Cancer Chemother Pharmacol (2011) 68:279–284
DOI 10.1007/s00280-010-1485-8

ORIGINAL ARTICLE

*UGT1A1*1/*28* and **1/*6* genotypes have no effects on the efficacy and toxicity of FOLFIRI in Japanese patients with advanced colorectal cancer

Yu Sunakawa · Wataru Ichikawa · Ken-ichi Fujita · Fumio Nagashima · Hiroo Ishida · Keishi Yamashita · Keiko Mizuno · Keisuke Miwa · Kaori Kawara · Yuko Akiyama · Kazuhiro Araki · Wataru Yamamoto · Toshimichi Miya · Masaru Narabayashi · Yuichi Ando · Takashi Hirose · Shigehira Saji · Yasutsuna Sasaki

Received: 13 July 2010 / Accepted: 30 September 2010 / Published online: 19 October 2010

Abstract
Purpose Differences in efficacy and toxicity between *UDP-glucuronosyltransferase* (*UGT*) *1A1*1/*1* and **1/*6* or **1/*28* genotypes remain unclear in Japanese patients.
Methods Patients with advanced colorectal cancer who received irinotecan combined with 5-fluorouracil plus *l*-leucovorin (FOLFIRI) as first-line therapy were divided into two groups: those with *UGT1A1*1/*1* genotype and those with *UGT1A1*1/*6* or **1/*28* genotype. Efficacy and toxicity were compared between these groups retrospectively.
Results Forty-two patients (24 **1/*1* and 18 **1/*6* or **1/*28*) were evaluated. The response rate was 48% in **1/*1* group and 56% in **1/*6* or **1/*28* group ($P = 0.847$). Median progression-free survival was 8.6 months in **1/*1* group and 8.5 months in **1/*6* or **1/*28* group ($P = 0.888$). No hematologic or non-hematologic toxic effects were clearly related to *UGT1A1*1/*6* or **1/*28* during the first cycle or throughout the entire course of chemotherapy.
Conclusions There were no significant differences in the efficacy or toxicity of FOLFIRI between patients with *UGT1A1*1/*1* genotype and those with *UGT1A1*1/*6* or **1/*28* genotype. Our results suggest that patients with the latter genotypes can receive FOLFIRI at the same dose of irinotecan as those with the *UGT1A1*1/*1* genotype receive.

Keywords *UGT1A1*6* · *UGT1A1*28* · Heterozygote · Irinotecan · Efficacy · Toxicity

Y. Sunakawa · W. Ichikawa · K. Fujita (✉) · F. Nagashima · H. Ishida · K. Yamashita · K. Mizuno · K. Miwa · K. Kawara · Y. Akiyama · K. Araki · W. Yamamoto · T. Miya · M. Narabayashi · Y. Ando · T. Hirose · S. Saji · Y. Sasaki
Department of Medical Oncology, International Medical Center-Comprehensive Cancer Center, Saitama Medical University, 1397-1 Yamane, Hidaka, Saitama 350-1298, Japan
e-mail: fujitak@saitama-med.ac.jp

W. Ichikawa
Department of Clinical Oncology, National Defense Medical College, 3-2, Namiki, Tokorozawa, Saitama 359-8513, Japan

K. Fujita · F. Nagashima · Y. Akiyama · Y. Sasaki
Project Research Laboratory, Research Center for Genomic Medicine, Saitama Medical University, 1397-1 Yamane, Hidaka, Saitama 350-1241, Japan

Introduction

Irinotecan is a topoisomerase I inhibitor that is widely used for the treatment of metastatic colorectal cancer and other solid tumors. This drug can cause unpredictable, severe, potentially fatal toxicities, such as neutropenia or delayed diarrhea. Irinotecan is a prodrug that is converted by carboxylesterase 2 to its active 7-ethyl-10-hydroxycamptothecin metabolite (SN-38) which is further metabolically detoxified by hepatic UDP-glucuronosyltransferase (UGT) 1A1 to an inactive metabolite, SN-38 glucuronide (SN-38G) [1]. Many pharmacogenetic studies have demonstrated that polymorphisms of the *UGT1A1* gene, especially *UGT1A1 *28*, underlie irinotecan-related toxicity [2, 3]. Asians have a lower allele frequency of *UGT1A1*28*, although *UGT1A1*28* is seen in both Asians and whites (allele frequency of 16 and 39%, respectively) [4]. In contrast, single nucleotide polymorphisms in exon 1 of the *UGT1A1* gene, *UGT1A1*6*, which is related to decreased catalytic activity for SN-38 [5], occurs at a relatively high allele frequency in Asians (about 20%), but not in whites [6–8].

