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Short Communication

Delayed Elimination of SN-38 in Cancer Patients with Severe Renal Failure

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ABSTRACT:

This prospective study is designed to examine the effects of severe renal failure on the pharmacokinetics of irinotecan. The pharmacokinetics of irinotecan, 7-ethyl-10-hydroxycamptothecin (SN-38), and SN-38 glucuronide (SN-38G) in three cancer patients with severe renal failure [creatinine clearance (Ccr) ≤20 ml/min] who were undergoing dialysis and received 100 mg/m^2 irinotecan as monotherapy were prospectively compared with those in five cancer patients with normal renal function (Ccr ≥60 ml/min). To ensure that the subjects had similar genetic backgrounds of *UDP-glucuronosyltransferase* (*UGT*) *1A1*, patients with *UGT1A1*1/*1*, **1/*6*, or **1/*28* were enrolled. The estimated terminal elimination rate constant of SN-38 in patients undergoing dialysis was approximately one tenth of that in patients with normal renal function (P = 0.025). Approximately 50% of SN-38 was dialyzed with a 2.1-m^2 dialysis membrane, whereas 27% was dialyzed with a 1.5-m^2 membrane. Our results showed that the elimination of SN-38 was significantly delayed in patients with severe renal failure compared with patients with normal renal function. We demonstrated that SN-38 was partly dialyzed.

Introduction

Several lines of evidence have demonstrated that severe renal failure differentially affects drug uptake or efflux transporters and drug-metabolizing enzymes in the liver. Even drugs that are predominantly eliminated by hepatic transport and metabolism can be affected by severe renal failure, leading to unexpected consequences, such as atypical pharmacokinetics and an increased risk of adverse drug reactions. High levels of uremic toxins in such patients are partially implicated in these effects (Nolin et al., 2008).

Irinotecan is extensively metabolized in the liver to an active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), by carboxylesterase, which is then conjugated predominantly by liver UDP-glucuronosyltransferase (UGT) 1A1 to form inactive SN-38 glucuronide (SN-38G) (chemical structures; http://www.pharmgkb.org/search/pathway/irinotecan/metabolites.html). Polymorphisms in *UGT1A1* gene, such as *UGT1A1*28* and **6*, can cause reduced glucuronidation of SN-38, thus resulting in severe irinotecan-induced toxicity. *UGT1A1*6/*6*, **28/*28*, and **6/*28* genotypes have been linked to significantly decreased conversion of SN-38 to SN-38G and severe neutropenia in Asians (Minami et al., 2007).

Transporters expressed in the liver are also implicated in the pharmacokinetics of irinotecan and its metabolites. The uptake of SN-38 from the systemic circulation by hepatocytes is mediated by organic anion transporter peptide 1B1 (OATP1B1) (Nozawa et al., 2005). ATP-binding cassette transporters such as ABCC2, ABCB1, and ABCG2 govern the biliary excretion of irinotecan and its metabolites (http://www.pharmgkb.org/do/serve?objId = PA2001&objCls = Pathway).

Because irinotecan is extensively metabolized and transported in the liver, attention has been focused on the hepatic factors underlying interpatient variability in pharmacokinetics of irinotecan. Studies examining the pharmacokinetics of irinotecan in renally impaired patients are scant. The pharmacokinetics of irinotecan in patients with mild renal impairment who had a creatinine clearance (Ccr) of 35 to 66 ml/min were similar to those in patients with normal renal function (de Jong et al., 2008). Although several case reports have examined the effects of more severe renal dysfunction requiring dialysis on the pharmacokinetics or toxicity of irinotecan (Venat-Bouvet et al., 2007; Czock et al., 2009), no prospective study has been performed; nevertheless, such rare patients are given irinotecan in clinical practice.

Therefore, we prospectively examined the pharmacokinetics of irinotecan, SN-38, and SN-38G in cancer patients with severe renal failure who were undergoing dialysis compared with patients with normal renal function. We enrolled patients with *UGT1A1*1/*1*, **1/*6*, or **1/*28* to ensure that the subjects had similar genetic backgrounds of *UGT1A1*.

Materials and Methods

Materials. Irinotecan, SN-38, and SN-38G were purchased from Toronto Research Chemicals (North York, Canada). All chemicals and solvents were of the highest grade commercially available.

