

Effects of oral administered S-1 on the pharmacokinetics of SN-38, irinotecan active metabolite, in patients with advanced colorectal cancer

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ABSTRACT

Previous studies have assessed the efficacy and safety of combined treatment with irinotecan (CPT-11) and S-1, containing tegafur, a prodrug of 5-FU, in the treatment of colorectal and gastric cancer. The objective of this study was to describe the interaction between CPT-11 and S-1 in four patients with colorectal cancer. Coadministration of S-1 changed the pharmacokinetic behavior of CPT-11 and its metabolites. In particular, maximum plasma concentration and area under the plasma concentration curve (AUC) of SN-38 was markedly decreased by coadministration of S-1 ($P < 0.05$). For SN-38, the ratio of AUC with S-1 to AUC without S-1 was 0.51 ± 0.20 (mean \pm S.D.). A significant difference in drug interaction among individual patients was observed ($P < 0.05$). We conclude that the plasma concentration of SN-38 was decreased by oral administration of S-1 in patients with colorectal cancer. This observation might be important for clinical decisions regarding combination therapy.

INTRODUCTION

Irinotecan (CPT-11, 7-ethyl-10-[4-[1-piperidino]-1-piperidino]carbonyloxy-camptothecin), an inhibitor of DNA topoisomerase I, is an important chemotherapy agent, particularly for colorectal and small-cell lung cancers.^{1,2} The active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), is enzymatically formed from CPT-11 by hepatic carboxylesterases (CES).³ *In vitro* studies suggest that SN-38 is 100 to 1,000 times more potent than the parent compound, CPT-11.⁴ SN-38 is subsequently conjugated in the liver by uridine diphosphate glucuronosyltransferase (UGT)1A, forming the inactive metabolite SN-38 glucuronide (SN-38G).⁵ CPT-11, SN-38, and SN-38G are excreted into the bile and urine. The biliary excreted SN-38G is deconjugated by bacterial β -glucuronidases in the intestinal lumen.⁶ Furthermore, some of the biliary CPT-11, SN-38, and SN-38G is reabsorbed from the intestinal lumen, forming an enterohepatic recirculation loop. CPT-11 and its metabolites are excreted by the efflux transporters P-glycoprotein (P-gp/ABCB1), multidrug resistance-associated protein 2 (MRP2/ABCC2), and breast cancer resistance protein (BCRP/ABCG2), via a hepatobiliary pathway.^{7,8} These complicated metabolic profiles of CPT-11 are likely to result in inter-individual variability in the pharmacokinetics and pharmacodynamics of this drug.⁹

Recently the safety and efficacy of combination therapy with CPT-11 and S-1, which is an oral anticancer agent comprised of tegafur, a prodrug of 5-fluorouracil (5-FU), gimeracil

and potassium oxonate, were investigated in Japanese patients with colorectal cancer.^{10,11}

Moreover, we have reported that coadministration of S-1 decreased plasma concentration of the active metabolite SN-38 in colorectal cancer patient and rats.^{12,13} We herein examined the effect of oral coadministration of S-1 on the pharmacokinetic profiles of CPT-11, SN-38, and SN-38G in four patients with advanced colorectal cancer.

METHODS

Patients

Four patients with advanced colorectal cancer were enrolled in this study. Patient characteristics are summarized in Table 1. This study was approved by the institutional review board of Kumamoto University Hospital. Informed consent was obtained from each patient.

Pharmacokinetics Analysis

The present study was performed 2 weeks later after the previous treatment. Irinotecan was given before the consecutive administration of S-1. Furthermore, we started administration of S-1 about 1 week later after administration of irinotecan. In the last day of administration of S-1, irinotecan was administered. S-1 was orally administered at a dose of 100 or 120 mg/m²/day for 4 to 7 consecutive days. CPT-11 was administered as a 90-minute intravenous infusion at a dose of 100 to 200 mg/m². Blood samples were obtained at 30 and 90 minutes after the start of infusion, and periodically after the end of CPT-11 infusion from

the arm opposite the injection site and collected in tubes containing ethylene diamine tetra-acetic acid as an anticoagulant. These samples were immediately centrifuged at 1000 g for 5 min, and the resulting plasma specimens were stored at -80°C until analysis. The plasma concentration of CPT-11 and its metabolites was determined by high-performance liquid chromatography, as reported previously.¹⁴ There was a linear relationship between area under the curves (AUC) of irinotecan and irinotecan doses (<350mg/m²).¹⁵ Accordingly, Plasma concentrations were corrected to a CPT-11 dose of 100 mg/m². The pharmacokinetic parameters for CPT-11 and its metabolites were derived by noncompartmental methods using WinNonlin version 3.1 software (Pharsight, Cary, NC). AUC was calculated by the linear trapezoidal rule from 0 to 24 hours.

Statistical Analysis

Differences were analyzed statistically using Student's t-test and two-way ANOVA.

A value of $P < 0.05$ was considered significant.