Since *UGT1A1*28* and **6* are separately located on two different alleles, *UGT1A1*6/*6*, **28/*28,* and **6/*28* genotypes are found in Asians. These *UGT1A1* genotypes have been linked to severe neutropenia in Asians [7, 8].

Pharmacodynamic differences in efficacy and toxicity have not been detected between the *UGT1A1*1/*28* and **1/*1* genotypes in whites [9]. However, whether *UGT1A1*1/*1* and **1/*6* or *1/**28* genotypes are associated with differences in efficacy and toxicity in Asians remains uncertain; nevertheless, the frequency of *UGT1A1*1/*6* or **1/*28* genotype is higher in Japanese patients with cancer (about 45%; **1/*6* [29%], **1/*28* [16%]) [6–8]. To ensure clinical safety and effectiveness, it is important to compare the efficacy and toxicity of irinotecan between Japanese patients with *UGT1A1*1/*6* or **1/*28* genotypes and patients with *UGT1A1*1/*1* genotype.

In clinical practice, irinotecan is frequently combined with 5-fluorouracil plus *l*-leucovorin (FOLFIRI) for the first-line treatment of advanced colorectal cancer [10]. We therefore retrospectively investigated the relations between the *UGT1A1*1/*6* or **1/*28* genotypes and efficacy and toxicity in patients with advanced colorectal cancer who received FOLFIRI as first-line chemotherapy, and compared those with *UGT1A1*1/*1* genotypes.

Patients and methods

Study design

This retrospective study was performed at Saitama Medical University Hospital and International Medical Center. The primary objective was to compare the efficacy and toxicity of FOLFIRI as first-line chemotherapy between patients with the *UGT1A1*1/*1* genotype and those with **1/*6* or **1/*28* genotype. All patients signed written informed consent for *UGT1A1* genotyping of their peripheral blood samples. The study protocol for *UGT1A1* genotyping was approved by the Institutional Review Board of Saitama Medical University.

Treatment

Patients were treated with FOLFIRI as described by Tournigand et al. [11] (*l*-leucovorin 200 mg/m^2 as a 2-h intravenous infusion and irinotecan 180 mg/m^2 as a 90-min intravenous infusion, followed by a bolus intravenous injection of 5-fluorouracil 400 mg/m^2 and a 46-h intravenous infusion of 5-fluorouracil 2,400 mg/m^2, repeated every 2 weeks).

Treatment was discontinued if grade 3 or 4 toxicity recurred in a subsequent cycle, despite dose reduction. Treatment was continued until disease progression, unacceptable adverse events, or withdrawal of consent by the patient.

Efficacy and toxicity assessments

In patients who had received FOLFIRI for at least 2 months, responses were assessed by computed tomography or magnetic resonance imaging according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [12]. Efficacy was evaluated on the basis of the overall response rate and progression-free survival (PFS). PFS was defined as the date of starting treatment with FOLFIRI to the date of disease progression as defined by the RECIST criteria or to the date of death from any cause. The same imaging method was used for baseline tumor measurements and tumor reassessments.

Toxicity was evaluated according to National Cancer Institute Common Toxicity Criteria for Adverse Events, Version 3.0, in all patients who had received FOLFIRI at least once. Complete blood counts and hepatic and renal function tests were performed before the initiation of each cycle. Patients were questioned specifically about nausea and vomiting, mucositis, diarrhea, and appetite at the beginning of every cycle.

Statistical analysis

PFS was calculated by the Kaplan–Meier method with JMP version 6 software (SAS Institute, Cary, NC). The deadline for data evaluation was December 31, 2009. The statistical significance of differences in PFS between subgroups was assessed by the log-rank test, using JMP software.

The chi-square test or Fisher's two-tailed exact test was used to evaluate the association of *UGT1A1* genotype with efficacy and toxicity. Correlations were considered statistically significant when the two-tailed *P* value was less than 0.05.

UGT1A1 genotyping

Genomic DNA was extracted from peripheral blood, stored at −80°C until analysis, with the use of a QIAamp Blood Kit (QIAGEN, Hilden, Germany).

