ORIGINAL ARTICLE

Phase I study of irinotecan for previously treated lung cancer patients with the *UGT1A1*28* or *6 polymorphism: Results of the Lung Oncology Group in Kyushu (LOGIK1004A)

Minoru Fukuda[1], Midori Shimada[2], Takeshi Kitazaki[2], Seiji Nagashima[3], Kohji Hashiguchi[2], Noriyuki Ebi[4], Koichi Takayama[5], Yoichi Nakanishi[6], Hiroshi Semba[7], Taishi Harada[6], Takashi Seto[8], Isamu Okamoto[6], Yukito Ichinose[9] & Kenji Sugio[10,11]

1 Clinical Oncology Center, Nagasaki University Hospital, Nagasaki, Japan
2 Division of Respiratory Diseases, Department of Internal Medicine, Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki, Japan
3 Department of Medicine, National Hospital Organization Nagasaki Medical Center, Nagasaki, Japan
4 Department of Respiratory Oncology Medicine, Iizuka Hospital, Fukuoka, Japan
5 Department of Pulmonary Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan
6 Research Institute for Disease of the Chest, Graduate School of Medical Sciences, Kyusyu University, Fukuoka, Japan
7 Department of Respiratory Medicine, Kumamoto Regional Medical Center, Kumamoto, Japan
8 Department of Thoracic Oncology, National Kyusyu Cancer Center, Fukuoka, Japan
9 Clinical Research Institute, National Kyusyu Cancer Center, Fukuoka, Japan
10 Department of Thoracic and Breast Surgery, Oita University Faculty of Medicine, Oita, Japan
11 Lung Oncology Group in Kyusyu, Fukuoka, Japan

Abstract

Background: Various polymorphisms have been detected in the UDP-glucuronosyltransferase 1A (*UGT1A*) gene, and *UGT1A1*28* and *UGT1A1*6* have important effects on the pharmacokinetics of irinotecan and the risk of severe toxicities during irinotecan therapy. This study was conducted to determine the maximum tolerated dose (MTD) of irinotecan chemotherapy according to the *UGT1A1* genotype in previously treated lung cancer patients with the *UGT1A1*28* or *UGT1A1*6* polymorphism.

Methods: The eligibility criteria were as follows: lung cancer patients that had previously been treated with anticancer agents other than irinotecan, possessed the *UGT1A1*28* or *UGT1A1*6* polymorphism (group A included *28/*28, *6/*6, and *28/*6, and group B included *28/− and *6/−), were aged ≤75 years old, had a performance score of 0–1, and exhibited adequate bone marrow function. The patients were scheduled to receive irinotecan on days 1, 8, 15, 22, 29, and 36.

Results: Four patients were enrolled in this trial. Two patients were determined to be ineligible. The remaining two patients, who belonged to group B, received an initial irinotecan dose of 60 mg/m^2, but did not complete the planned treatment because of diarrhea and leukopenia. Thus, in group B patients, 60 mg/m^2 was considered to be the MTD of irinotecan. The study was terminated in group A because of poor case recruitment.

Conclusions: The MTD of irinotecan for previously treated lung cancer patients that are heterozygous for the *UGT1A1*28* or *UGT1A1*6* gene polymorphism is 60 mg/m^2.

Introduction

Irinotecan hydrochloride, a water-soluble prodrug that exhibits anticancer activity based on the inhibition of topoisomerase I, is widely used against solid tumors, including lung, colorectal, gastric, gynecological, and other types of cancer.[1–4] However, it causes adverse events, such as severe neutropenia and diarrhea, in 13–25% of patients.[5,6] Irinotecan is metabolized by carboxylesterase to form its active metabolite, SN-38, which is subsequently metabolized by various uridine-diphosphate glucuronosyltransferase 1A (UGT1A) isoforms, including UGT1A1, to an inactive metabolite, SN-38 glucuronide (SN-38G), in the liver.[7] A number of polymorphisms have been detected in the UGT1A gene, and multiple studies have found that they have important effects on the pharmacokinetics of irinotecan and the risk of severe toxicities during irinotecan therapy.[8–15]

UGT1A1*28 is associated with decreased UGT1A1 expression and activity.[16,17] UGT1A1*28 exhibits higher and lower frequencies in Caucasians and Asians, respectively.[10–13,18,19] UGT1A1*6 is also associated with reduced UGT1A1 enzyme activity and is more common in Asians.[14,20–22]. Both UGT1A1*28 and UGT1A1*6 are related to greater or more prolonged exposure to SN-38 and the occurrence of adverse events in irinotecan chemotherapy.[9–12] To resolve the problems associated with the effects of patient variability on the risk of irinotecan-related toxicities and optimize treatment tolerance, the individualization of irinotecan doses according to the patient's UGT1A1 genotype has been proposed.

