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Prospective Phase II Study of FOLFIRI for mCRC in Japan, Including the Analysis of *UGT1A1*28/*6* Polymorphisms

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Objectives: This is the first phase II study to evaluate the efficacy and tolerability of the first-line FOLFIRI, as well as the influence of uridine diphosphate glucuronosyl transferase 1, family polypeptide A1 gene (*UGT1A1*) **28/*6* polymorphism, in Japanese metastatic colorectal cancer patients.

Methods: Fifty-two patients were enrolled in this study and were administrated FOLFIRI (irinotecan; 150 mg/m^2) as first-line chemotherapy. Thirty-nine patients accepted the evaluation of *UGT1A1* genotypes. In patients with *UGT1A1*28* homozygosity, the starting dose was reduced (100 mg/m^2) according to the Food and Drug Administration recommendation and our previous phase I study.

Results: After a median follow-up period of 22 months, complete response was achieved in 1.9%, partial response in 38.5 %, stable disease in 51.9% and progressive disease in 3.9%. The overall response rate was 40.4%, the disease control rate was 92.3% and the median overall survival time was 22.3 months. The major toxicity was grade 3–4 neutropenia in 44.2%. There was no definite relation between *UGT1A1*28*, **6* polymorphisms and toxicity. However, homozygosity for *UGT1A1*28* or *UGT1A1*6* and double heterozygosity for both *UGT1A1*28* and *UGT1A1*6* were significantly associated with severe neutropenia in metastatic colorectal cancer patients ($P < 0.001$).

Conclusions: FOLFIRI is effective and tolerable for Japanese metastatic colorectal cancer patients. Homozygosity for *UGT1A1*28* or **6* and heterozygosity for both *UGT1A1*28* and **6* are associated with severe neutropenia.

Key words: FOLFIRI, irinotecan, metastatic colorectal cancer, neutropenia, UGT1A1 polymorphism

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INTRODUCTION

Colorectal cancer is the one of the most common cancers worldwide and remains the third leading cause of cancer-related death in Japan. For many years, the main treatment for metastatic colorectal cancer (mCRC) consisted of 5-fluorouracil (5-FU) modulated by leucovorin (LV) (1). Since 1990, remarkable progress in treatment has been made with the release of several drugs, such as oxaliplatin and irinotecan (2,3). Irinotecan shows definite activity against advanced mCRC both in chemotherapy-naïve and previously treated patients (4–8). Recently, several molecular-targeting drugs, such as bevacizumab and cetuximab, have been combined with first- and second-line chemotherapy, such as the FOLFOX or FOLFIRI regimens (9–11). In Japan, there have been a few studies of phases I and II, on the safety and efficacy of FOLFIRI therapy. Although the standard dose of irinotecan is 180 mg/m^2 in western countries, the ministry of Health, Labor and Welfare had decided that the recommended dose of irinotecan was 150 mg/m^2. Therefore, it is difficult for us to perform the clinical study with 180 mg/m^2 of the irinotecan dose in Japan. This study is a phase II study, administered every 2 weeks as first-line treatment for chemotherapy-naïve patients with mCRC, in order to compare the efficacy and the safety of FOLFIRI treatment (irinotecan 150 mg/m^2) with them in western FOLFIRI treatment (irinotecan 180 mg/m^2) more clinically in several institutions in Japan.

Irinotecan is an inhibitor of DNA topoisomerase I. One of the main enzymes involved in the metabolism of irinotecan is uridine diphosphate glucuronosyl transferase, which converts the active metabolite of irinotecan (SN38) to an inactive glucuronide (12). The uridine diphosphate glucuronosyltransferase 1 family, polypeptide A1 gene (*UGT1A1*) **28* polymorphism reduces the enzyme activity, which may lead to severe toxicity in patients treated with irinotecan (12–15). The activity of UGT1A1 depends on the number of TA repeats in the promoter region of the gene [the wild type has six repeats (TA6) and *UGT1A1*28* has seven repeats (TA7)]. The TA7 allele is associated with decreased expression of the enzyme and less effective glucuronidation of SN 38. Therefore, patients with TA7/TA7 have higher exposure to SN38 and an increased risk of side effects (13–16). Accordingly, the second aim of this study was to investigate the relation between *UGT1A1*28/*6* polymorphism and irinotecan-induced toxicities in Japanese patients with mCRC treated by the FOLFIRI regimen.

