Title: 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

Yoichi Nakamura[1] M.D., Ph.D.; Hiroshi Soda[2] M.D., Ph.D.; Mikio Oka[3] M.D., Ph.D.; Akitoshi Kinoshita[4] M.D., Ph.D.; Minoru Fukuda[5] M.D., Ph.D.; Masaaki Fukuda[6] M.D., Ph.D.; Hiroshi Takatani[6] M.D., Ph.D.; Seiji Nagashima[2] M.D., Yoshifumi Soejima[7] M.D., Ph.D.; Takashi Kasai[6] M.D., Ph.D.; Katsumi Nakatomi[1] M.D., Ph.D.; Noriyuki Masuda[8] M.D., Ph.D.; Kazuhiro Tsukamoto[9] M.D., Ph.D.; and Shigeru Kohno[1] M.D., Ph.D.

[1]Second Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan

[2]Sasebo General Hospital, Sasebo, Japan

[3]Division of Respiratory Disease, Department of Medicine, Kawasaki Medical School, Kurashiki, Japan

[4]National Nagasaki Medical Center, Ohmura, Japan

[5]Nagasaki Municipal Hospital, Nagasaki, Japan

[6]Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki, Japan

[7]Ureshino Medical Center, Ureshino, Japan

[8]Kitasato University School of Medicine, Sagamihara, Japan

[9]Department of Pharmacotherapeutics, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Running Title: Randomized Phase II of Irinotecan-based Therapy

Correspondence to: Yoichi Nakamura

Second Department of Internal Medicine, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

Tel: +81-(95)-849-7274; **Fax:** +81-(95)-849-7285; **E-mail:** yi-nakamu@umin.ac.jp

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Study Registration: Japan Pharmaceutical Information Center. JapicCTI-050111

ABSTRACT

Hypothesis: Irinotecan-containing regimens are known to be active and tolerable in patients with non-small-cell lung cancer (NSCLC). A randomized phase II trial was conducted to evaluate the efficacy of irinotecan plus paclitaxel or gemcitabine for previously untreated stage IIIB or stage IV NSCLC.

Patients and Methods: Previously untreated patients with adequate organ function who gave written informed consent were randomly assigned to receive irinotecan (50 mg/m^2 on days 1, 8, and 15) plus paclitaxel (180 mg/m^2 on day 1) every 4 weeks (IP group) or irinotecan (100 mg/m^2 on days 1 and 8) plus gemcitabine (1,000 mg/m^2 on days 1 and 8) every 3 weeks (IG group). The primary end-point was the response rate. We also evaluated the relations of response and toxicity to polymorphisms of the uridine diphosphate glucuronosyltransferase (UGT) gene.

Results: Eighty patients were enrolled, and 78 patients were assessable (38 in the IP group and 40 in the IG group). The response rate was 31.6% (95% confidence interval: 17.5% to 48.7%) in the IP group and 20.0% (9.1% to 35.6%) in the IG group. The median progression-free survival time was 86 days and 145 days, respectively. Both regimens were well tolerated. The most common severe adverse event was grade 4 neutropenia, (36.8% and 10.0%, respectively), which was associated with *UGT1A1*6* and *UGT1A1*27*. UGT polymorphisms did not correlate with response.

Conclusions: Irinotecan plus paclitaxel may be more active against NSCLC than irinotecan plus gemcitabine. The *UGT1A1*6* and *UGT1A1*27* genotypes might be useful predictors of grade 4 neutropenia in patients who receive irinotecan-based

chemotherapy.

Key words: NSCLC, irinotecan, paclitaxel, gemcitabine, *UGT1A1*6*, *UGT1A1*27*

INTRODUCTION

Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of all cases of lung cancer and remains the leading cause of cancer-related death in many countries. [1] Several third-generation agents are available for the treatment of advanced NSCLC. One of these agents combined with cisplatin or carboplatin has been considered standard therapy for previously untreated advanced NSCLC.[2]

However, approximately one-third of all patients with advanced NSCLC do not clinically benefit from platinum-based chemotherapy, [2] and non-platinum regimens show equivalent efficacy with a different toxicity profile. [3] Recent studies have reported that biological factors such as expression of excision repair cross-complementation group 1 mRNA confer resistance of NSCLC to platinum agents. [4] This finding suggests that non-platinum regimens might be preferable in certain patients with biological markers of platinum resistance.

