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CLINICAL TRIAL REPORT

A phase I pharmacokinetics study of 9-nitrocamptothecin in patients with advanced solid tumors

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Abstract
Purpose 9-Nitrocamptothecin (9-NC) is a novel orally administered camptothecin analog. The purpose of this study is to evaluate the pharmacokinetics and safety of 9-nitrocamptothecin in patients with advanced solid tumors.
Methods The 23 patients for a single-dose pharmacokinetic experiment were divided into 3 dosing cohorts. The dosage of 9-nitrocamptothecin capsule was 1.25, 1.5 and 1.75 mg/m^2, respectively. The 8 patients for a multiple-dose pharmacokinetic study were orally administered 9-nitrocamptothecin 1.5 mg/m^2 for 5 consecutive days. Determination of the plasma concentration of 9-nitrocamptothecin was performed by high-performance liquid chromatography-ultraviolet detector technique, and determination of plasma concentration of 9-aminocamptothecin was performed by high-performance liquid chromatography-fluorescence detector technique.
Results In the single-dose pharmacokinetic study, the mean ± SD 9-nitrocamptothecin C_{max} were 94.49 ± 41.38, 115.56 ± 63.27 and 147.57 ± 38.19 ng/mL; AUC_{0-36} were 877.14 ± 360.90, 961.33 ± 403.58 and 1,189.75 ± 405.80 ng h/mL, respectively; the mean ± SD 9-aminocamptothecin C_{max} were 12.85 ± 6.46, 10.72 ± 6.58 and 28.74 ± 31.94 ng/mL; AUC_{0-36} were 157.61 ± 111.61, 88.71 ± 39.51 and 173.52 ± 122.19 ng h/mL, respectively. In the multiple-dose pharmacokinetic study, the mean ± SD 9-nitrocamptothecin AUC_{ss} was 907.04 ± 736.47 ng h/mL, C_{max} was 85.98 ± 47.52 ng/mL, C_{min} was 18.91 ± 22.50 ng/mL, C_{av} was 37.79 ± 30.69 ng/mL, DF was 2.16 ± 0.87; the mean ± SD 9-aminocamptothecin AUC_{ss} was 442.73 ± 308.39 ng h/mL, C_{max} was 34.83 ± 18.31 ng/mL, C_{min} was 10.32 ± 6.95 ng/mL, C_{av} was 18.45 ± 12.85 ng/mL, DF was 1.34 ± 0.42. Comparing single-dose 1.5 mg/m^2 group with multiple-dose 1.5 mg/m^2 group, no significant difference was observed in 9-NC pharmacokinetic parameters, but with respect to the metabolite, significant differences were observed in C_{max} and AUC. The toxicity of 9-NC varied from mild to moderate. No grade 3 or grade 4 toxicity was observed during the study. There was 2- to 13-fold variabilities in 9-NC and 9-AC exposure among different patients for any given dose of 9-NC.
Conclusions All participants had good tolerance throughout the study. 9-NC and 9-AC exposure did not increase proportionally to the dose ranging from 1.25 to 1.75 mg/m^2. After 5-day continuous administration, accumulation was observed in the metabolite 9-AC, but not in 9-NC.

Keywords 9-Nitrocamptothecin · 9-Aminocamptothecin · Pharmacokinetics · High-performance liquid chromatography · Drug-screening assays · Antitumor

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Introduction

The camptothecin analogs are topoisomerase I-inhibiting anticancer agents and have a wide range of anticancer activities [3, 7]. Currently approved camptothecin analogs (i.e., topotecan and irinotecan) are only available for i.v. administration [2, 4]. 9-Nitrocamptothecin (9-NC) is a novel orally administered camptothecin analog [11]. Oral administration of 9-NC could maximize patient convenience. In vivo, 9-NC is partly metabolized to the metabolite, 9-aminocamptothecin (9-AC) [6, 12]. Previous in vitro and in vivo studies showed that 9-NC effectively inhibited several tumor types and noteworthy clinical responses have been observed in patients with refractory cancer. In a phase II study of 9-NC at the dose of 1.5 mg/m^2 in 29 patients with heavily refractory ovarian, tubal or peritoneal cancer, two responses were observed. Thirty-four percent of patients had stable disease [17]. Particularly, Stehlin and his colleagues reported that 9-NC is safe and efficacious as first-line therapy for the treatment of advanced pancreatic cancer. As second-line therapy in treating gemcitabine failures, 9-NC has also shown some modest success [15].