PATIENTS AND METHODS

Sample Size Estimation

The sample size was calculated on the basis that a response rate was expected to 55%. Given the sample size of 43 eligible chemotherapy-naive patients with advanced or recurrent metastatic colorectal adenocarcinoma, 95% two-sided confidence intervals for the rate was calculated to be within 15% using the normal approximation to the binominal variable. In addition, we need 47 patients to observe an adverse reaction of anticipated incidence 5% with a given 90% probability. Therefore, we planned to enroll 50 patients in consideration with 10% drop-out.

Eligibility

Patients with histologically proven advanced or recurrent metastatic colorectal adenocarcinoma that could not be cured surgically were enrolled. The subjects were all chemotherapy-naïve. Patients who had received just an adjuvant 5-FU-based chemotherapy were eligible after a month or more intervals. Other eligibility criteria were an age between 20 and 80 years, Eastern Cooperative Oncology Group performance status (PS) of 0–2, at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, a life expectancy of at least 3 months and adequate organ function (bone marrow: leukocytes $>3000/mm^3$, neutrophils $>1500/mm^3$ and platelets $>100\,000/mm^3$, liver: serum bilirubin <1.5 mg/dl and aspartate aminotransferase/alanine aminotransferase <100 U/l: kidneys; serum creatinine <1.20 mg/dl, no heart failure and no respiratory disease).

This study was conducted according to the Declaration of Helsinki and approved by the Ethics and Scientific Committee of each participating institution.

Genotyping of *UGT1A1*

Genomic DNA was extracted from 7 ml of whole blood collected into a tube with EDTA-2Na by the conventional NaI method. Then the number of TA repeats in the *UGT1A1* promoter region was determined by fragment sizing. PCR was performed as described previously (14). To confirm the genotype data obtained by fragment size analysis, direct sequencing was performed and genotypes were assigned based on the number of TA repeats in each allele (6/6 or 7/7). In addition, *UGT1A1*6* polymorphism (G71R(*6)) was analyzed by the polymerase chain reaction-restriction fragment length polymorphism method, as described elsewhere (13).

Treatment

Irinotecan was given at a dose of 150 mg/m^2 as a 90 min intravenous infusion on day 1. LV was given at a dose of 200 mg/m^2 as a 120 min intravenous infusion, followed by 5-FU (400 mg/m^2 as a bolus and then 2400 mg/m^2 as a 46 h intravenous infusion) on days 1 and 2. In patients with homozygosity for *UGT1A1*28*, starting dose of irinotecan was reduced to 100 mg/m^2, referring to the recommendation of an advisory meeting by the subcommittee of the Food and Drug Administration Center or Drug Evaluation and Research held in November 2004 (http://www.fda.gov/) and our previous phase I study in which maximum tolerated dose of biweekly irinotecan was 100 mg/m^2 for patients with

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the *UGT1A1*28* heterozygosity (13). Treatment was repeated every 2 weeks until disease progression or dose-limiting toxicity occurred. Blood tests and clinical evaluation were performed every 2 weeks, before treatment. Chemotherapy could be administered if the leukocyte count was $>3000\ mm^3$, neutrophils count was $>1500\ mm^3$, platelet count was $>75\,000\ mm^3$ and clinical toxicity was resolved or grade 1.

Monitoring

Before each cycle, patients underwent clinical examination and hematology tests. All toxicities were reported according to the National Cancer Institute-Common Cytotoxicity Criteria (NCI-CTC) version 3. Computed tomography scans were repeated every 8 weeks or earlier if worsening of the clinical condition occurred.

Dose Reduction Criteria

Toxicity was assessed before starting each 2-week cycle, using the NCI-CTC. Chemotherapy was delayed until recovery to grade 1 hematologic and non-hematologic toxicity, if white blood cells were $<1500/m^3$, neutrophils were $<500/m^3$ or platelets were $<50\,000/m^3$, or more than or equal to grade 2 persisting non-hematologic toxicity. 5-FU and irinotecan infusion doses were reduced to the 80% dosage in subsequent cycles, in case of grade 3–4 toxicity. If any toxicity required a delay of >2 weeks, the patient was withdrawn from the study due to toxicity.

Calculation Method of the Relative Dose Intensity

The relative dose intensity (RDI) was calculated as the dose received (mg/m^2) divided by the protocol dose and expressed as a percentage. The overall RDI was calculated as the sum of each RDI divided by the number of cycles received.