The G71R polymorphism (**6*) was analyzed by the polymerase chain reaction-restriction fragment length polymorphism method, and the TATA box polymorphism (**28*) was analyzed by the direct sequencing method as described by Fujita et al. [13].

Results

Patients

Between April 2005 and December 2009, 42 consecutive patients with advanced colorectal cancer were studied. The baseline characteristics of patients are summarized in Table 1. Most patients were in good overall physical condition, although 50% had at least two metastatic sites. All patients had a performance status of 0 or 1 according to the Eastern Cooperative Oncology Group scale, with adequate bone marrow, liver, and renal function. The *UGT1A1* genotype was **1/*1* in 24 patients and **1/*6* or **1/*28* in 18. There were no differences in the characteristics between the two groups.

Efficacy

Response was assessable in 39 of the 42 patients who received FOLFIRI as first-line therapy (Table 2). One patient (3%) had a complete response (CR), and 19 (49%) had a partial response (PR). The overall response rate (CR + PR) was 51% (20/39). The overall response rates were similar in **1/*1* group (48%) and **1/*6* or **1/*28* group (56%, $P = 0.847$).

The Kaplan–Meier curves for PFS in the patients with both groups are shown in Fig. 1. Median PFS was similar in **1/*1* group (8.6 months) and **1/*6* or **1/*28* group (8.5 months, $P = 0.888$).

Toxicity

Table 3 compares toxic effects between **1/*1* group and **1/*6* or **1/*28* group. During the first cycle of chemotherapy, the frequency of grade 3 or 4 neutropenia in **1/*1* group did not differ significantly from that in **1/*6* or **1/*28* group ($P = 0.675$). The incidence of febrile neutropenia was 4% in **1/*1* group and 0% in **1/*6* or **1/*28* group ($P = 0.883$). There was no significant difference in non-hematologic toxicity between groups. During the entire course of chemotherapy, there were also no significant differences in any toxic effects between groups (Table 3).

The dose of irinotecan was reduced in 18 of the 42 patients: 11 (61%) in **1/*1* group and 7 (39%) in **1/*6* or **1/*28* group. The reduced dose of irinotecan was 150 mg/m^2. The proportion of patients in whom the dose of irinotecan was reduced was similar in **1/*1* group (61%) and **1/*6* or **1/*28* group (39%, $P > 0.05$, chi-square test).

Discussion

This is the first study to show that the efficacy and toxicity of FOLFIRI as first-line chemotherapy did not significantly differ between *UGT1A1*1/*1* and *UGT1A1*1/*6* or **1/*28* genotype in Japanese patients with advanced colorectal cancer. Our results suggest that patients with *UGT1A1*1/*6* or **1/*28* genotype can receive FOLFIRI at the same dose of irinotecan as those with *UGT1A1*1/*1* genotype.

Only a few studies have evaluated the effects of *UGT1A1*1/*6* or **1/*28* genotype on the efficacy of

Table 1 Patient characteristics

Characteristic	All ($n = 42$)
Sex	
Male/female	27/15
Age (year)	
Median	60 (39–72)[a]
ECOG performance status	
0/1	33/9
Primary tumor site	
Colon/rectum	20/22
Metastatic site	
Liver/lung/lymph nodes/others	21/18/12/11
Number of metastatic sites	
1/≥2	19/19
Mean total bilirubin (mg/dl)	0.5 (0.3–1.1)[a]
Mean creatinine clearance (ml/min)[b]	88.2 (47.7–186)[a]
UGT1A1 genotype	
**1/*1*	24 (57%)
**1/*28*	5 (12%)
**1/*6*	13 (31%)

[a] Numbers in parentheses are ranges

[b] Creatinine clearance was calculated with the Cockcroft–Gault equation

Table 2 Association of *UGT1A1* genotype with tumor response

Genotype group	Number of patients			
	All ($n = 42$)	**1/*1* ($n = 24$)	**1/*6* or **1/*28* ($n = 18$)	*P* value[a]
Complete response	1	1	0	
Partial response	19	10	9	
Stable disease	12	9	3	
Progressive disease	7	3	4	
Not evaluable	3	1	2	
Overall response rate (%)	51	48	56	0.847

Responses were assessed by computed tomography or magnetic resonance imaging according to the RECIST criteria

[a] Comparison of response between **1/*1* and **1/*6* or **1/*28* groups by chi-square test