However, the optimal 9-NC treatment regimen is not yet established. Previous pharmacokinetic studies in Caucasian participants have shown that the advised dose of 9-NC is at 1.0–2.0 mg/m^2 per day (orally) for 4–5 consecutive days on a weekly basis. Moreover, oral administration of 9-NC has shown extensive interpatient and intrapatient variability [19]. No pharmacokinetic study of 9-NC in Asian participants was reported. Thus, this study was performed to evaluate the plasma pharmacokinetics of 9-NC and 9-AC in Chinese participants and to observe the toxicities evident in the body after oral administration of 9-NC.

Materials and methods

Patient selection

The study was approved by the Ethics Committee at Tianjin Medical University Cancer Hospital. All participants were informed about the program of the study and signed informed consent forms before beginning. To be eligible, patients were required to have an advanced solid malignancy confirmed by histology and their tumors had to have been proven to be unresponsive to standard therapy (or no standard therapy had been applied). Other inclusion criteria were as follows: age of 18–70 years; measurable or evaluable disease; Karnofsky performance status $\geq$70; survival expectancy over 3 months; adequate bone marrow function as defined by WBC count $\geq 3.0 \times 10^9$/L, absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 100.0 \times 10^9$/L, hemoglobin $\geq$90.0 g/L; adequate hepatic function (ALT, AST $\leq$ 1.5 times the upper limit of normal [ULN], total bilirubin level $\leq$1.0 times ULN); adequate renal function (serum creatine $\leq$1.5 times ULN); no obvious cardiac and pneumonic disorders. In addition, participants were required to be able to swallow oral medication and have adequate venous access to permit repeated blood sampling. Participants were required to have had no surgery, chemotherapy, biotherapy, endocrine therapy and radiotherapy for at least 4 weeks prior to the start of the study. Patients of childbearing age were required to use contraception.

Study drugs and administration

9-NC capsules were supplied from Qilu Pharmaceutical Co., Ltd (Shandong, China). The capsule strengths were 0.1, 0.2, 0.25 and 1 mg. 9-NC was administrated orally on an empty stomach. The study was designed as an open-label, single-arm study. Based on the outcomes of preclinical pharmacological and toxicological studies, the initial dose of 9-NC for the single-dose pharmacokinetic study was designed to be 1.25 mg/m^2. The dosage was sequentially increased 2 times to 1.5 and 1.75 mg/m^2. In the multiple-dose pharmacokinetic study, 8 patients were enrolled. Patients were continuously given a dose of 1.5 mg/m^2 daily for 5 days.

Pharmacokinetic sample collection

On the single-dose pharmacokinetic study, blood samples (5 mL) were obtained before administration of 9-NC, and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24 and 36 h after administration. With regard to the multiple-dose pharmacokinetic study, at the 1st and 5th day, blood samples (5 mL each time) were collected before administration of 9-NC, and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24 and 36 h after administration. On the 2nd, 3rd and 4th day, blood specimens (5 mL) were taken before the drug administration. Blood samples were collected in heparinization tubes and then centrifuged at 3,000 rpm (4°C) for 10 min to obtain plasma, which was stored at −80°C for determination.