Statistical Analysis

The primary endpoint of this study was the response rate to the FOLFIRI based on RECIST, while overall survival (OS), progression-free survival (PFS) and time to treatment failure (TTF) were the secondary endpoints. OS was calculated from the day of the enrollment to death. PFS was determined from the day of the enrollment to the date without any progression or death. Patients alive at the final survival analysis or had not progressed at the time of the final analysis were censored using the last contact date. Survival curves were drawn by the Kaplan–Meier method. To assess the relation between toxicity and *UGT1A1* polymorphism, the chi-square test was used. Statistical significance was accepted when the *P* value was <0.05.

RESULTS

From November 2005 to May 2007, 52 patients with mCRC received treatment with FOLFIRI as the first-line chemotherapy and were investigated prospectively. Their characteristics are described in Table 1. All patients were evaluated for toxicity and for response to treatment. Thirty-nine patients accepted to evaluate for *UGT1A1* genotypes.

Response

After a median follow-up period of 22 months, 1 patient (1.9%) showed complete response, 20 patients (38.5%) had partial response, 27 patients (51.9 %) had stable disease, 2 patients (3.9%) had progressive disease and 2 patients (3.9%) were not evaluated. The overall response rate was 40.4% and disease control rate was 92.3%. The median PFS

Table 1. Patients characteristics

	$N = 52$
Sex	
Male	32
Female	20
Age	
Median	64
Range	35–79
PS	
0/1	44/8
Metastatic focus	
Liver	27
Lung	12
Lymph node	15
Others	15

PS, performance status.

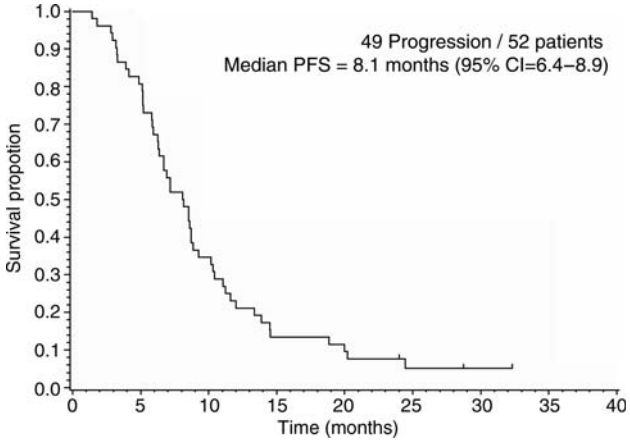

Figure 1. The progression-free survival (PFS) rate of all enrolled patients. The median PFS time was 8.1 months.

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was 8.1 months (Fig. 1), and the median OS was 22.3 months (Fig. 2). The median time from initiation of treatment to documentation of failure was 6.1 months (Fig. 3). There were no statistical relations between PFS, OS or TTF and *UGT1A1*28* polymorphism (data not shown).

Relative Dose Intensity

For the first four cycles, the median relative dose intensities of irinotecan, 5-FU (bolus), 5-FU (infusion) and LV are shown in Table 2. Each drug was administered substantially according to schedule. The RDI of irinotecan was 84% in our FOLFIRI treatment (irinotecan 150 mg/m^2), and the RDI had not been so different from it of western FOLFIRI treatment (irinotecan 180 mg/m^2), 85.9% reported by Tournigand et al. (7) in western countries. The RDI of irinotecan showed no differences between patients who were wild type, heterozygous or homozygous for *UGT1A1*28* polymorphism (data not shown).

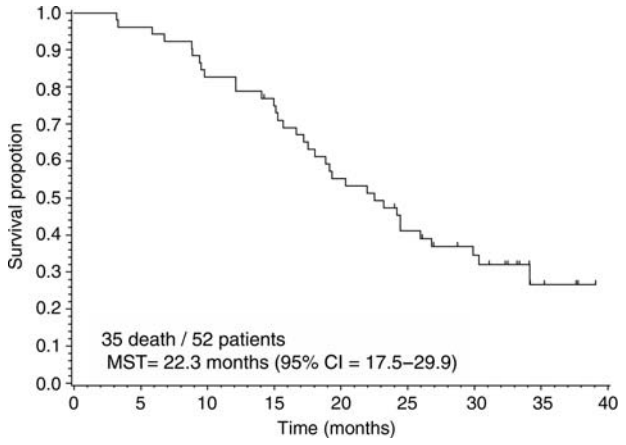

Figure 2. The overall survival (OS) rate of all enrolled patients. The median survival time was 22.3 months.