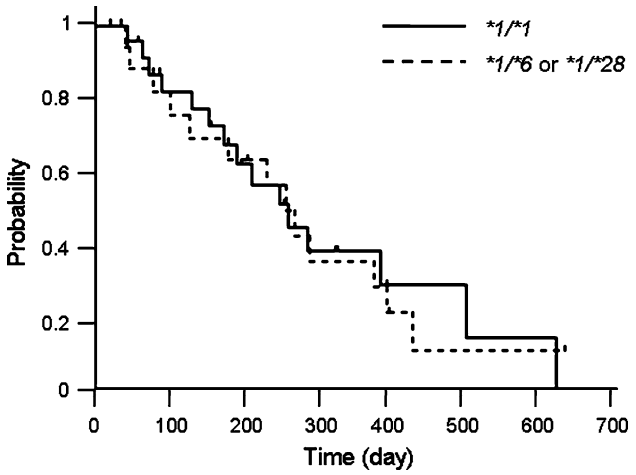

Fig. 1 Kaplan–Meier curves for PFS in patients with *UGT1A1*1/*1* and **1/*6** or *1/*28*. *Solid line* represents *UGT1A1*1/*1* and *dotted line* indicates *UGT1A1*1/*6* or **1/*28*

irinotecan in Japanese patients. As for *UGT1A1*6,* a polymorphism specific to Asians, Han et al. [8] showed that Korean patients with non-small-cell lung cancer who harbored *UGT1A1*6/*6* and received irinotecan plus cisplatin had lower tumor response rates and shorter PFS and overall survival than those with other genotypes (*UGT1A1*1/*1* plus *UGT1A1*1/*6*). However, the relation between *UGT1A1*1/*6* and response was not examined or compared with the relation between *UGT1A1*1/*1* and response. As for *UGT1A1*28*, one study reported that this polymorphism is associated with a non-significant trend toward a better response in Japanese patients with cancer [3]. In contrast, Marcuello et al. [14] reported that the presence of one or two allele(s) of *UGT1A1*28* was not associated with a significantly higher response rate or a survival advantage in patients with metastatic colorectal cancer who received irinotecan. In patients with colorectal caner treated with FOLFIRI, the presence of *UGT1A1*28/*28* was associated with a significantly better response rate and a longer time to progression (TTP) than was the presence of *UGT1A1*1/*1* [9, 15]. Interestingly, Toffoli et al. [9] and Cecchin et al. [15] demonstrated a longer TTP in patients with *UGT1A1*1/*28* than in those with wild type, despite no significant difference in response rate between these genotypes.

Toffoli et al. [9] and Cecchin et al. [15] showed that the *UGT1A1*28/*28* genotype was associated with a significantly increased risk of grade 3 or 4 hematologic toxicity during the first cycle of FOLFIRI treatment, but not the entire course of treatment. They found no differences in grade 3 or 4 toxicity between *UGT1A1*1/*28* and **1/*1* during either the first cycle or the entire course of chemotherapy. We similarly evaluated the effects of *UGT1A1*1/*6* or **1/*28* genotype on irinotecan-induced severe toxicity during the first cycle and the entire course of treatment. We found no significant association between the *UGT1A1* genotype groups and grade 3 or 4 toxicity, consistent with the results of Toffoli et al. and Cecchin et al.

Araki et al. [16] reported no significant difference in the area under the plasma concentration–time curve (AUC) ratio of SN-38 to SN-38G between patients heterozygous for *UGT1A1*6* or **28* and those with **1/*1*. Han et al. [8] also found no significant difference between *UGT1A1*1/*28* and **1/*1* with respect to AUC ratio or irinotecan-induced toxicity, consistent with our results. These findings

