


ORIGINAL ARTICLE

Relationship between *UGT1A1**27 and *UGT1A1**7 polymorphisms and irinotecan-related toxicities in patients with lung cancer

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Abstract

Background: The objective of this study was to evaluate the effects of gene polymorphisms, including *UGT1A1**7, *27, and *29, on the safety of irinotecan therapy.

Methods: The eligibility criteria were: lung cancer patients scheduled to undergo irinotecan therapy, aged ≥ 20 years, with a performance status of 0–2. Thirty-one patients were enrolled and their blood was collected and used to examine the frequency of *UGT1A1**6, *7, *27, *28, and *29 polymorphisms and the concentrations of irinotecan, SN-38, and SN-38G after irinotecan therapy.

Results: The patients' characteristics were as follows: male/female 25/6, median age 71 years (range 55–84), stage IIB/IIIA/IIIB/IV 2/6/11/12, and adenocarcinoma/squamous cell carcinoma/small cell carcinoma/other 14/10/3/4, respectively. The $-/-$, *6/ $-$, *7/ $-$, *27/ $-$, *28/ $-$, and *29/ $-$ *UGT1A1* gene polymorphisms were observed in 10 (32%), 10 (32%), 2 (6%), 2 (6%), 7 (23%), and 0 (0%) cases, respectively. The *UGT1A1**27 polymorphism occurred separately from the *UGT1A1**28 polymorphism. The lowest leukocyte counts of the patients with the *UGT1A1**27 and *UGT1A1**6 gene polymorphisms were lower than those observed in the wild-type patients. SN-38 tended to remain in the blood for a prolonged period after the infusion of irinotecan in patients with *UGT1A1**27 or *UGT1A1**28 polymorphisms. No severe myelotoxicity was seen in the patients with *UGT1A1**7.

Conclusion: *UGT1A1**27 can occur separately from *UGT1A1**28 and is related to leukopenia during irinotecan treatment. *UGT1A1**7 is less relevant to irinotecan-induced toxicities, and *UGT1A1**29 seems to have little clinical impact.

Introduction

Irinotecan, a semisynthetic water-soluble prodrug that is metabolized to the active metabolite SN-38, which inhibits the function of DNA topoisomerase I by stabilizing a reversible enzyme-DNA cleavable complex, is widely used against solid tumors including lung, colorectal, gastric,

gynecological, and other types of cancer.^{1–5} However, it causes adverse events, such as severe neutropenia and diarrhea, in 13–25% of patients.^{6,7} Genetic polymorphisms of the *UGT1A1* gene can alter the glucuronidation of SN-38 and have a major influence on its pharmacokinetics and toxicity.⁸ The genetic polymorphisms *UGT1A1**28 and *UGT1A1**6 have already been shown to be associated with

decreased UGT1A1 activity, increased SN-38 levels, and a greater risk of adverse events during irinotecan chemotherapy.^{9–12}

The *UGT1A1**27 polymorphism is in linkage disequilibrium with *UGT1A1**28, and a previous study reported that they always co-occur (i.e. they represent a haplotype).¹³ In addition, the *UGT1A1**27 polymorphism has been demonstrated to reduce the enzyme activity of UGT in basic research.¹⁴ However, the impact of *UGT1A1**27 on the toxicity of irinotecan is poorly understood because it exhibits a low frequency of 0.5–1%. *UGT1A1**7 and *UGT1A1**29 affect the common exons of UGT1A1 isoforms, producing substantial reductions in their functional activities, and the *UGT1A1**7 polymorphism is prevalent among patients that suffer irinotecan treatment-related hospitalization or severe irinotecan-related toxicities.^{15,16}

Hence, we conducted a study of polymorphisms of the *UGT1A1* gene. The main objectives of this study were to determine the clinical impact and pharmacokinetic effects of *UGT1A1**27 and other gene polymorphisms in patients who receive irinotecan-based chemotherapy.

Methods

The study protocol was reviewed and approved by the ethics committee of Nagasaki Municipal Hospital (Nagasaki Harbor Medical Center City Hospital). Written informed consent was obtained from all study participants. This study was an independent collaborative (un-sponsored) group study.