Study Design. Patients who were candidates to receive the 100 mg/m^2 irinotecan monotherapy, satisfying the eligibility criteria listed below, were prospectively enrolled in this study. All patients were divided into two groups:

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ABBREVIATIONS: UGT, UDP-glucuronosyltransferase; SN-38, 7-ethyl-10-hydroxycamptothecin; SN-38G, SN-38 glucuronide; OATP1B1, organic anion transporter peptide 1B1; Ccr, creatinine clearance; CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid; IA, indoleacetic acid; IS, indoxyl sulfate; HA, hippuric acid; λ_z, terminal elimination rate constant.

1) those with a Ccr calculated by the Cockcroft-Gault equation of 60 ml/min or higher and 2) those with a Ccr of 20 ml/min or less who were receiving dialysis. To ensure that the subjects had similar genetic backgrounds of *UGT1A1*, patients with *UGT1A1*1/*1*, **1/*6*, or **1/*28* were enrolled, and patients with *UGT1A1*28/*28*, **6/*6*, or **6/*28* were excluded. The effects of severe renal failure on the pharmacokinetics of irinotecan, SN-38, and SN-38G were studied.

Eligibility. All patients were 20 years or older and had metastatic/recurrent, histologically confirmed solid tumors and an Eastern Cooperative Oncology Group performance status of 0 to 2. No patient had received chemotherapy or radiotherapy within the past 4 weeks. Each patient was confirmed to have adequate bone marrow and liver functions. All patients signed a written informed consent form, granting permission for their peripheral blood samples and medical information to be used for research purposes. The study protocol was approved by the Institutional Review Board of Saitama Medical University.

Treatment. All patients received irinotecan monotherapy as described in its package insert, according to approved usage in Japan. Irinotecan was given at a dose of 100 mg/m^2, either weekly for the first 3 weeks of a 4-week cycle or every 2 weeks. In every 2-week regimen, this lower dose of 100 mg/m^2 was used instead of 150 mg/m^2 at the discretion of the attending physician. Patients with severe renal failure underwent dialysis three times a week and received irinotecan monotherapy on the next day of a dialysis. The interval between the end of the dialysis and the infusion of irinotecan was approximately 17 h.

***UGT1A1* Genotyping.** *UGT1A1*6* and **28* were analyzed using methods as described elsewhere (Araki et al., 2006).

Pharmacokinetic Analysis of Irinotecan and Its Metabolites. Blood samples for pharmacokinetic analysis were obtained at the time of the first dose of irinotecan. The blood samples were taken at the beginning of the irinotecan infusion and 0, 0.25, 0.5, 1, 2, 4, 8, and 24 h after the end of the 1.5-h infusion. Patients with severe renal failure underwent dialysis 1 to 2 h after obtaining the last blood sample. In these patients, blood samples were also taken immediately before starting dialysis, 1 and 2 h after starting dialysis, and immediately after the completion of the dialysis. Total (lactone and carboxylate) plasma concentrations of irinotecan, SN-38, and SN-38G were analyzed by reverse-phase high-performance liquid chromatography (Araki et al., 2006). The plasma concentration-time data of irinotecan and its metabolites were analyzed by a standard noncompartmental method using WinNonlin, version 5.2 software (Pharsight, Mountain View, CA).

Determination of Uremic Toxins. Plasma concentrations of uremic toxins, including 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF), indoxyl sulfate (IS), indoleacetic acid (IA), and hippuric acid (HA), at the beginning of the irinotecan infusion were measured by high-performance liquid chromatography (Nishio et al., 2008).

Statistical Analysis. Pearson's χ^2 test, Fisher's exact test, or the Mann-Whitney *U* test was used to compare patient characteristics between the two groups according to renal function. The Mann-Whitney *U* test was used to analyze differences in pharmacokinetic measurements between the two groups. Differences were considered statistically significant when the two-tailed *P* value was less than 0.05. All analyses were performed with JMP version 7 software (SAS Institute, Inc., Cary, NC).