Table 3 Most common adverse events

Adverse event	First cycle				P^a	Entire course of chemotherapy				P^a
	Grade 1–4		Grade 3–4			Grade 1–4		Grade 3–4		
	**1/*1* ($n = 24$)	**1/*6* or **1/*28* ($n = 18$)	**1/*1* ($n = 24$)	**1/*6* or **1/*28* ($n = 18$)		**1/*1* ($n = 24$)	**1/*6* or **1/*28* ($n = 18$)	**1/*1* ($n = 24$)	**1/*6* or **1/*28* ($n = 18$)	
Hematologic										
Neutropenia	13 (54%)	9 (50%)	4 (17%)	3 (17%)	0.675	20 (83%)	11 (61%)	8 (33%)	6 (33%)	0.740
Leukopenia	8 (33%)	3 (16%)	2 (8%)	1 (6%)	0.795	15 (63%)	7 (39%)	2 (8%)	2 (11%)	0.819
Febrile neutropenia	1 (4%)	0 (0%)	1 (4%)	0 (0%)	0.883	1 (4%)	0 (0%)	1 (4%)	0 (0%)	0.883
Non-hematologic										
Diarrhea	6 (25%)	2 (11%)	0 (0%)	1 (6%)	0.883	11 (46%)	6 (33%)	0 (0%)	1 (6%)	0.883
Nausea	8 (33%)	8 (44%)	0 (0%)	0 (0%)	0.440	17 (71%)	13 (72%)	2 (8%)	0 (0%)	0.601
Vomiting	6 (21%)	4 (22%)	0 (0%)	0 (0%)	0.440	8 (33%)	7 (39%)	2 (8%)	0 (0%)	0.601
Mucositis	2 (8%)	3 (17%)	1 (4%)	0 (0%)	0.883	7 (29%)	6 (33%)	1 (4%)	0 (0%)	0.883
Anorexia	10 (42%)	9 (50%)	0 (0%)	1 (6%)	0.883	14 (58%)	11 (61%)	0 (0%)	1 (6%)	0.883
Infection	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.440	2 (8%)	2 (11%)	0 (0%)	1 (6%)	0.883

[a] Difference in the frequencies of grade 3–4 adverse events between **1/*1* and **1/*6* or **1/*28* group

support the results of our study. Mimani et al. [7] reported that the AUC ratio observed in almost all patients with the *UGT1A1*1/*6* or **1/*28* genotype treated with irinotecan mono- or combination–therapy at doses ranging from 60 to 150 mg/m^2 was significantly lower than that in those with **1/*1*. However, they did not show differences in toxicities seen between patients with *UGT1A1*1/*28* or **1/*6* and those with **1/*1*.

A recent meta-analysis by Hoskins et al. [17] pointed out that the predictive power of *UGT1A1*28* genotype for irinotecan-induced severe neutropenia increased according to the irinotecan dose increment. Ichikawa et al. [18] provided a theoretical consideration for the analysis by Hoskins et al. by demonstrating the dose-dependent increase in the AUC ratio that was in parallel with the increase in irinotecan-induced severe toxicity. Based on these findings, the AUC ratio and severe toxicities of irinotecan seen in patients with *UGT1A1*1/*6* or **1/*28* might be higher than those seen in patients with **1/*1* when the higher dose of irinotecan is administered.

A limitation of the present study is hypothesis generating, because of the retrospective design and relatively small study group. Prospective studies involving larger numbers of patients should be planned to confirm our hypothesis, even though many patients are now treated with FOLFIRI combined with monoclonal antibodies such as bevacizumab or cetuximab as first-line therapy for advanced colorectal cancer in Japan.

In conclusion, the efficacy and toxicity of FOLFIRI did not differ significantly between patients with the *UGT1A1*1/*6* or **1/*28* genotype and those with the *UGT1A1*1/*1* genotype. Our results suggest that patients with *UGT1A1*1/*6* or **1/*28* can receive FOLFIRI at a similar dose of irinotecan to that used in patients with *UGT1A1*1/*1*.

Acknowledgments This study was supported in part by the Grant-in-Aid for Cancer Research 21S-8-1 from the Ministry of Health, Labour and Welfare of Japan, and in part by a grant-in-aid for "Support Project of Strategic Research Center in Private Universities" from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) to Saitama Medical University Research Center for Genomic Medicine.