Patients and treatment

The patient eligibility criteria were as follows: a histologically and/or cytologically confirmed diagnosis of lung cancer, scheduled irinotecan therapy, age \geq 20 years, a performance status of 0–2, and written informed consent. Treatment commenced within a week of enrollment. Irinotecan was administered as a single agent or as part of combination chemotherapy. Irinotecan dissolved in 250 mL of 5% dextrose or normal saline was infused intravenously (i.v.) over 60 minutes. Irinotecan treatment was postponed if the patient's leukocyte count fell to $< 3000/\mu\text{L}$, their platelet count dropped to $< 10 \times 10^4/\mu\text{L}$, or diarrhea occurred on the day of the planned infusion or the previous day; treatment was abandoned if it could be re-started within a week.

The doses of the chemotherapy agents were as follows.^{13,14,17–20} Small cell lung cancer: (i) irinotecan single agent, 100 mg/m² weekly; (ii) irinotecan combined with cisplatin, 60 mg/m² on days 1, 8, and 15 and 60 mg/m² on day 1 every four weeks, respectively; (iii) irinotecan/cisplatin with concurrent radiotherapy, 40 mg/m² on days

1, 8, and 15 and 60 mg/m² on day 1 repeated every four weeks, respectively; and (iv) irinotecan combined with carboplatin, 50 mg/m² on days 1, 8, and 15 and an area under the curve (AUC) value of 5 on day 1 repeated every four weeks, respectively. Non-small cell lung cancer: (i) irinotecan single agent, 100 mg/m² weekly; (ii) irinotecan combined with cisplatin, 60 mg/m² on days 1, 8, and 15 and 80 mg/m² on day 1 repeated every four weeks, respectively; (iii) irinotecan/cisplatin with concurrent radiotherapy, 50 mg/m² on days 1, 8, and 15 and 60 mg/m² on day 1 repeated every four weeks, respectively; and (iv) irinotecan combined with carboplatin, 50 mg/m² on days 1, 8, and 15 and an AUC value of 5 on day 1 repeated every four weeks, respectively.

Genotyping assay, drug concentration, and response evaluation

Genomic DNA was extracted from 2 mL of peripheral blood in each patient. The *UGT1A1**6, *UGT1A1**7, *UGT1A1**27, and *UGT1A1**29 gene polymorphisms were detected via the PCR direct DNA sequencing method. The *UGT1A1**28 gene polymorphism was detected using the polyacrylamide gel electrophoresis method. The drug concentrations of irinotecan, SN-38, and SN-38G were evaluated at 0, 1, 3, and 24 hours after the administration of irinotecan therapy by analyzing 3 mL blood samples. Venous blood samples were collected on day 1 in 5 mL glass tubes containing heparin before the administration of irinotecan, as well as at 0 and 1, 3, and 24 hours after the first infusion of irinotecan, for pharmacokinetic analysis. The plasma concentrations of irinotecan, SN-38, and SN-38G were determined via high-performance liquid chromatography, and AUC values were calculated using the trapezoidal method in WinNonlin version 4.01 (Pharsight Corporation, Mountain View, CA, USA). Drug toxicity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.²¹ Before the first cycle, a blood cell count, urinalysis, and biochemistry tests were performed to assess renal and hepatic function and electrolyte levels. These tests were repeated during treatment, while other examinations of marker levels were repeated as necessary.

Statistical analysis

Toxicities were compared between the groups of patients with each *UGT1A1* gene polymorphism using the chi-squared test. The lowest levels of various parameters were compared using the unpaired *t*-test between the groups of patients with each *UGT1A1* gene polymorphism. Data are expressed as mean \pm standard deviation values. Progression-free survival (PFS) was defined as the period

from the start of irinotecan therapy to the determination of treatment failure (death or the documentation of disease progression) or the date of censoring at the last follow-up examination. Overall survival (OS) was defined as the period from the start of irinotecan therapy until death from any cause or the date of censoring at the last follow-up examination. Survival was evaluated using the Kaplan–Meier method, and differences in survival were analyzed using the log-rank test. The *t*-test was used to determine the significance of any differences between the groups, and Fisher's exact test was used to compare count data. All *P* values were two-sided, and statistical significance was accepted at *P* < 0.05. SPSS version 23.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