Analytical assays

9-nitrocamptothecin standard (purity 99.2%, batch number 0507001) and 9-aminocamptothecin standard (purity 99%, batch number 0511007) were supplied from Qilu Pharmaceutical Co., Ltd (Shandong, China). Camptothecin standard (purity 98.9%, manufacture date 28 Nov, 2005) was obtained from Lishizhen Pharmaceutical Co., Ltd (Wuhan, China). Acetonitrile and methanol were HPLC-grade reagents and purchased from Concord Technology

Co., Ltd (Tianjin, China). HPLC-grade water was prepared in a Milli-Q system (Millipore, USA). All other reagents were in analytical grade.

The chromatographic system consisted of a Model PC3000 chromatography pump (LabAlliance, USA), a Model 500 UV–Visible detector (LabAlliance, USA), a Model LC305 fluorescence detector (LabAlliance, USA), a Kromasil C_{18} column (250 × 4.6 mm, 5 μm) and a N2000 data processing system (Zhejiang, China). C_{18} solid-phase extraction columns were used for sample pretreatment.

Determination of the plasma concentration of 9-NC was performed by high-performance liquid chromatography–ultraviolet detector method, and determination of plasma concentration of 9-AC was performed by high-performance liquid chromatography–fluorescence detector method as described previously [22, 23]. The lower limit of quantitation (LLQ) for 9NC was 5 ng/mL, and the assays were linear from 5 to 1,000 ng/mL. The LLQ for 9-AC was 0.5 ng/mL, and the assays were linear from 0.5 to 100 ng/mL.

Pharmacokinetic data analysis

The plasma concentration–time data were analyzed using non-compartmental methods. The pharmacokinetic analysis system-DAS 2.1 (Anhui, China) is applied to assess pharmacokinetic parameters. The peak plasma concentration (C_{max}) and time to peak plasma concentration (T_{max}) were obtained by experimental observations. The elimination half-life ($t_{1/2}$) was calculated as 0.693MRT (mean retention time). The AUC from zero to infinity ($AUC_{0-\infty}$) was equivalent to the sum of the areas from time zero to the time of the last measured concentration, calculated by using the linear trapezoidal method (until C_{max}) and the log-trapezoidal method (until the last measurable concentration), and the extrapolated area. The extrapolated area was determined by dividing the final measured concentration by the slope of the terminal log-linear phase. Trough values on days 2, 3, and 4 were averaged on each day for each dose level.

Statistical analysis

All statistical tests were two tailed and significance was set at the 0.05 level. Differences in the mean values of physical examinations and pharmacokinetic parameters among the three groups were compared by analysis of variance (ANOVA) or Kruskal–Wallis test (K–W H test). For differences between two groups, *t*-test or Wilcoxon test was employed.

Results

Subject characteristic

Twenty-three patients were enrolled in the single pharmacokinetic study, and no statistically significant differences were found in age, height, weight, body surface area and BMI among 3 groups via analysis of variance. Eight patients were enrolled in the multiple pharmacokinetic study. The characteristics of patients are shown in Table 1.

Single-dose pharmacokinetic study

9-NC and 9-AC plasma concentration–time profiles at each dose level are shown in Fig. 1. Main pharmacokinetic parameters are summarized in Table 2. Following a single dose of 1.25, 1.5 and 1.75 mg/m^2 in patients, 9-NC and 9-AC plasma levels increased rapidly and reached the peak about 3 h after oral administration of 9-NC, and then decreased slowly. The distribution volume of 9-AC was greater than that of 9-NC, indicating that 9-AC was distributed more widely. No significant difference was observed in 9-NC and 9-AC pharmacokinetic parameters among the three dosing groups ($P > 0.05$).

Multiple-dose pharmacokinetic study

9-NC and 9-AC plasma concentration–time profiles of 9-NC and 9-AC after oral administration 9-NC 1.5 mg/m^2 for 5 days are shown in Fig. 2. Main pharmacokinetic parameters are summarized in Table 3. Comparing the single-dose 1.5 mg/m^2 group with the multiple-dose 1.5 mg/m^2 group, no significant difference was observed in C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{\frac{1}{2}z}$, $CL_{z/F}$, and $V_{z/F}$ ($P > 0.05$).