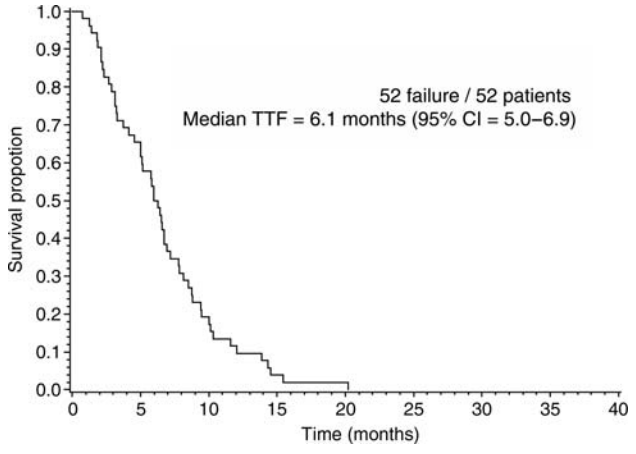

Figure 3. The time to treatment failure (TTF) rate of all enrolled patients. The median time was 6.1 months.

Table 2. Relative dose intensity (first four cycles)

RDI	Irinotecan	5-FU (bolus)	5-FU (continuous)	LV
Average	0.84	0.85	0.85	0.88
Median	0.89	0.89	0.89	0.89

RDI, relative dose intensity; FU, fluorouracil; LV, leucovorin.

Toxicity

Grade 3–4 neutropenia occurred in 23 patients (44.2%), only grade 4 neutropenia occurred in 6 patients (15.4%) and two of them (5.1%) developed febrile neutropenia, while grade 3–4 diarrhea only developed in each one patient (1.9%) , as shown in Table 3. The relation between the baseline serum bilirubin level and the degree of neutropenia could not be observed significantly (data not shown).

UGT1A1 Polymorphism and Dose Reduction

The genotyping analysis of *UGT1A1*28* polymorphism is additional. Therefore, only in the institutions permitted by the each ethical committee, the genotyping test had been performed, not in all institutions. We evaluated the *UGT1A1*28* genotype in 39 patients, as shown in Table 4.

Only one patient was homozygous for *UGT1A1*28* and treatment was started at an irinotecan dose of 100 mg/m^2 in this patient. Although the starting dose of irinotecan was reduced, grade 4 neutropenia still occurred. *UGT1A1*28* genotype was seemed to be a predictive marker of severe neutropenia, there was no significant relation between

Table 3. Major adverse events of FOLFIRI treatment

	N = 52 (%)
Leukopenia	8 (15.4)
Neutropenia	23 (44.2)
Anemia	3 (5.8)
Nausea	3 (5.8)
Emesis	1 (1.9)
Anorexia	6 (11.5)
Diarrhea	1 (1.9)

Table 4. Uridine diphosphate glucuronosyl transferase 1 family, polypeptide A1 gene (*UGT1A1*) **28* polymorphism and neutropenia

	Grade	TA6/TA6, *n* = 32 (82.1%)	TA6/TA7, *n* = 6 (15.4%)	TA7/TA7, *n* = 1 (2.6%)	*P* value
Neutropenia	3–4	12 (37.5%)	4 (66.7%)	1 (100%)	0.514
	0–2	20 (62.5%)	2 (33.3%)	0 (0%)	

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Table 5. *UGTA1A1*6* polymorphism and neutropenia

	Grade	G/G, $n = 26$ (66.7%)	G/A, $n = 12$ (30.8)	A/A, $n = 1$ (2.6%)	P value
Neutropenia	3–4	11 (42.3%)	5 (41.7%)	1 (100%)	0.514
	0–2	15 (57.7%)	7 (58.3%)	0 (0%)	

Table 6. Neutropenia stratified by *UGTA1A1*28/*6* genotype

	Grade	DW, $n = 21$ (53.8%)	SV, $n = 14$ (35.9%)	DV, $n = 4$ (10.3%)	P value
Neutropenia	3–4	3 (14.3%)	1 (7.1%)	4 (100%)	0.001
	0–2	18 (85.7%)	13 (92.9%)	0 (0%)	

DW, double wild type; SV, single variant type; DV, double variant type.

*UGT1A1*28* polymorphism and the toxicity, as shown in Table 4 ($P = 0.215$). Additionally, we also determined the *UGT1A1*6* genotypes, as shown in Table 5. One patient was homozygous and 12 patients were heterozygous for *UGT1A1*6*. There was no relation between *UGT1A1*6* polymorphism and neutropenia, as shown in Table 5 ($P = 0.514$). Then, we have determined the combination of *UGT1A1*28* and *UGT1A1*6* genotypes. When analysis of the *UGT1A1*6* and *UGT1A1*28* polymorphisms was combined, the following genotypes of *UGT1A1* were obtained: double wild type (either no variant) in 21 patients (53.8%), single heterozygous (either variant) in 14 patients (35.9%) and homozygous or double heterozygous in 4 patients 10.3%), as shown in Table 6. While the incidence of grade 4 neutropenia was not significantly associated with *UGT1A1*28/*6* polymorphism ($P = 0.854$), the incidence of grade 3 or 4 neutropenia was significantly increased among patients who were either homozygous or double heterozygous for *UGT1A1*28/*6* ($P < 0.001$), as shown in Table 6.