Results

Thirty-one patients were enrolled in this study between February 2009 and September 2010, and all received chemotherapy including irinotecan. *UGT1A1* gene polymorphisms, toxicities, and drug concentrations were evaluated in all patients. The baseline patient characteristics are shown in Table 1. The median age of the patients was 71, and the frequencies of male gender, stage IV disease, and adenocarcinoma were relatively high. The *6/–, *7/–, *27/–, or *28/– *UGT1A1* polymorphism was observed in 21 (68%) patients (Table 2). There were no homozygous or complex heterozygous polymorphisms, nor was the *29/– polymorphism detected. The *UGT1A1**27 polymorphism was detected in two patients who did not possess the *UGT1A1**28 polymorphism (Table 3). The subjects lived in

Table 1 Patient characteristics

Characteristics	No. of patients
Gender	
Male	25
Female	6
Age (years)	
Median	71
Range	55–84
Stage	
II B	2
III A	6
III B	11
IV	12
Histology	
Adenocarcinoma	14
Squamous cell carcinoma	10
Small cell carcinoma	3
Non-small cell carcinoma	2
Adenosquamous cell carcinoma	1
LCNEC	1

LCNEC, large cell neuroendocrine carcinoma.

Table 2 Patients with *UGT1A1* gene polymorphisms

	Total	–/–	*6/–	*7/–	*27/–	*28/–	*29/–
N	31	10	10	2	2	7	0
(%)	(100)	(32)	(32)	(6)	(6)	(23)	(0)

There were no homozygous or complex heterozygous polymorphisms. The frequency of *UGT1A1* gene polymorphisms was 68%.

Nagasaki City; however, none of them were affected by the atomic bombing of the city.

Treatment administration

Irinotecan was administered as part of combination chemotherapy in 23 (74%) patients, and was combined with cisplatin in 12 (39%), gemcitabine in 10 (32%), and carboplatin in 1 (3%) patient. The remaining eight patients (26%) were administered irinotecan monotherapy. Radiotherapy was administered concurrently in 20 (65%) patients: 60 Gy in 17 (85%) and 50 Gy in 3 (15%). The treatment dose of irinotecan was 100 mg/m² in 11 (35%) patients, 60 mg/m² in 3 (10%), 55 mg/m² in 1 (3%), 50 mg/m² in 13 (42%), 40 mg/m² in 2 (6%), and 30 mg/m² in 1 (3%) patient.

Toxicity

Grade 3 or worse toxicities experienced according to the types of *UGT1A1* gene polymorphisms possessed by the patients are listed in Table 4. Fourteen (45%) of the 31 patients experienced grade 3 or worse toxicities, and 5 (16%) suffered grade 4 toxicities. There was one treatment-related death, which occurred in a patient with the *UGT1A1**28 polymorphism who developed radiation pneumonitis. One of the two patients with *UGT1A1**27 suffered febrile neutropenia and grade 3 leukopenia. The frequencies of leukopenia and neutropenia (≥ grade 3) were higher (43–50%) in patients with the *6, *27, and *28 polymorphisms than in the wild-type (10–20%) patients. Diarrhea (≥ grade 3) was only observed in patients with the *6 polymorphism. There were no significant differences in the toxicities experienced by the patients with each *UGT1A1* gene polymorphism.