Safety

A summary of toxicities for patients is presented in Table 4. The toxicity profiles of the single-dose pharmacokinetic study and multiple-dose pharmacokinetic study were similar. Overall, non-hematologic toxicity was more common than hematologic toxicity. The most common toxicities for all patients were hemoglobin, leukocytes, proteinuria, ALT, AST and cardiac ischemia. All adverse events were grade 1 or 2.

Discussion

9-Nitrocamptothecin is an orally administered derivative of the natural plant alkaloid camptothecin [11]. 9-NC is partially metabolized in vivo to become 9-AC [6, 12]. In order

Table 1 Patients' characteristics

	Single dose			Multiple dose
	1.25 mg/m^2 ($n = 7$)	1.5 mg/m^2 ($n = 8$)	1.75 mg/m^2 ($n = 8$)	1.5 mg/m^2 ($n = 8$)
Sex				
Male	3	5	3	6
Female	4	3	5	2
Age (years)	51 ± 6.4	48.8 ± 10.2	58.1 ± 7.2	50.9 ± 11.2
Height (cm)	166 ± 6	165 ± 10	163 ± 7	169 ± 7
Weight (kg)	63.4 ± 11.3	68.8 ± 9.6	69.1 ± 11.3	68.7 ± 7.4
Body Surface Area (m^2)	1.70 ± 0.16	1.76 ± 0.17	1.75 ± 0.16	1.79 ± 0.12
BMI (kg m^{-2})	22.8 ± 3.4	25.2 ± 1.6	25.9 ± 4.0	24.1 ± 2.1
Diagnose				
Lung	1	1	0	1
Ovary	2	0	2	1
Colorectal	1	1	3	2
Other (breast, kidney, stomach, cervix, endometrium, bladder)	3	6	3	4
Prior therapy				
Chemotherapy	5	8	4	6
Radiotherapy	2	4	3	3
Biotherapy	1	2	1	1