Based on these findings, we conducted a phase I study of irinotecan therapy for previously treated lung cancer patients with the UGT1A1*28 or UGT1A1*6 polymorphism. The main objective of this study was to determine the maximum-tolerated dose (MTD) of irinotecan chemotherapy according to the UGT1A1 genotype.

Patients and methods

The study protocol was reviewed and approved by the protocol committee of the Lung Oncology Group in Kyusyu (LOGiK) and the ethics committee of each participating institution. Written informed consent was obtained from all study subjects. This study was an independent collaborative (unsponsored) group study and was registered at the University Hospital Medical Information Network (UMIN) in Japan (UMIN000006095).

Patients and evaluation

The patient eligibility criteria for this study were as follows: a histologically and/or cytologically confirmed diagnosis of lung cancer; previous treatment with an anticancer agent other than irinotecan; possessing the UGT1A1*28 or UGT1A1*6 polymorphism (group A included *28/*28, *6/*6, and *28/*6, and group B included *28/− and *6/−); aged ≤75 years old; having an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1; displaying adequate bone marrow function (a leukocyte count of ≥ 3000/μL, a neutrophil count of ≥1500 μL, a hemoglobin level of ≥9.0 g/dL, and a platelet count of ≥10.0 × 10^4 μL); alanine transaminase and aspartate transaminase levels of <100 IU/L; a serum bilirubin level of ≤1.5 mg/dL; a serum creatinine level of ≤1.5 mg/dL; an arterial blood oxygen partial pressure of ≥60 torr or an SpO2 of ≥90%; and no medical problems that were severe enough to prevent compliance with the study protocol. The exclusion criteria were as follows: the detection of interstitial pneumonia on a chest X-ray; pericardial or pleural effusion, superior vena cava syndrome, or a metastatic brain tumor that required treatment; other active malignancies; pregnancy or possible pregnancy; mental disease that made it difficult for the subject to complete the study; a fever of ≥38°; severe complications, including myocardial infarction, that occurred within three months; uncontrolled angina pectoris, heart failure, diabetes mellitus, and hypertension; diarrhea; and paralysis of the intestine or ileus.

Genotyping assay and toxicity evaluation

After obtaining blood samples from patients who were scheduled to undergo irinotecan treatment, genomic DNA was isolated from them. UGT1A1*28 and UGT1A1*6 polymorphisms were analyzed using the Invader assay (BML, Inc., Tokyo, Japan). Drug toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v 3.0 (CTCAE). Before the first cycle of treatment, a blood cell count, urinalysis, and biochemistry tests were performed to assess the patients' renal and hepatic function and electrolyte levels. These examinations were repeated during treatment, while other tests were repeated as necessary.

Treatment

Treatment commenced within one week of enrollment. The patients were scheduled to receive irinotecan treatment on days 1, 8, 15, 22, 29, and 36. We administered an initial dose of 60 mg/m² and planned to increase the irinotecan dose in 10-mg/m² steps, as shown in Table 1. Irinotecan dissolved in 250 mL of 5% dextrose was infused intravenously over 60 minutes. The irinotecan therapy was postponed if the patient exhibited a leukocyte count of <3000 μL, a neutrophil count of <1500 μL, or a platelet count of <10 × 10^4 μL or suffered diarrhea on the day of

Table 1 Dose escalation plan

Dose level	Irinotecan (mg/m^2)
1	60
2	70
3	80
4	90
5	100

Dose escalation was conducted in both groups A and B.

or the day before treatment. Postponement of the irinotecan therapy for ≤1 week was permitted, but it was decided that the treatment must be completed no later than day 50.

Outcomes

Dose-limiting toxicities (DLT) were evaluated during the first cycle and were defined as follows: grade 4 leukopenia or neutropenia that lasted for ≥4 days; grade 3 febrile neutropenia; a platelet count of <20 000 μL; grade 3 or worse non-hematological toxicities except for nausea, vomiting, baldness, and anemia; and patients that did not complete the treatment.