The lowest leukocyte counts of the wild-type, *6/–, *7/–, *27/–, and *28/– patients were 3140 ± 1290/μL, 2050 ± 1119/μL, 5250 ± 2616/μL, 1650 ± 495/μL, and 2371 ± 1291/μL, respectively (Fig 1a). Patients with the *UGT1A1**27 and *UGT1A1**6 gene polymorphisms demonstrated significantly lower leukocyte counts than the wild-type patients (*P* < 0.05, non-parametric test). The lowest neutrophil counts of the wild-type, *6/–, *7/–, *27/–, and *28/– patients were 1927 ± 1369/μL, 1125 ± 885/μL, 3993 ± 2185/μL, 1043 ± 335/μL, and 1196 ± 816/μL,

Table 3 Patients with *UGT1A1**27 gene polymorphisms

Gender	Age	Histology	Stage	*6	*7	*27	*28	*29
M	55	Small	IIIB	Wild	Wild	Hetero	Wild	Wild
F	67	Adeno	IIIB	Wild	Wild	Hetero	Wild	Wild

Adeno, adenocarcinoma; hetero, heterozygous; small, small cell carcinoma.

Table 4 *UGT1A1* gene polymorphisms and toxicities (≥grade 3)

	-/-	*6/-	*7/-	*27/-	*28/-
Febrile neutropenia	0	1	0	1	0
(%)	(0)	(10)	(0)	(50)	(0)
Leukopenia	1	5	0	1	3
(%)	(10)	(50)	(0)	(50)	(43)
Neutropenia	2	5	0	1	3
(%)	(20)	(50)	(0)	(50)	(43)
Anemia	2	2	0	0	0
(%)	(20)	(20)	(0)	(0)	(0)
Thrombocytopenia	0	0	0	0	1
(%)	(0)	(0)	(0)	(0)	(14)
Diarrhea	0	3	0	0	0
(%)	(0)	(30)	(0)	(0)	(0)
Pneumonitis	0	0	1	0	1†
(%)	(0)	(0)	(50)	(0)	(14)

†Grade 5.

respectively. The lowest hemoglobin levels of these patients were 10.5 ± 1.9 g/dL, 9.5 ± 2.1 g/dL, 10.5 ± 0.9 g/dL, 10.6 ± 0.7 g/dL, and 10.7 ± 2.1 g/dL, respectively. The lowest platelet counts of the patients were 15.0 ± 2.4 × 10⁴/μL, 12.3 ± 4.4 × 10⁴/μL, 24.6 ± 12.9 × 10⁴/μL, 14.7 ± 2.5 × 10⁴/μL, and 11.8 ± 4.7 × 10⁴/μL, respectively. There were no differences in the lowest neutrophil counts, hemoglobin levels, or platelet counts between the wild-type patients and those with gene polymorphisms (Fig 1b–d).

Efficacy

The treatment response was assessable in 28 of the 31 patients. The overall response rate was 71% (complete response 7%, partial response 64%). Two patients with the *UGT1A1**6 polymorphism achieved complete responses. In detail, 7 of 10 wild-type patients (70%), 9 of 10 *6/- (90%) patients, 1 of 1 *7/- (100%) patients, 2 of 2 *27/- (100%) patients, and 1 of 5 *28/- (20%) patients exhibited responses to treatment. At the time of the survival assessment performed in September 2016, three patients were still alive, while 28 had died. The median PFS of the 31 patients was 6.3 months, and their one and two-year survival rates were 34.2% and 21.4%, respectively. The median PFS of the different *UGT1A1* polymorphism groups were as follows: heterozygous *UGT1A1**6, 9.6 months; heterozygous *UGT1A1**7, 6.0 months; heterozygous *UGT1A1**27, 5.9 months; and heterozygous *UGT1A1**28, 6.3 months. The median OS of the 31 patients

was 11.1 months, and their one and two-year survival rates were 45.2% and 25.8%, respectively. The median OS of the various *UGT1A1* polymorphism groups were as follows: heterozygous *UGT1A1**6, 19.1 months; heterozygous *UGT1A1**7, 9.0 months; heterozygous *UGT1A1**27, 9.8 months; and heterozygous *UGT1A1**28, 10.6 months. Kaplan–Meier plots and log-rank tests did not detect any differences in PFS or OS between the four groups.

