI groups, the exposure to SN-38 was significantly higher in the FOLFIRI group than in the IRIS group. This may be attributed to differences in the dose of CPT-11 (150 mg/m<sup>2</sup> in the FOLFIRI group and 125 mg/m<sup>2</sup> in the IRIS regimen) or to differences in the genetic background of metabolic enzymes (*e.g.*, UGT1A1) between the IRIS and FOLFIRI groups, although we could not confirm the reasons for this in the present study. With regard to adverse events, the incidence of neutropenia tended to be higher in the FOLFIRI group while the incidence of diarrhea tended to be higher in the IRIS group. Moreover, from the results of the pharmacokinetic/pharmacodynamic analysis, patients experiencing neutropenia in this study showed significantly higher exposure to SN-38 (but not to CPT-11 and SN-38G) than those who did not experience neutropenia. These

results are consistent with previous reports suggesting that SN-38 exposure is associated with haematological toxicity (31-33). In contrast, despite reports suggesting a correlation between the occurrence of diarrhea and exposure to CPT-11 or SN-38, we found no evidence of any correlation between diarrhea and CPT-11, SN-38, or SN-38G exposure in this study.

The present study has some limitations, and these preclude a definitive conclusion. Firstly, the sample size was too small to evaluate the pharmacokinetic profile. Secondly, there were imbalances in the sample size and sex ratio between the two groups because participation in this additional study was not a stratification factor. Thirdly, *UGT1A1* genetic polymorphisms, which are important in interpreting the pharmacokinetic profile of CPT-11, were not determined in the present study.

## Conclusion

We observed no time-dependent changes in the pharmacokinetics of CPT-11, SN-38, and SN-38G during treatment cycles, nor did we observe any clinically important effects of repeated administration of S-1 on the pharmacokinetics of CPT-11 and its metabolites in the IRIS group. However, our data suggest that the greater exposure to SN-38 in the FOLFIRI group was associated with a higher incidence of neutropenia in that group compared with the IRIS group.

## Conflicts of interest

The Authors declare that they have no conflicts of interest to disclose.

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