RESULTS

Figure 1 shows the plasma concentration-time profiles of CPT-11, SN-38, and SN-38G with or without S-1, corrected to a CPT-11 dose of 100 mg/m² in the four patients with colorectal cancer. Coadministration of S-1 did not significantly affect the pharmacokinetic behavior of CPT-11 and SN-38G, but it reduced the concentration of SN-38

by approximately 50% ($P < 0.05$). Corrected mean AUCs ($\text{ng}\cdot\text{hr}/\text{mL}$) were as follows (without S-1 vs. with S-1): CPT-11: 8731.7 ± 3934.0 vs. 7491.4 ± 4284.2 ; SN-38: 186.9 ± 166.0 vs. 71.9 ± 26.6 ; SN-38G: 1663.1 ± 1518.2 vs. 2123.3 ± 3113.4 . Furthermore, coadministration of S-1 resulted in a remarkable decrease in the corrected C_{max} of SN-38 (20.7 ± 8.7 ng/mL (without S-1) vs. 7.4 ± 2.1 ng/mL (with S-1); $P < 0.05$). However, coadministration of S-1 did not significantly change C_{max} of CPT-11 or SN-38G.

Figure 2 shows the ratio of AUC with S-1 to AUC without S-1 for CPT-11 (0.84 ± 0.15), SN-38 (0.51 ± 0.20), and SN-38G (0.74 ± 0.25). Significant differences in this drug interaction were observed among individual patients ($P < 0.05$, two-way ANOVA).

DISCUSSION AND CONCLUSION

The efficacy of combination therapy with CPT-11 and S-1 has been widely recognized.^{10, 11} However, the literature contains little information on the pharmacokinetics of this combination therapy. This information could be useful to allow clinicians to evaluate combination chemotherapy based on pharmacological properties.

The present results show that coadministration of S-1 changes the pharmacokinetic behaviors of CPT-11 and its metabolites in colorectal cancer patients. In particular, coadministration of S-1 significantly decreased plasma concentration of SN-38. We previously reported that, in rats, the mechanism of drug interaction between CPT-11 and S-1

involved up-regulation of BCRP in the liver, resulting in an increased rate of biliary excretion of SN-38 accompanied by a decrease in the C_{max} and AUC of SN-38.¹³ There are few previous reports of drug-related regulation of BCRP protein levels in vivo. Aryl hydrocarbon receptor agonists and progesterone were found to significantly increase the level of BCRP protein in vitro.^{15, 16} However, the relation between the components of S-1 and these mechanisms is not known. BCRP-mediated biliary excretion of SN-38 might be involved in the mechanism(s) for drug interaction between S-1 and CPT-11 in human. Previous studies have shown that the plasma concentration and AUC of SN-38 declined during combination therapy with CPT-11 and 5-FU, compared with isolated administration of CPT-11, in colorectal cancer patients¹⁸ and rats.¹⁹ It was hypothesized that administration of 5-FU inhibits the enzymatic hydrolysis of CPT-11 to SN-38 by CES. However, we previously reported that the hydrolysis of *p*-NPA, a substrate of CES, was not inhibited by tegafur, gimeracil, potassium oxonate, and 5-FU.¹³ Furthermore, oral administration of S-1 did not affect the hydrolysis of CPT-11 to SN-38 in rat liver microsomes. Therefore, inhibition of hydrolysis by coadministration of S-1 could not be responsible for the altered pharmacokinetics of CPT-11 and its metabolites. SN-38 is conjugated with glucuronic acid by UGT1A to form the inactive metabolite SN-38G. A decrease in the AUC of SN-38 could be caused by increased activity of UGT1A related to coadministration of S-1. However, we found that the plasma concentration of SN-38G did not vary with coadministration of S-1, suggesting that increased UGT1A activity was not

responsible for the decrease in AUC of SN-38.

The piperidine ring of CPT-11 is oxidized to inactive metabolites 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]carbonyloxycamptothecin (APC) or 7-ethyl-10-(4-amino-1-piperidino)carbonyloxycamptothecin (NPC) by cytochrome P450 (CYP)3A4 and CYP3A5.²⁰ Accordingly, CYP3A might cause this drug interaction. However, APC and NPC formation from CPT-11 was not detected (data not shown), suggesting that S-1 had no effect on CYP3A. In this study, we showed that coadministration of S-1 decreased the plasma concentration of SN-38 in four colorectal cancer patients. These findings might be helpful for further optimizing the dosing schedule of CPT-11 with S-1 for cancer patients, based on pharmacokinetic data.

ABBREVIATIONS

APC, 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]carbonyloxycamptothecin; AUC, area under the plasma concentration curve; BCRP, breast cancer resistance protein; CES, carboxylesterase; C_{max} , maximum plasma concentration; CPT-11, 7-ethyl-10-[4-[1-piperidino]-1-piperidino]carbonyloxycamptothecin; CYP, cytochrome P450; NPC, 7-ethyl-10-(4-amino-1-piperidino)carbonyloxycamptothecin; MRP2, multidrug resistance-associated protein 2; P-gp, P-glycoprotein; SN-38, 7-ethyl-10-hydroxycamptothecin; SN-38G, SN-38 glucuronide; UGT, uridine diphosphate glucuronosyltransferase. 5-FU, 5-fluorouracil.