DISCUSSION

Irinotecan-based therapy is important, not only as first-line but also as second-line chemotherapy, combined with bevacizumab and cetuximab. The safety and efficacy of FOLFIRI have already been assessed by several phase II and III studies (6,7). However, there have been no prospective phase II studies investigating the influence of *UGT1A1* polymorphism in Japan. In this study, the overall response rate was 40.4%, the disease control rate was 92.3%, the median PFS was 8.1 months and the median OS was 22.3 months (Result, Figs 1 and 2). Therefore, we confirmed the efficacy of the FOLFIRI (irinotecan 150 mg/m^2) fully, even though the recommended dose of irinotecan in Japan is less than in western countries, as previously reported (6–9). On the other hand, grade 3–4 neutropenia occurred in 23 patients (43.4%) although grade 3–4 diarrhea only occurred in 1 patient (1.9%), (Table 3). With regard to diarrhea in Japanese mCRC patients, our findings are slightly different from those of previous studies performed in western countries. Although we need to be constantly on guard for neutropenia due to irinotecan, we suggest that FOLFIRI (irinotecan; 150 mg/m^2) is an effective first-line regimen for Japanese patients with mCRC that shown manageable toxicity.

Several pharmacogenetic trials have demonstrated an association between the *UGT1A1*28* genotype and hematological toxicity, diarrhea or both induced by irinotecan (13–17). In this study, we investigated the association between toxicity and *UGT1A1*28* polymorphism. Only one patient was homozygous for *UGT1A1*28*. Although treatment was started with a reduced dose of irinotecan (100 mg/m^2), serious neutropenia still occurred in this patient. While the *UGT1A1*28* polymorphism is found in Japanese and Caucasians, the (TA7/TA7) allele frequency is very lower in Japanese (17).

Recently, Hoskins et al. (18) reported that the risk of severe neutropenia was strongly associated with *UGT1A1*28* polymorphism at higher irinotecan doses ($>$150 mg/m^2), not at lower doses ($\leq$150 mg/m^2). Therefore, we could not have demonstrated a relation between *UGT1A1*28* polymorphism and irinotecan-related toxicities.

On the other hand, Takano et al. (19) reported that the *UGT1A1*6* polymorphism is a potential predictor of severe neutropenia derived by irinotecan in Japanese patients with homozygosity or heterozygosity of *UGT1A1*6* polymorphism. In our study, serious neutropenia has been occurred in only one patient with homozygosity and five patients (41%) with heterozygosity for *UGT1A1*6*. However, heterozygosity of *UGT1A1*6* is not related to severe neutropenia, as shown in Table 5.

Then, we investigated whether combined *UGT1A1*28* and *UGT1A1*6* polymorphism had an influence on irinotecan toxicity. As shown in Table 6, we confirmed that homozygosity for *UGT1A1*28* or *UGT1A1*6* and double heterozygosity for both *UGT1A1*6* and *UGT1A1*28* were significantly associated with severe neutropenia in our mCRC patients when compared with the rate of neutropenia in patients who were wild type for both *UGT1A1*6* and *UGT1A1*28*, as reported previously (17).

Irinotecan is one of the key chemotherapy agents for mCRC patients, shown a positive correlation between treatment with 5-FU/LV, irinotecan and oxaliplatin and improvement of their OS time (20). Evaluation of *UGT1A1*28* and *UGT1A1*6* polymorphism before irinotecan treatment may allow us to predict severe toxicities derived from irinotecan and perform chemotherapy more effectively.

AUTHORS' CONTRIBUTIONS

H.N., M.K., K.T., K.F., T.K. N.N. and H.K. contributed to the section of results. K.O. contributed to the section of

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statistical analysis. M.O., Y.H. and N.O. contributed to the analysis of *UGT1A1* polymorphisms. J.S., S.H. and H.M. contributed to the planning and to the section of discussion.

Conflict of interest statement

None declared.

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Appendix

In addition to the authors listed in the author field, following are the authors who contributed equally to this study.

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