References

1. Mathijssen RHJ, van Alphen RJ, Verweij J, Loos WJ, Nooter K, Stoter G, Sparreboom A (2001) Clinical pharmacokinetics and metabolism of irinotecan (CPT-11). Clin Cancer Res 7:2182–2194
2. Innocenti F, Undevia SD, Iyer L, Xian Chen P, Das S, Kocherginsky M, Karrison T, Janisch L, Ramirez J, Rudin CM, Vokes EE, Ratain MJ (2004) Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol 22:1382–1388
3. Ando Y, Saka H, Ando M, Sawa T, Muro K, Ueoka H, Yokoyama A, Saitoh S, Shimokata K, Hasegawa Y (2000) Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. Cancer Res 60:6921–6926
4. Beutler E, Gelbart T, Demina A (1998) Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism? Proc Natl Acad Sci USA 95:8170–8174
5. Gagne JF, Montminy V, Belanger P, Journault K, Gaucher G, Guillemette C (2002) Common human UGT1A polymorphisms and the altered metabolism of irinotecan active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38). Mol Pharmacol 62:608–617
6. Akiyama Y, Fujita K, Nagashima F, Yamamoto W, Endo H, Sunakawa Y, Yamashita K, Ishida H, Mizuno K, Araki K, Ichikawa W, Miya T, Narabayashi M, Kawara K, Sugiyama M, Hirose T, Ando Y, Sasaki Y (2008) Genetic testing for UGT1A1*28 and *6 in Japanese patients who receive irinotecan chemotherapy. Ann Oncol 19:2089–2090
7. Minami H, Sai K, Saeki M, Saito Y, Ozawa S, Suzuki K, Kaniwa N, Sawada J, Hamaguchi T, Yamamoto N, Shirao K, Yamada Y, Ohmatsu H, Kubota K, Yoshida T, Ohtsu A, Saijo N (2007) Irinotecan pharmacokinetics/pharmacodynamics and UGT1A genetic polymorphisms in Japanese: roles of UGT1A1*6 and *28. Pharmacogenet Genomics 17:497–504
8. Han J-Y, Lim H-S, Shin ES, Yoo Y-K, Park YH, Lee J-E, Jang I-J, Ho Lee D, Soo Lee J (2006) Comprehensive analysis of UGT1A polymorphisms predictive for pharmacokinetics and treatment outcome in patients with non-small-cell lung cancer treated with irinotecan and cisplatin. J Clin Oncol 24:2237–2244
9. Toffoli G, Cecchin E, Corona G, Russo A, Buonadonna A, D'Andrea M, Pasetto LM, Pessa S, Errante D, De Pangher V, Giusto M, Medici M, Gaion F, Sandri P, Galligioni E, Bonura S, Boccalon M, Biason P, Frustaci S (2006) The role of UGT1A1*28 polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer. J Clin Oncol 24:3061–3068
10. Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M, Gruia G, Awad L, Rougier P (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 355:1041–1047
11. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 22:229–237
12. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
13. Fujita K, Ando Y, Nagashima F, Yamamoto W, Eodo H, Araki K, Kodama K, Miya T, Narabayashi M, Sasaki Y, Endo H, Ando M, Hasegawa Y, Sekido Y, Shimokata K, Ueoka H, Sugiyama T, Ichiki M, Saka H, Sawa T, Muro K, Yokoyama A, Saitoh S (2007) Genetic linkage of UGT1A7 and UGT1A9 polymorphisms to UGT1A1*6 is associated with reduced activity for SN-38 in Japanese patients with cancer. Cancer Chemother Pharmacol 60:515–522
14. Marcuello E, Altes A, Menoyo A, Del Rio E, Gomez-Pardo M, Baiget M (2004) UGT1A1 gene variations and irinotecan treatment in patients with metastatic colorectal cancer. Br J Cancer 91:678–682

15. Cecchin E, Innocenti F, D'Andrea M, Corona G, De Mattia E, Biason P, Buonadonna A, Toffoli G (2009) Predictive role of the UGT1A1, UGT1A7, and UGT1A9 genetic variants and their haplotypes on the outcome of metastatic colorectal cancer patients treated with fluorouracil, leucovorin, and irinotecan. J Clin Oncol 27:2457–2465
16. Araki K, Fujita K, Ando Y, Nagashima F, Yamamoto W, Endo H, Miya T, Kodama K, Narabayashi M, Sasaki Y (2006) Pharmacogenetic impact of polymorphisms in the coding region of the UGT1A1 gene on SN-38 glucuronidation in Japanese patients with cancer. Cancer Sci 97:1255–1259
17. Hoskins JM, Goldberg RM, Qu P, Ibrahim JG, McLeod HL (2007) UGT1A1*28 genotype and irinotecan-induced neutropenia: dose matters. J Natl Cancer Inst 99:1290–1295
18. Ichikawa W, Araki K, Fujita K, Yamamoto W, Endo H, Nagashima F, Tanaka R, Miya T, Kodama K, Sunakawa Y, Narabayashi M, Ando Y, Akiyama Y, Kawara K, Sasaki Y (2008) Re: UGT1A1*28 genotype and irinotecan-induced neutropenia: dose matters. J Natl Cancer Inst 100:224–225