Data are expressed as mean ± SD

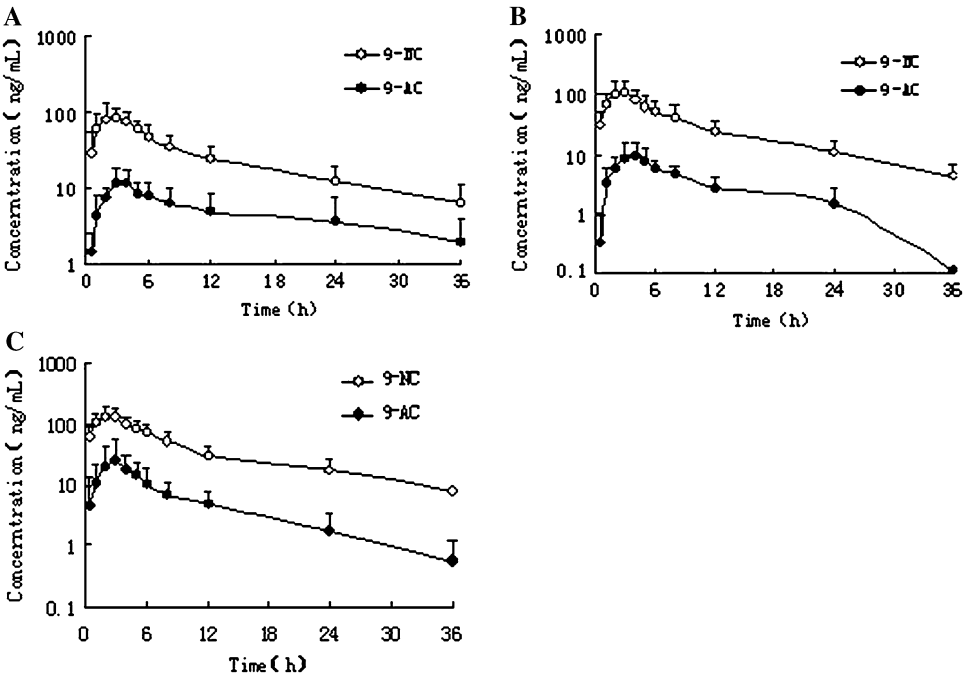

Fig. 1 **a** Mean plasma concentration versus time plot after single administration of 9-NC 1.25 mg/m^2. **b** Mean plasma concentration versus time plot after single administration of 9-NC 1.5 mg/m^2. **c** Mean plasma concentration versus time plot after single administration of 9-NC 1.75 mg/m^2

to fully study the pharmacokinetics of 9-NC, both 9-NC and 9-AC should be considered. Because 9-NC can absorb ultraviolet light and is not highly fluorescent, 9-NC in human plasma was assessed by HPLC–UV analytical method. Previous studies demonstrated that the conversion of 9-NC to 9-AC is relatively minor (i.e., 12–25%). Since 9-AC can fluoresce [14], 9-AC in human plasma was measured by HPLC–fluorescence method in order to obtain high sensitivity. The lower limit of quantitation (LLQ) for 9-NC and 9–AC were 5 and 0.5 ng/mL, respectively. The results indicated that the method was specific, sensitive and convenient for assessment of 9-NC in biological samples.

Table 2 9-NC and 9-AC pharmacokinetic parameters after single administration of 9-NC 1.25, 1.5 and 1.75 mg/m^2

Parameters	1.25 mg/m^2		1.5 mg/m^2		1.75 mg/m^2	
	9-NC ($n = 7$)	9-AC ($n = 6$)	9-NC ($n = 8$)	9-AC ($n = 8$)	9-NC ($n = 8$)	9-AC ($n = 8$)
AUC_{0-t}/ng h mL^{-1}	877.14 ± 360.90	157.61 ± 111.61	961.33 ± 403.58[a]	88.71 ± 39.51[a]	1,189.75 ± 405.80[a,d]	173.52 ± 122.19[a,d]
$AUC_{0-\infty}$/ng h mL^{-1}	977.36 ± 415.99	193.97 ± 172.24	1,047.35 ± 436.54[a]	105.10 ± 53.44[a]	1,385.39 ± 523.37[a,d]	205.72 ± 134.44[a,d]
MRT_{0-t}/h	9.60 ± 2.26	10.34 ± 4.28	9.16 ± 2.29[a]	8.77 ± 1.71[a]	7.99 ± 1.05[a,d]	8.16 ± 2.82[a,d]
$MRT_{0-\infty}$/h	13.23 ± 4.75	15.43 ± 10.19	12.45 ± 4.69[a]	13.05 ± 5.27[a]	11.98 ± 3.62[a,d]	14.33 ± 14.91[a,d]
$t_{1/2z}$/h	9.13 ± 3.63	9.96 ± 7.18	9.17 ± 3.73[a]	8.57 ± 4.66[a]	8.65 ± 3.02[a,d]	9.69 ± 10.88[a,d]
T_{max}/h	3.00 ± 0.82	3.67 ± 0.52	3.00 ± 0.54[a]	3.63 ± 0.92[a]	2.63 ± 0.92[a,d]	3.13 ± 0.99[a,d]
CL_z/F/L·h^{-1} m^{-2}	1.42 ± 0.39	12.45 ± 11.90	1.68 ± 0.73[a]	18.27 ± 10.53[a]	1.46 ± 0.66[a,d]	12.13 ± 6.78[a,d]
V_z/F/L m^{-2}	18.32 ± 8.62	133.19 ± 111.38	22.40 ± 13.46[a]	205.74 ± 144.51[a]	16.33 ± 3.58[a,d]	131.28 ± 93.90[a,d]
C_{max}/ng mL^{-1}	94.49 ± 41.38	12.85 ± 6.46	115.56 ± 63.27[a]	10.72 ± 6.58[a]	147.57 ± 38.19[a,d]	28.74 ± 31.94[a,d]