Regarding dose escalation, three patients were enrolled at each dose level, and the dose was escalated to the next level if none of the patients experienced DLT. When two or more patients experienced DLT, the dose level was defined as the MTD. When one of the three patients experienced DLT, an additional three patients were treated at the same level. If none of the additional patients experienced DLT, the dose was escalated to the next level. If one or more of the additional patients experienced DLT, the dose level was defined as the MTD. The recommended dose of this regimen for a phase II study was defined as the highest dose level below the MTD. Dose escalation was performed based solely on the data for the first course of chemotherapy. The irinotecan dose was reduced to 70% when DLT occurred during the first treatment cycle.

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 on which the patient was censored. Overall survival (OS) was defined as the period from the start of irinotecan therapy until death from any cause or the date on which the patient was censored. Survival was evaluated using the Kaplan–Meier method.

Results

Four patients were enrolled in this trial between December 2011 and November 2012. One patient with the *UGT1A1 *28/*28* polymorphism, in group A, was determined to be ineligible for the study by external reviewers because she was suffering from interstitial pneumonia, and a patient with the *UGT1A1 *6/*6* polymorphism, who also belonged to group A, was considered to be ineligible because of their age. The remaining two patients, who both belonged to group B, had their toxicities, responses, and survival evaluated. The patients' baseline characteristics are shown in Table 2. The patients both possessed the *UGT1A1 *28/−* genotype and started receiving irinotecan at a dose of 60 mg/m^2. In the first patient, irinotecan therapy was successfully administered on days 1, 15, 22, 29, and 36, but was postponed on day 8 because of diarrhea. His PS worsened, and the irinotecan therapy was postponed from day 43 onwards. He did not complete the planned treatment and was judged as having reached DLT. In the second patient, irinotecan therapy was successfully administered on days 1, 15, and 29, but was postponed on days 8, 22, and 36 because of grade 2 leukopenia. Thus, it was administered every two weeks, but the patient did not complete the planned treatment because of DLT. The administration of six consecutive weekly rounds of 60 mg/m^2 irinotecan was difficult in group B; thus, 60 mg/m^2 was considered to be the MTD. The study was terminated because of poor case recruitment in group A.

Toxicity and efficacy

The hematological and non-hematological toxicities experienced by each patient are listed in Table 3. The only grade 3–4 hematological toxicity experienced by the patients was anemia, which occurred in the first patient. There were no cases of febrile neutropenia, hepatotoxicity, interstitial lung injuries, or treatment-related death. None of the toxicities were severe; however, the patients could not complete the treatment on schedule. In addition, no objective tumor responses were observed, and both patients exhibited progressive disease. At the time of the survival assessment, both patients had already died. The patients' median PFS and OS values were 33 and 66 days, respectively.

Table 2 Patient characteristics

Group	Dose	*UGT*	Age	Gender	Histology	TNM	Stage	Previous
B	60	*28/−	63	M	Adeno	T2aN3M1b	IV	PEM + CB, S1
B	60	*28/−	65	M	Small	T2bN3M1a	IV	AMR + CB

AMR, amrubicin; CB, carboplatin; PEM, pemetrexed; TNM, tumor node metastasis.

Table 3 Toxicities and treatment completion

Group	Hb	Leuko	Neutro	Plt	FN	Nausea	Vomiting	Diarrhea	AST	ALT	Cr	ILD	Compl	DLT
B	3	0	0	0	0	2	0	1	0	0	0	0	No	Yes
B	1	2	1	1	0	1	0	0	0	0	0	0	No	Yes

ALT, increased alanine transaminase levels; AST, increased aspartate aminotransferase levels; Compl, treatment completion; Cr, increased serum creatinine levels; DLT, dose-limiting toxicity; FN, febrile neutropenia; Hb, hemoglobin; ILD, interstitial lung injury; Leuko, leukopenia; Neutro, neutropenia; Plt, thrombocytopenia.