Results and Discussion

A total of nine Japanese patients with cancer, including three patients with severe renal failure who underwent dialysis, were prospectively enrolled in the present study from May 2005 through April 2010 at Saitama Medical University. During this period, more than 500 patients with cancer received a variety of irinotecan-containing chemotherapy regimens in our university. Among the nine patients enrolled, one patient with normal renal function was excluded because the patient was homozygous for *UGT1A1*6*. The patient characteristics are shown in Table 1.

The elimination of SN-38 was significantly delayed in patients with severe renal failure compared with those without renal failure (Fig. 1A). The terminal elimination rate constant (λ_z) of SN-38 in patients undergoing dialysis [0.00841 ± 0.0037 (mean ± S.D.) 1/h] was approximately one tenth of that in patients with normal renal function (0.0813 ± 0.034 1/h) ($P = 0.025$). No change was observed in the pharmacokinetics of SN-38 in patients who had relatively mild renal failure with a Ccr between 35 and 66 ml/min compared with patients who had normal renal function (de Jong et al., 2008). These results suggest that the severe but mild renal failure causes the alteration of the SN-38 pharmacokinetics. The λ_z estimated for irinotecan and SN-38G were not significantly different between two groups [renal failure versus normal, 0.101 ± 0.0058 versus 0.120 ± 0.045 1/h, $P = 0.070$ (irinotecan); 0.0310 ± 0.014 versus 0.0611 ± 0.034 1/h, $P = 0.18$ (SN-38G)] (Fig. 1, B and C).

TABLE 1

Patient characteristics

Patients	Underwent Dialysis	Normal Renal Function	*P*
Age (year)	67 (56–76)[c]	60 (42–65)	0.24[e]
Sex (male/female)	2/1[d]	3/2	1.0[f]
Performance status (0/1/2)	0/3/0	1/3/1	NA
Tumor type			NA
Ovary	1	2	
Colorectal	1	2	
Gastric	1	0	
Lung	0	1	
Number of prior chemotherapy (1/2/3)	2/0/1	0/5/0	NA
Renal disease			
	Chronic renal failure Diabetic kidney disease Polycystic kidney		
UGT1A1 genotype			
**1/*1*	0	1	NA
**1/*6*	3	2	
**1/*28*	0	2	
Total bilirubin (mg/dl)	0.5 (0.3–0.7)	0.4 (0.3–0.6)	0.44[g]
Serum creatinine (mg/dl)	7.7 (5.3–9.3)	0.68 (0.49–0.99)	0.025
Creatinine clearance (ml/min)[a]	7.09 (6.67–13.3)	82.6 (64.7–124)	0.025
Plasma concentrations of uremic toxins (μM)[b]			0.025
CMPF	81.1 (41.4–90.0)	8.71 (0–20.9)	0.017
Indoxyl sulfate	93.0 (53.3–94.1)	0 (0–12.0)	0.025
Indoleacetic acid	3.07 (2.56–8.00)	1.40 (0–1.53)	0.025
Hippuric acid	80.5 (28.5–144)	4.52 (3.26–6.87)	0.025

NA, not applicable.

[a] Creatinine clearance was calculated with the Cockcroft-Gault equation; [b] measured just before the irinotecan infusion; [c] median (range); [d] number; [e] Pearson χ^2 test. [f] Fisher's exact test; [g] Mann-Whitney *U* test.