Data are expressed as mean ± SD

[a] $P > 0.05$ versus 1.25 mg/m^2 group

[d] $P > 0.05$ versus 1.5 mg/m^2 group

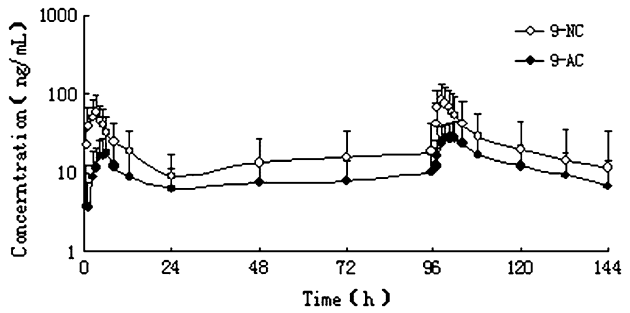

Fig. 2 9-NC and 9-AC plasma concentration versus time plot after oral administration 9-NC 1.5 mg/m^2 for 5d. $n = 8$. Data are expressed as Mean ± SD

Table 3 9-NC and 9-AC pharmacokinetic parameters after oral administration of 9-NC 1.5 mg/m^2 for 5d

Parameters	9-NC ($n = 8$)	9-AC ($n = 8$)
AUC_{ss}/ng h mL^{-1}	907.04 ± 736.47	442.73 ± 308.39
$AUC_{(0-t)}$/ng h mL^{-1}	1,266.26 ± 1,254.51	662.27 ± 498.08
$AUC_{(0-\infty)}$/ng h mL^{-1}	2,214.92 ± 3,624.84	1,141.50 ± 1,074.20
$MRT_{(0-t)}$/h	13.65 ± 3.55	16.58 ± 3.94
$MRT_{(0-\infty)}$/h	28.67 ± 30.85	45.75 ± 44.86
$VRT_{(0-t)}$/h^2	144.58 ± 45.20	156.35 ± 51.68
$VRT_{(0-\infty)}$/h^2	1,817.90 ± 3,936.24	4,126.79 ± 7,953.46
$t_{1/2z}$/h	21.25 ± 21.88	32.59 ± 32.61
T_{max}/h	2.00 ± 0.76	4.25 ± 1.83
CL_z/F/L h^{-1} m^{-2}	2.02 ± 2.05	3.72 ± 4.77
V_z/F/L m^{-2}	36.65 ± 27.14	76.91 ± 42.77
C_{max}/ng mL^{-1}	85.98 ± 47.52	34.83 ± 18.31
C_{min}/ng mL^{-1}	18.91 ± 22.50	10.32 ± 6.95
C_{av}/ng mL^{-1}	37.79 ± 30.69	18.45 ± 12.85
DF	2.16 ± 0.87	1.34 ± 0.42

Data are expressed as mean ± SD

In the single-dose pharmacokinetic study, plasma concentration of 9-NC and 9-AC increased rapidly and reached the peak about 3 h after oral administration of 9-NC, and then decreased slowly. However, 9-NC and 9-AC exposure did not increase proportionally to the dose ranging from 1.25 to 1.75 mg/m^2. No significant difference was observed in the main pharmacokinetic parameters among the three dosing groups. In the multiple-dose pharmacokinetic study, the 9-NC mean trough and average concentrations remained low. Comparing the single-dose 1.5 mg/m^2 group with the multiple-dose 1.5 mg/m^2 group, no significant difference was observed in 9-NC pharmacokinetic parameters, but with respect to the metabolite, significant difference was observed in C_{max} and AUC. It was indicated that accumulation was observed in 9-AC with repeated doses of 9-NC, but not in 9-NC. The pharmacokinetic parameters were consistent with the previous study in which also Chinese participants were enrolled [21], but not consistent with previous international studies [18]. Some possibilities for the differences are presented here. First, there may be a difference between Asian participants and Caucasian participants. The study enrolling Caucasians indicated that the mean ± SD 9-NC AUC and C_{max} at 1.5 mg/m^2 were 557 ± 379 and 52.9 ± 27.7 ng/ml, respectively, which were lower than the results of this study. However, the mean ± SD 9-AC AUC and C_{max} were 256 ± 102 ng h/ml and 17.5 ± 11.5 ng/ml, respectively, which were higher than the results of this study [18]. Then, a difference of methodology applied in different laboratories may be responsible for the contrast.