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LEGENDS FOR FIGURES

Fig. 1. Plasma concentration-time profiles of CPT-11 (A), SN-38 (B), and SN-38G (C) with (closed circle) or without S-1 (open circle) from four colorectal cancer patients who received CPT-11 at 100 to 200 mg/m² as a 90-min intravenous infusion. Plasma concentrations were corrected to a CPT-11 dose of 100 mg/m². All data are expressed as mean ± S.D. *P<0.05, significant difference from without S-1 at the same point (Student's t-test).

Fig. 2. The ratio of AUC with S-1 to AUC without S-1 for CPT-11, SN-38, and SN-38G in each patient (circle, square, triangle, lozenge) and average (horizontal bar).

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

Table 1. Characteristics of the four patients

	Case 1	Case 2	Case 3	Case 4
Gender	Male	Female	Female	Male
Age (Years)	62	70	70	65
Disease state	stage 4	stage 4	stage 4	stage 4
Previous treatment	Surgery	Surgery	Surgery	Surgery
	5-FU	CPT-11	CPT-11	CPT-11
	CPT-11			
	Cisplatin/5-FU			
Dose of CPT-11 (mg/m²)	100	100	200	150
Dose of S-1 (mg/m²/day)	120	100	100	120

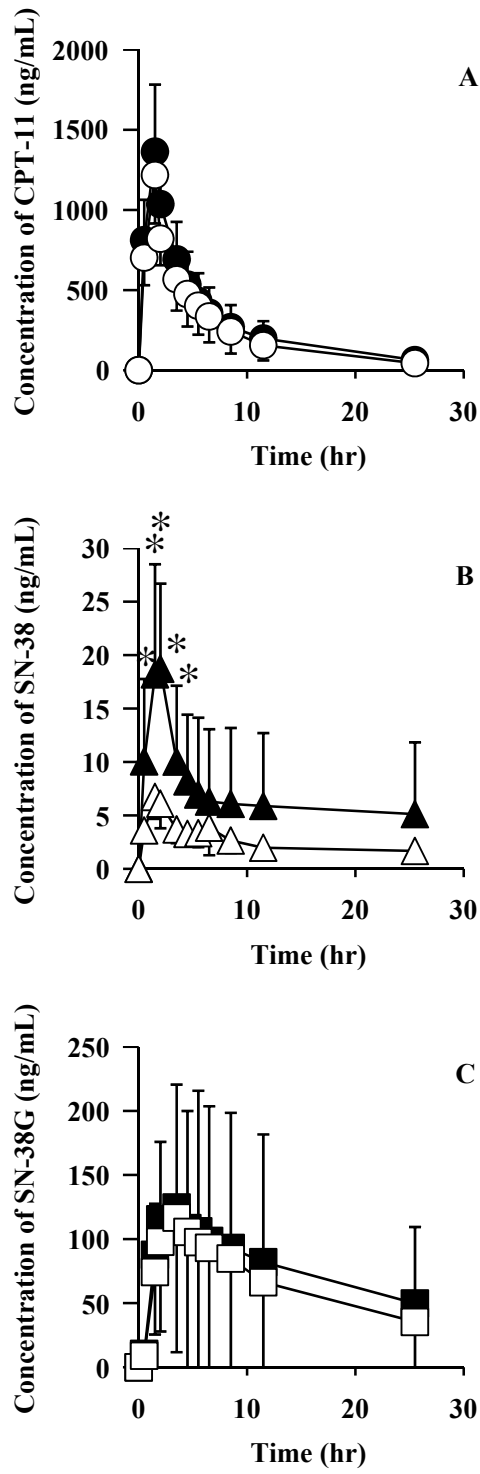


Figure. 1

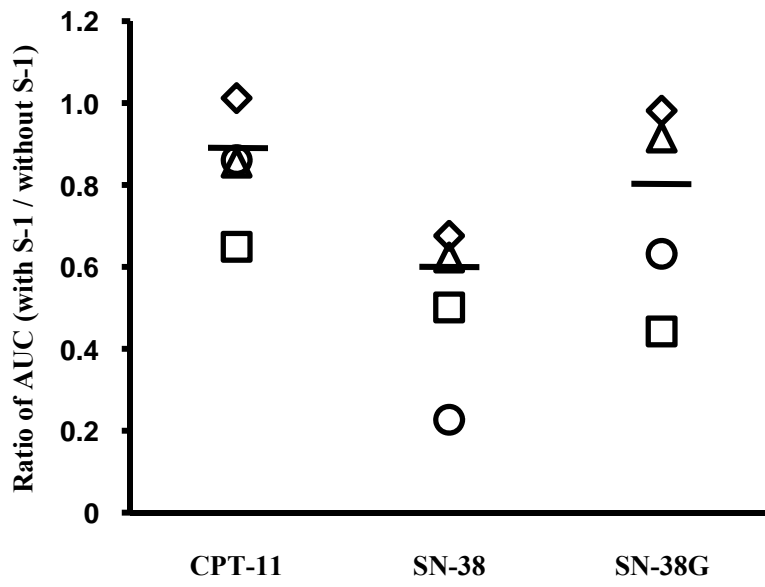


Figure. 2