Discussion

The results of this phase I study demonstrated that a weekly irinotecan dose of 60 mg/m^2 is the MTD for previously treated lung cancer patients that are heterozygous for the *UGT1A1*28* or *UGT1A1*6* polymorphism. In addition, they suggested that leukopenia is a DLT of such treatment. It was has been reported that the recommended dose of weekly irinotecan for previously untreated patients with advanced non-small-cell lung cancer was 100 mg/m^2 (although the effects of gene polymorphisms were not considered in this study), and the DLT of this regimen were found to include myelosuppression and diarrhea.[23] Therefore, prior treatment and *UGT1A1* gene polymorphisms are associated with a 40% lower MTD.

SN-38, the active metabolite of irinotecan, is detoxified when it is glucuronidated by UGT1A (isoform 1A1, 1A7, 1A9, or 1A10). Patients with the *UGT1A1*28* polymorphism display a significantly lower SN-38 glucuronidation rate than those with the normal allele and suffer more severe diarrhea and neutropenia.[10,24] Thus, *UGT1A1*28* polymorphisms have been considered to be predictors of irinotecan toxicity by the United States Food and Drug Administration since 2005. In a meta-analysis of nine studies that included a total of 821 patients, Hoskins *et al.* assessed the association between the irinotecan dose and the risk of irinotecan-related hematological toxicities (grade 3 or 4) in patients with the *UGT1A1*28/*28* genotype.[25] They found that the risk of toxicities was higher among the patients with the *UGT1A1*28/*28* genotype than among those with the *UGT1A1*1/*1* or *UGT1A1*1/ *28* genotype at both medium and high doses of irinotecan. However, all of the genotypes were associated with similar risks of toxicities at lower doses of irinotecan (100–125 mg/m^2), which are commonly used in clinical practice. In the present study, two patients with the *UGT1A1* *28/−* genotype received lower doses of irinotecan. The first patient was administered weekly irinotecan, except on day 8, and did not complete the planned treatment. Although this patient was considered to have developed a DLT according to previously described criteria, it was unclear whether they had actually developed a true DLT, which is considered to be one of the limitations of this study. The first patients' poorer PS was associated with

disease progression and was not associated with DLT; however, after discussion, the protocol committee decidedto attribute the result to DLT. The second patient could not be administered irinotecan on a weekly basis and ended up receiving irinotecan biweekly instead, which supports the suggestion that 60 mg/m^2 is the MTD of irinotecan in our study population. After re-examining the dose escalation protocol used, the protocol committee recommended that we end the study and start a new one with a different protocol.

In Asian studies, the *UGT1A1*6* allele has been found to be associated with low glucuronidation activity and severe toxicity. Minami *et al.* analyzed cases of Japanese cancer patients treated with irinotecan in order to determine if any associations existed between genetic polymorphisms and toxicities, and demonstrated that homozygotes and double heterozygotes of *6 and *28 were significantly associated with severe neutropenia.[26] Han *et al.* reported that homozygosity for *UGT1A1*6* was associated with a high risk of severe neutropenia during irinotecan treatment.[12] We encountered a case in which a patient that was heterozygous for the *UGT1A1*6* polymorphism suffered life-threatening severe leukopenia, neutropenia, febrile neutropenia, thrombocytopenia, and diarrhea after irinotecan-based chemotherapy.[27] Thus, we had planned to include patients that were heterozygous for the *UGT1A1*6* polymorphism in group B; however, no such patients were enrolled in the present study.

Our study was terminated in group A, which was intended to include patients that possessed the *28/*28, *6/ *6, or *28/*6 polymorphism, because of poor case recruitment. In a meta-analysis that reviewed the data presented in nine studies, which included a total of 10 sets of patients (total number of patients: 821), 10.2% (84) of the patients displayed the *UGT1A1*28/*28* genotype.[26] However, large inter-ethnic differences of *UGT1A1* gene polymorphism distribution are observed between Western and Asian countries.[11,28] In another *UGT1A1* gene polymorphism study of 48 evaluable patients conducted during the same period as our group, the *28/*28, *6/*6, and *28/*6 polymorphisms were only detected in 0% (0 patients), 2% (1), and 2% (1) of patients, respectively.[29] One patient that was homozygous for the *UGT1A1*6* polymorphism experienced

grade 3 neutropenia and grade 3 diarrhea, whereas another patient that was classified as a *UGT1A1*28/*6* compound heterozygote did not experience any grade 3 or worse toxicities. In five Japanese *UGT1A1* studies (*n* = 612), the *28/*28*, *6/*6*, and *28/*6* polymorphisms were detected at frequencies of 2.7%, 2.5%, and 2.9%, respectively.[11,13,15,27,30] Therefore, it might be difficult to recruit *UGT1A1* homozygote and compound heterozygote lung cancer patients to irinotecan dose-escalating studies in Japan.