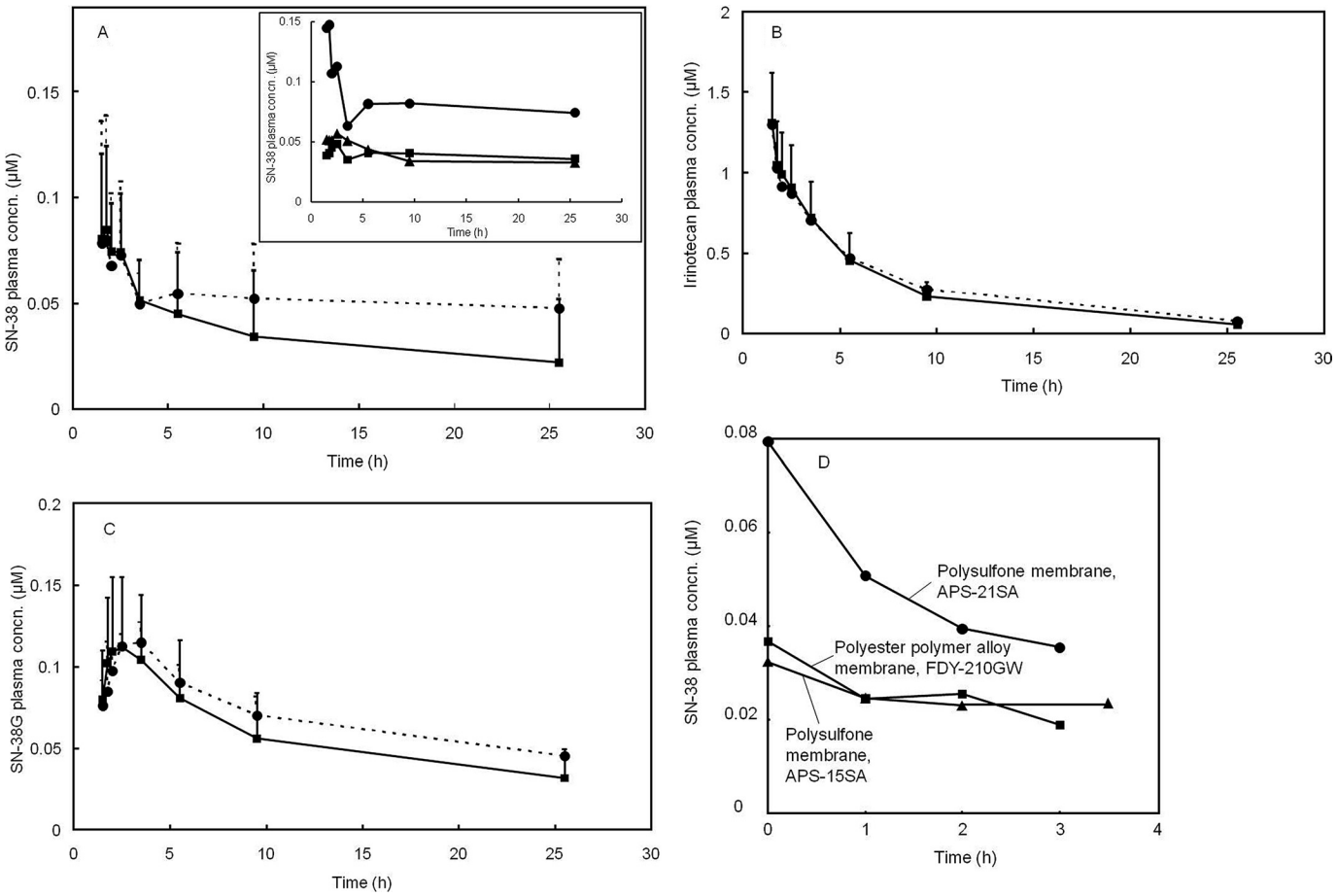

FIG. 1. Pharmacokinetics of SN-38, irinotecan, and SN-38G in patients undergoing dialysis and in those with normal renal function. A, SN-38; B, irinotecan; C, SN-38G; D, pharmacokinetics of SN-38 during dialysis. In A, B, and C, closed circles and dotted lines show the pharmacokinetic data from patients with severe renal failure (n = 3). Closed squares and solid lines indicate the pharmacokinetic data obtained from patients with normal renal function (n = 5). Each data point with error bar represents the mean ± S.D. Time 0 is the start of the irinotecan infusion. Individual pharmacokinetics of SN-38 obtained from three patients with severe renal failure are show in A. Symbols used to represent each of the respective three patients are the same as those used in D. In D, dialysis membranes used for each of the respective three patients are shown.