Pharmacokinetics

A pharmacokinetic analysis of irinotecan involving all 31 patients was performed. The plasma concentration time curves of irinotecan, SN-38, and SN-38G are shown according to the *UGT1A1* gene polymorphisms possessed by the patients in Figure 2. The patients with *UGT1A1**27 and *UGT1A1**28 polymorphisms exhibited small increases in their plasma SN-38G levels, and retained clinically sufficient plasma SN-38 concentrations for longer periods after the infusion of irinotecan compared to the wild-type patients. In contrast, clinically sufficient plasma concentrations of SN-38 were observed for prolonged periods in the patients with *UGT1A1**7. The area under the plasma concentration-time curve values of irinotecan, SN-38, and SN-38G were 2620.0 ± 1820.6 ng/h/mL, 137.8 ± 161.0 ng/h/mL, and 3796.3 ± 2512.8 ng/h/mL in the wild-type patients; 2801.1 ± 1461.2 ng/h/mL, 172.0 ± 116.8 ng/h/mL, and 2131.7 ± 1399.2 ng/h/mL in the heterozygous *UGT1A1**6 patients; 2231.3 ± 1360.2 ng/h/mL, 238.6 ± 138.0 ng/h/mL, and 773.9 ± 280.2 ng/h/mL in the heterozygous *UGT1A1**7 patients; 1856.2 ± 583.8 ng/h/mL, 392.3 ± 491.1 ng/h/mL, and 2484.4 ± 339.5 ng/h/mL in the heterozygous *UGT1A1**27 patients; and 5536.6 ± 3369.5 ng/h/mL, 463.9 ± 386.3 ng/h/mL, and 3231.3 ± 1906.4 ng/h/mL in the heterozygous *UGT1A1**28 patients, respectively. The associations between each genotype and the AUC ratio (AUC of SN-38G/AUC of SN-38) were evaluated in 31 patients and are shown in Figure 3. The AUC ratios of the patients with *UGT1A1* gene polymorphisms did not differ significantly but tended to be lower than those of the wild-type patients.

Discussion

The present study attempted to determine the clinical impact of the *UGT1A1**7, *UGT1A1**27, and *UGT1A1**29 gene polymorphisms in patients who receive irinotecan-