Negoro *et al.* conducted the first single agent irinotecan phase I trial in Japan with a weekly schedule of days 1, 8, 15, 22, 29, 36.[23] In contrast, Rothenberg *et al.* conducted a phase I and pharmacokinetic trial of single agent irinotecan in the United States with a weekly schedule of days 1, 8, 15, 22, followed by a two-week rest period.[31] Although we used a weekly schedule of days 1, 8, 15, 22, 29, and 36 in the present study, a weekly schedule of days 1, 8, 15, 22, followed by a two-week rest may be preferable, as recommended by the irinotecan interview form.

In conclusion, 60 mg/m^2 is considered to be the MTD of irinotecan for previously treated lung cancer patients that are heterozygous for the *UGT1A1*28* or *UGT1A1*6* gene polymorphism.

Acknowledgment

Disclosure

No authors report any conflict of interest.

References

1 Boku N, Yamamoto S, Fukada H *et al.* Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: A randomized phase 3 study. *Lancet Oncol* 2009; **10**: 1063–9.

2 Bodurka DC, Levenback C, Wolf JK *et al.* Phase II trial of irinotecan in patients with metastatic epithelial ovarian cancer or peritoneal cancer. *J Clin Oncol* 2003; **21**: 291–7.

3 Noda K, Nishiwaki Y, Kawahara M *et al.* Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002; **346**: 85–91.

4 Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. *N Engl J Med* 2005; **352**: 476–87.

5 Fukuoka M, Niitani H, Suzuki A *et al.* A phase II study of CPT-11, a new derivative of camptothecin, for previously untreated non-small-cell lung cancer. *J Clin Oncol* 1992; **10**: 16–20.

6 Shimada Y, Yoshino M, Wakui A *et al.* Phase II study of CPT-11, a new camptothecin derivative, in metastatic colorectal cancer. CPT-11 Gastrointestinal Cancer Study Group. *J Clin Oncol* 1993; **11**: 909–13.

7 Kawato Y, Aonuma M, Hirota Y, Kuga H, Sato K. Intracellular roles of SN-38, a metabolite of the camptothecin derivative CPT-11, in the antitumor effect of CPT-11. *Cancer Res* 1991; **51**: 4187–91.

8 de Forni M, Bugat R, Chabot GG *et al.* Phase I and pharmacokinetic study of the camptothecin derivative irinotecan, administered on a weekly schedule in cancer patients. *Cancer Res* 1994; **54**: 4347–54.

9 Hahn KK, Wolff JJ, Kolesar JM. Pharmacogenetics and irinotecan therapy. *Am J Health Syst Pharm* 2006; **63**: 2211–7.

10 Innocenti F, Undevia SD, Iyer L *et al.* Genetic variants in the UGP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. *J Clin Oncol* 2004; **22**: 1382–8.

11 Ando Y, Saka H, Ando M *et al.* Polymorphisms of UGP-glucuronosyltransferase gene and irinotecan toxicity: A pharmacogenetic analysis. *Cancer Res* 2000; **60**: 6921–6.

12 Han JY, Lim HS, Shin ES *et al.* Comprehensive analysis of *UGT1A1* polymorphisms predictive for pharmacokinetics and treatment outcome in patients with non-small-cell lung cancer treated with irinotecan and cisplatin. *J Clin Oncol* 2006; **24**: 2237–44.

13 Sai K, Saeki M, Saito Y *et al.* *UGT1A1* haplotypes associated with reduced glucuronidation and increased serum bilirubin in irinotecan-administered Japanese patients with cancer. *Clin Pharmacol Ther* 2004; **75**: 501–15.

14 Jinno H, Tanaka-Kagawa T, Hanioka N *et al.* Glucuronidation of 7-ethyl-10-hydroxycamptothecin (SN-38), an active metabolite of irinotecan (CPT-11), by human UGT1A1 variants, G71R, P229Q, and Y486D. *Drug Metab Dispos* 2003; **31**: 108–13.