In this study, most of the drug remained in 9-NC form, and the mean ratio of 9-NC–9-AC conversion was 10–1, which is consistent with previous studies [6, 12]. The minor conversion of 9-NC–9-AC was significant because IDEC Pharmaceuticals Corporation terminated the clinical

Table 4 Toxicity summary (by number of patients)

Toxicity (CTC)	Single dose ($n = 23$)				Multiple dose ($n = 8$)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	7	1	0	0	3	1	0	0
Leukocytes	2	0	0	0	2	0	0	0
Neutrophils	0	0	0	0	1	0	0	0
Platelets	1	0	0	0	0	0	0	0
ALT	1	0	0	0	2	0	0	0
AST	0	0	0	0	2	0	0	0
Bilirubin	0	0	0	0	1	0	0	0
PTT	1	0	0	0	0	0	0	0
Hypocalcemia	1	0	0	0	1	0	0	0
Proteinuria	3	0	0	0	2	0	0	0
Cardiac ischemia	4	0	0	0	1	0	0	0

development of 9-AC in 1999 due to lack of efficacy [16]. Several studies have showed significant interpatient variability in the pharmacokinetics of orally administered camptothecin analogs [2, 10, 19]. The present study also demonstrated relatively high interpatient and intrapatient pharmacokinetic variability of 9-NC and 9-AC. There was 2- to 13-fold variability in 9-NC and 9-AC exposure among different patients for any given dose of 9-NC. Moreover, the conversion of 9-NC–9-AC is highly variable (3:1–32:1), which was consistent with a previous in vivo study [8]. It has been indicated that the high variability could be due to variability in oral absorption, the effect of food, pH of the gastric tract, and hepatic and extrahepatic conversion of 9-NC–9-AC [8]. The ATP-binding cassette (ABC) transporter superfamily contains membrane proteins that transport a wide variety of substrates across extra- and intracellular membranes [5]. ABC transporters have been reported to alter the pharmacokinetics of camptothecin analogs and are associated with camptothecin resistance [1, 9, 13]. Zamboni and his colleagues reported interindividual variability in 9-AC disposition, but not in 9-NC disposition, may be influenced, in part, by *ABCG2* genotype. In contrast, there was no evidence for relationships between *ABCB1* and *ABCC2* genotypes and the disposition of 9-NC or 9-AC [20]. However, further pharmacogenetic studies should be performed to determine the factors related to the pharmacokinetic variability.

The toxicity profile of 9-NC varied from mild to moderate. No grade 3 or grade 4 toxicity was observed during the study. Generally, non-hematologic toxicity was found to be more common than hematologic toxicity. The most common toxicities for all patients were hemoglobin, leukocytes, proteinuria, ALT, AST and cardiac ischemia.

In conclusion, all participants had good tolerance throughout the study. 9-NC and 9-AC exposure did not increase proportionally to the dose ranging from 1.25 to 1.75 mg/m^2, indicating that the effect of dose level on single-dose pharmacokinetics of 9-NC and 9-AC was not significant. No accumulation was observed in 9-NC with repeated exposure to 9-NC at 1.5 mg/m^2, but accumulation was observed in 9-AC. In addition to evaluating the clinical efficacy and safety of 9-NC, further pharmacogenetic studies should be conducted in pivotal phase II/III clinical trials.

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