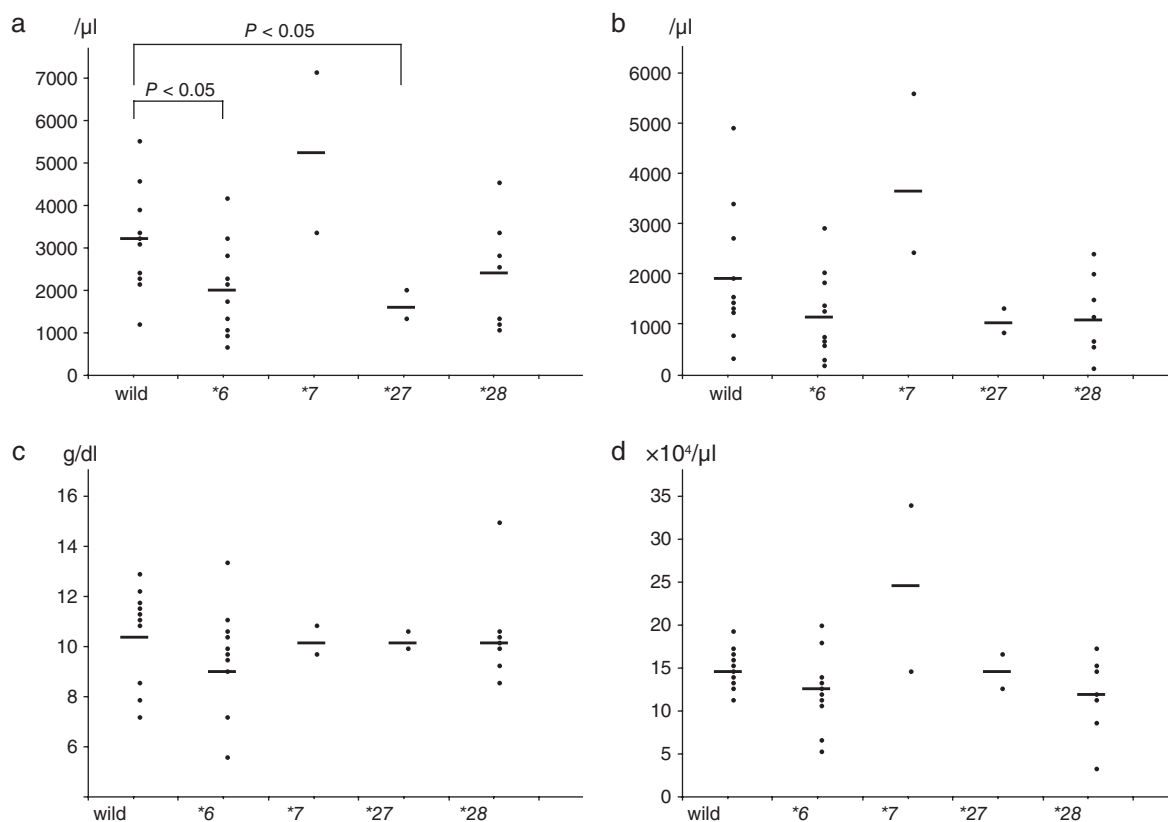


Figure 1 The lowest (a) leukocyte counts, (b) neutrophil counts, (c) hemoglobin levels, and (d) platelet counts observed in wild-type patients and those with *UGT1A1* gene polymorphisms.

based chemotherapy. Our results indicated that *UGT1A1**27 can occur separately from *UGT1A1**28 and is related to irinotecan-related leukopenia, *UGT1A1**7 is less relevant to irinotecan-related toxicities, and *UGT1A1**29 does not seem to have a clinical impact.

Irinotecan is a semi-synthetic prodrug that is metabolized by carboxylesterase to form the active metabolite SN-38, which is subsequently metabolized in the liver by *UGT1A1* to the inactive metabolite SN-38 glucuronide (SN-38G).²¹ *UGT1A1* is mainly expressed in the liver and is considered to be responsible for the inactivation of SN-38, and genetic polymorphisms in *UGT1A1* result in reduced enzyme activity and increased irinotecan toxicity. The most frequently studied *UGT1A1* gene polymorphism, *UGT1A1**28, has been determined to be an extremely strong risk factor for severe irinotecan-related toxicities, such as diarrhea and neutropenia, in Caucasians and Asians.^{9,10,22} Therefore, the *UGT1A1**28 polymorphism was defined as a predictor of irinotecan toxicity by the United States Food and Drug Administration in 2005. In our prospective phase II study and meta-analysis of Asian patients, the *UGT1A1**6 polymorphism was found to be associated with irinotecan-related neutropenia in both homozygotes and heterozygotes.^{23,24} The maximum tolerated doses of

irinotecan chemotherapy in cancer patients with *UGT1A1**28 or *UGT1A1**6 polymorphisms are 20–50% lower compared to those of wild type.^{25,26}

The *UGT1A1**27 gene was believed to be in linkage disequilibrium with *UGT1A1**28. Specifically, basic research suggested that these polymorphisms co-occur (form a haplotype) and reduce *UGT* enzyme activity.^{12,27} A previous study reported that out of three patients that were heterozygous for the *UGT1A1**27 gene polymorphism, two were homozygous and one was heterozygous for the *UGT1A1**28 gene polymorphism.¹⁰ We conducted a prospective study to determine the clinical impact of the *UGT1A1**27 gene polymorphism in patients that were confirmed to possess the *UGT1A1**28 haplotype and were receiving irinotecan-based chemotherapy.²⁸ However, we did not identify any patients that possessed both the *UGT1A1**27 and *28 gene polymorphisms; therefore, the abovementioned hypothesis might be inaccurate. In the present study, we found two patients with the *UGT1A1**27 polymorphism who also possessed the wild-type *UGT1A1**28 gene, and all seven of the patients with the *UGT1A1**28 polymorphism also possessed the wild-type *UGT1A1**27 gene. The two patients with the *UGT1A1**27 polymorphism lived in Nagasaki City; however, they were not affected by the atomic bombing of the city.