The mechanism(s) underlying the delayed elimination of SN-38 in patients with insufficient renal function remains speculative. In general, plasma concentrations of uremic toxins increase in parallel to the degree of renal impairment. In our patients, the concentrations of organic anion uremic toxins, such as CMPF, IS, IA, and HA, negatively correlated with Ccr (Table 1). These toxins are substrates of some organic anion transporters. CMPF and IS can directly inhibit OATP1B1 (Sun et al., 2006), which is responsible for the uptake of SN-38 from the systemic circulation by hepatocytes (Nozawa et al., 2005). Therefore, the delayed elimination of SN-38 in patients with severe renal failure might be attributed to the inhibition of OATP1B1 by these uremic toxins. Because ATP-binding cassette transporters involved in the efflux of SN-38 can transport organic anions, CMPF, IS, IA, and HA might serve as substrates of them, thereby inhibiting the efflux of SN-38, thus leading to the delayed elimination of SN-38. The elimination half-life of cerivastatin, a substrate of the nonrenal ABCB1, OATP, ABCC, and ABCG2, is approximately 1.5 times prolonged in patients with kidney disease (Nolin et al., 2008), indirectly supporting our hypothesis.

The significantly delayed elimination was observed only for SN-38, but not for SN-38G. All patients tested were likely to have similar glucuronidation capacity for SN-38, because they possessed *UGT1A1*1/*1*, **1/*6*, or **1/*28*. Uremic toxins measured in the present study only slightly inhibited the activity of UGT1A1-mediated SN-38 glucuronidation in vitro (data not shown). Given that, SN-38 glucuronidation may be similar between patients with and without severe renal failure. Therefore, the modification of transporter(s) responsible for SN-38 or SN-38G by a high concentration of uremic toxins in patients with severe renal dysfunction may cause the pharmacokinetic profiles of SN-38 and SN-38G. However, further studies are needed to clarify the mechanism.

Patients with severe renal failure underwent dialysis 1 to 2 h after the last blood sampling. Plasma concentration of SN-38 determined at 24 h after the end of irinotecan infusion and that measured immediately before the start of dialysis (1–2 h after the 24-h blood sampling) for each patient was almost equal, indicating that the λz of SN-38 seen at this period was nearly equal to zero. Assuming that the λz of SN-38 during the dialysis was nearly zero, approximately 50% of SN-38 was dialyzed in patients who received dialysis with a 2.1-m^2 polysulfone membrane APS-21SA (Asahi Kasei Kuraray Medical, Tokyo, Japan) or a polyester polymer alloy membrane FDY-210GW (Nikkiso, Tokyo, Japan) (Fig. 1D). SN-38 was dialyzed by 27% in a patient who underwent dialysis with a 1.5-m^2 polysulfone membrane APS-15SA (Asahi Kasei Kuraray Medical) (Fig. 1D). In contrast, SN-38 was not dialyzable in previous studies (Venat-Bouvet et al., 2007; Czock et al., 2009), but they did not mention the specifications of the dialyzer used. There may be differences between the specifications of dialyzers used in this study and previous studies.

All patients with severe renal failure suffered from grade 2, 3, or 4 neutropenia (National Cancer Institute Common Toxicity Criteria for Adverse Events, Version 3.0), even though dialyzes were performed. Grade 2 or 3 neutropenia was prolonged in two of these patients. The prolonged neutropenia resulted in the delay of the second irinotecan treatment until 24 or 34 days after the initial infusion. In contrast, no delay of the second irinotecan treatment caused by neutropenia was observed in patients with normal renal function. The delayed elimination of SN-38 may be one of the causes of prolonged neutropenia. If so, dialysis can be started earlier than 24 h after irinotecan infusion to lower the plasma SN-38 concentration. Alternatively, irinotecan infusion should be performed just after finishing the dialysis to minimize the effects of uremic toxins, if the delayed elimination of SN-38 is truly caused by uremic toxins. However, it should be necessary to further optimize the dialysis conditions, including the specification of the dialyzer, and the timing and duration of the dialysis for the better management of neutropenia in patients with severe renal failure.

In conclusion, the elimination of SN-38 in patients with severe renal failure was significantly delayed compared with that in patients with normal renal function. The SN-38 was in part dialyzed.

Authorship Contributions

Participated in research design: Fujita and Sasaki.

Conducted experiments: Akiyama and Sugiyama.

Contributed new reagents or analytic tools: Fujita.

Performed data analysis: Fujita, Kawara, Saji, Narabayashi, Ando, and Hirose.

Wrote or contributed to the writing of the manuscript: Fujita and Sasaki.

Other: Sunakawa, Miwa, Ishida, Yamashita, Mizuno, Ichikawa, Yamamoto, Nagashima, and Miya enrolled and followed patients, and Sasaki acquired funding for the research.

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