15 Nakamura Y, Soda H, Oka M *et al.* Randomized phase II trial of irinotecan with paclitaxel or gemcitabine for non-small cell lung cancer: Association of *UGT1A1*6* and *UGT1A1*27* with severe neutropenia. *J Thorac Oncol* 2011; **6**: 121–7.

16 Beutler E, Gelbart T, Demina A. Racial variability in the UDP-glucuronosyltransferase I (UGT1A1) promoter: A balanced polymorphism for regulation of bilirubin metabolism? *Proc Natl Acad Sci U S A* 1998; **95**: 8170–4.

17 Iyer L, Hall D, Das S *et al.* Phenotype–genotype correlation of in vitro SN-38 (active metabolite of irinotecan) and bilirubin glucuronidation in human liver tissue with UGT1A1 promoter polymorphism. *Clin Pharmacol Ther* 1999; **65**: 576–82.

18 Liu CY, Chen PM, Chiou TJ *et al.* UGT1A1*28* polymorphism predicts irinotecan-induced severe toxicities without affecting treatment outcome and survival in patients with metastatic colorectal carcinoma. *Cancer* 2008; **112**: 1932–40.

19 Ferraldeschi R, Minchell LJ, Roberts SA *et al.* *UGT1A1*28* genotype predicts gastrointestinal toxicity in patients treated with intermediate-dose irinotecan. *Pharmacogenomics* 2009; **10**: 733–9.

20 Takano M, Kato M, Yoshikawa T *et al.* Clinical significance of UDP-glucuronosyltransferase 1A1*6 for toxicities of combination chemotherapy with irinotecan and cisplatin in gynecologic cancers: A prospective multi-institutional study. *Oncology* 2009; **76**: 315–21.

21 Desai AA, Innocenti F, Ratain MJ. Pharmacogenomics: Road to anticancer therapeutics nirvana? *Oncogene* 2003; **22**: 6621–8.

22 Park SR, Kong SY, Rhee J *et al.* Phase II study of a triplet regimen of S-1 combined with irinotecan and oxaliplatin in patients with metastatic gastric cancer: Clinical and pharmacogenetic results. *Ann Oncol* 2011; **22**: 890–6.

23 Negoro S, Fukuoka M, Masuda N *et al.* Phase I study of weekly intravenous infusions of CPT-11, a new derivative of camptothecin, in the treatment of advanced non-small-cell lung cancer. *J Natl Cancer Inst* 1991; **83**: 1164–8.

24 Iyer L, Das S, Janisch L *et al.* UGT1A1*28 polymorphism as a determinant of irinotecan disposition and toxicity. *Pharmacogenomics J* 2002; **2**: 43–7.

25 Hoskins JM, Goldberg RM, Qu P, Ibrahim JG, McLeod HL. UGT1A1*28 genotype and irinotecan-induced neutropenia: Dose matters. *J Natl Cancer Inst* 2007; **99**: 1290–5.

26 Minami H, Sai K, Saeki M *et al.* Irinotecan pharmacokinetics/pharmacodynamics and UGT1A1 genetic polymorphisms in Japanese: Roles of UGT1A1*6 and *28. *Pharmacogenet Genomics* 2007; **17**: 497–504.

27 Ogawara D, Fukuda M, Nakamura Y *et al.* Life-threatening toxicity in a patient with *UGT1A1*6* heterozygous polymorphism after irinotecan-based chemotherapy: A case report. *Acta Med Nagasaki* 2014; **59**: 63–5.

28 Sai K, Saito Y. Ethnic differences in the metabolism, toxicology and efficacy of three anticancer drugs. *Expert Opin Drug Metab Toxicol* 2011; **7**: 967–88.

29 Fukuda M, Suetsugu T, Shimada M *et al.* Prospective study of the *UGT1A1*27* gene polymorphism for irinotecan therapy: Results of Lung Oncology Group in Kyusyu (LOGIK1004B). *Thorac Cancer* 2016; **7**: 467–72.

30 Araki K, Fujita K, Ando Y *et al.* Pharmacogenetic impact of polymorphisms in the coding region of the *UGT1A1* gene on SN-38 glucuronidation in Japanese patients with cancer. *Cancer Sci* 2006; **97**: 1255–9.

31 Rothenberg ML, Kuhn JG, Burris HA III *et al.* Phase I and pharmacokinetic trial of weekly CPT-11. *J Clin Oncol* 1993; **11**: 2194–204.