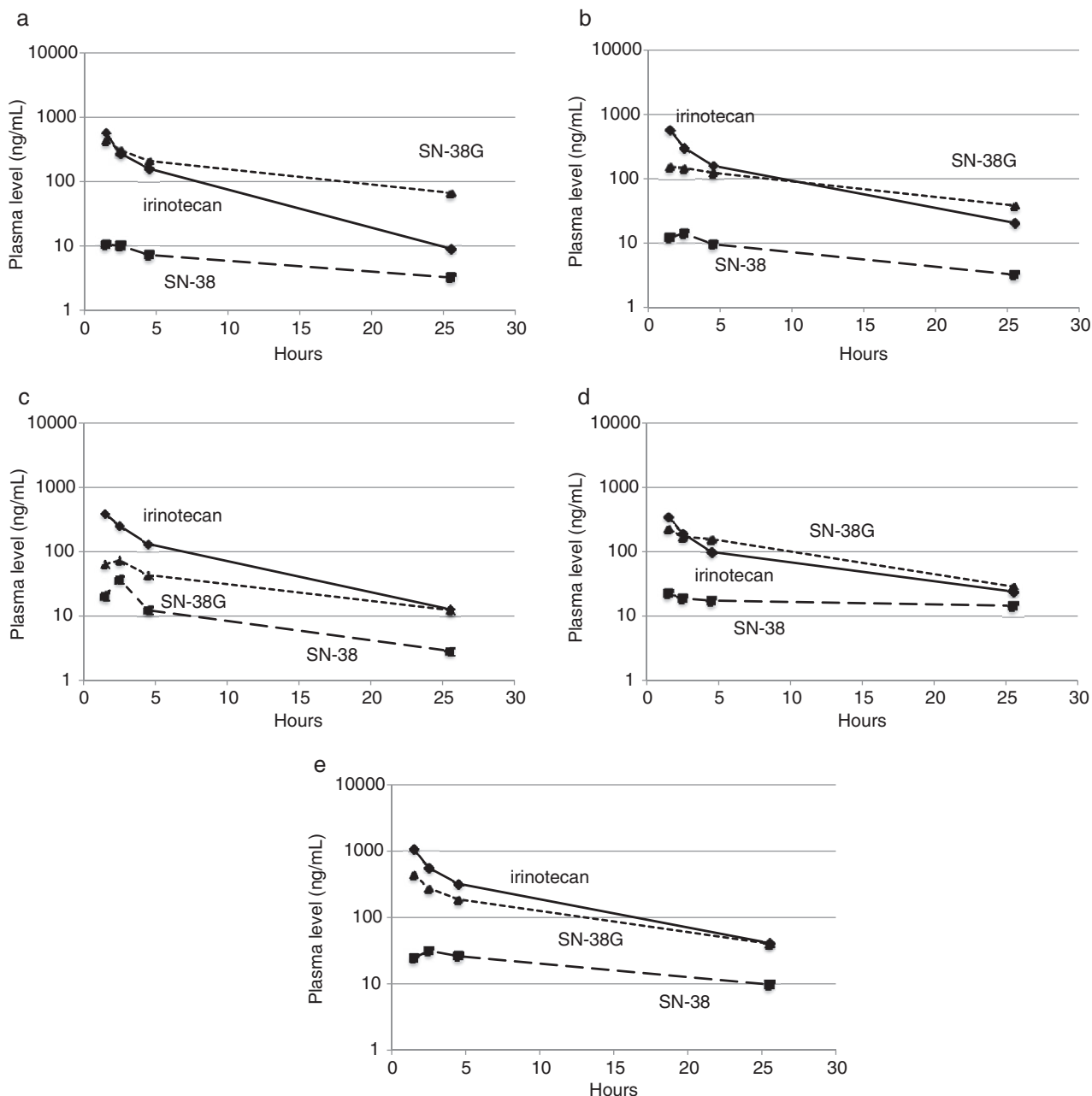


Figure 2 Blood concentration time curves of irinotecan, SN-38 and SN-38G (a) wild-type, (b) *UGT1A1**6, (c) *UGT1A1**7, (d) *UGT1A1**27, and (e) *UGT1A1**28 heterozygous gene polymorphisms.

The patients in our current study did not overlap in our previous two studies.^{26,28} Therefore, it seems that *UGT1A1**27 can occur separately from *UGT1A1**28 in some circumstances.

Only seven patients with the heterozygous *UGT1A1**27 gene polymorphisms treated with irinotecan have been reported in the literature (in 2 clinical studies). In our previous study of the *UGT* polymorphisms present in 77 patients, the heterozygous *UGT1A1**27 polymorphism

was found in four patients (5.2%), and three of the four patients experienced grade 4 neutropenia.²³ Ando *et al.* examined *UGT* polymorphisms in 118 patients, and the heterozygous *UGT1A1**27 polymorphism was found in three patients (2.5%), all three of which developed severe irinotecan-related toxicities (grade 4 leukopenia and/or grade 3 or worse diarrhea).¹⁰ The present study examined the *UGT* polymorphisms possessed by 31 patients, and the heterozygous *UGT1A1**27 polymorphism was found in

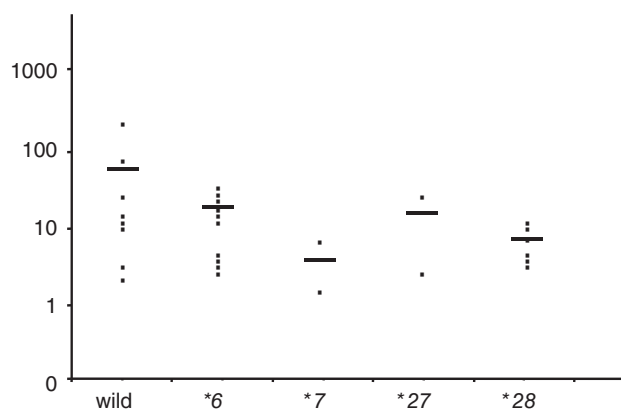


Figure 3 Area under the curve ratios of SN-38G/SN-38.

two patients (6.5%). One of these patients suffered febrile neutropenia. Taking the findings of the three studies together, 226 patients were examined for UGT polymorphisms, and the heterozygous *UGT1A1**27 polymorphism was found in nine patients, seven of whom experienced severe irinotecan-related toxicities. Therefore, the *UGT1A1**27 polymorphism was found at a frequency of 4.0% (9/226). All of these patients were heterozygous for the *UGT1A1**27 polymorphism, and 77.8% (7/9) experienced irinotecan-associated severe toxicities. Some of the patients possessed the *UGT1A1**28 polymorphism, whereas others did not. In the patients with *UGT1A1**27 and *UGT1A1**28 polymorphisms, a clinically sufficient blood concentration of SN-38 tended to be detected for up to 24 hours after the infusion of irinotecan. In patients with *UGT1A1**6 polymorphisms, blood concentration of SN-38 shows similar behavior with wild type, but irinotecan seems to retain comparatively high concentration and might be concerned with toxicities.

The *UGT1A1**7 gene polymorphism has only been detected in a few previous clinical studies.¹⁰ In the current study, we detected the *UGT1A1**7 gene polymorphism in two patients, at a frequency of 6.5%. The toxicities associated with this polymorphism were generally mild, and no cases of grade 3 or worse myelotoxicity were experienced. In addition, the period during which a clinically sufficient blood concentration of SN-38 was detected was not prolonged in these patients. One patient experienced pneumonitis after chemoradiotherapy, but recovered after being treated with corticosteroid therapy. Therefore, the *UGT1A1**7 polymorphism was found at a frequency of 1.3% (2/149; all cases were heterozygous) and was not associated with severe irinotecan-related toxicities. As for the *UGT1A1**29 gene polymorphism, the findings of the present and a previous study suggest that it has little clinical impact.¹⁰

In conclusion, *UGT1A1**27 and *UGT1A1**7 are both rare polymorphisms. *UGT1A1**27 can occur separately

from *UGT1A1**28 in some circumstances and is related to leukopenia during irinotecan treatment. On the other hand, *UGT1A1**7 is less relevant to irinotecan-induced toxicities, and *UGT1A1**29 seems to have little clinical impact.

Disclosure

No authors report any conflict of interest.

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