Irinotecan is a semi-synthetic derivative of camptothecin. The active metabolite of irinotecan (SN-38) inhibits topoisomerase-I activity by stabilizing the topoisomerase I-DNA cleavable complex.[5] Paclitaxel is an antimicrotubule agent that produces antitumor activity by promoting tubulin polymerization and stabilization of microtubules against depolymerization. Gemcitabine is an analog of the pyrimidine antimetabolite cytarabine, which produces antitumor activity by targeting the S-phase of the cell cycle.[6] These three drugs have different mechanisms of action, and their toxicity profiles do not overlap. Two phase I studies have assessed the combination of irinotecan and paclitaxel (IP) or irinotecan and gemcitabine (IG), and both regimens showed relatively good safety and efficacy as first-line treatment for advanced NSCLC.[7, 8] Therefore, we

conducted a randomized phase II study to determine which irinotecan-based regimen (IP or IG) is superior for use in a future large-scale trial.

It is well known that uridine diphosphate glucuronosyltransferase (UGT) gene polymorphisms affect the activity of key enzymes involved in irinotecan metabolism.[9-16] We also examined the association of polymorphisms of the *UGT1A1 (*6, *27, *28*, and **60)*, *UGT1A7 (*2, *3, *4)*, and *UGT1A9 (*22)* genes with the outcomes of IP and IG therapy.

PATIENTS AND METHODS

Eligibility criteria

Eligibility criteria were as follows: histologically or cytologically confirmed stage IIIB/IV NSCLC; no prior treatment; measurable and assessable disease; age between 20 and 75 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; adequate bone marrow function; adequate liver function; serum creatinine below the upper limit of normal. The exclusion criteria were superior vena cava syndrome, massive pleural effusion or ascites, symptomatic central nervous system metastasis, concomitant active malignancy, clinically significant cardiac disease, infection, watery diarrhea, paralytic ileus, and intestinal obstruction. Pregnant or breast-feeding women were also excluded. Written informed consent was obtained from all patients before treatment. The study protocol and the informed consent procedures were reviewed and approved by the Institutional Review Board of each participating hospital.

Treatment schedule

This was an open-label, randomized phase II trial. Eligible patients were registered with the data center and randomized to receive IP therapy (IP group) or IG therapy (IG group) by centralized dynamic allocation. The stratification factors used were performance status (0/1), stage (IIIB/IV), and institution.

In the IP group, irinotecan was given at a dose of 50 mg/m^2 on days 1, 8, and 15. Paclitaxel was given at a dose of 180 mg/m^2 on day 1 only. Premedication was administered 30 minutes before the paclitaxel infusion. This cycle was repeated every 4 weeks. Patients enrolled in the IG group received irinotecan at 100 mg/m^2 and gemcitabine at 1,000 mg/m^2 on days 1 and 8. This cycle was repeated every 3 weeks.

The treatment scheduled for days 8 and 15 or the start of the next cycle was delayed if the patient had a leukocyte count of <3,000 or >12,000/mm^3, a platelet count of <100,000/mm^3, diarrhea of ≥grade 1, and/or other nonhematologic toxicities of ≥grade 3 (except electrolyte abnormality, nausea, anorexia, and fatigue). If these toxic effects did not resolve sufficiently, the doses scheduled for days 8 and/or 15 were omitted. The patient was withdrawn from the study if the next cycle of therapy could not be started within 4 weeks from the previously administered dose. The treatment goal was for patients to receive at least 3 cycles in the IP group and 4 cycles in the IG group. Treatment was continued until there was evidence of disease progression, intolerable toxicity, or patient refusal. As for dose modification, if there was grade 4 neutropenia for ≥5 days, thrombocytopenia of grade 3-4, or nonhematologic toxicity of grade 3-4 (except electrolyte abnormality, nausea, anorexia, and fatigue), then the dose of paclitaxel in the IP

group or irinotecan in the IG group was reduced to 150 mg/m^2 and 80 mg/m^2, respectively. If grade 3-4 diarrhea occurred, only irinotecan was reduced to 80% of the previous dose in both arms.

Before enrollment, a complete medical history was obtained and physical examination was performed. In addition, a complete blood count, biochemistry tests, blood gas analysis, chest roentgenography, electrocardiography, computed tomography (CT) of the brain and chest, CT of the abdomen, and bone scintigraphy were performed. Patients were monitored at weekly intervals throughout treatment by physical examination, recording of toxicities, complete blood counts, and biochemistry tests.

The response was assessed at least every two cycles according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.0).[17] Toxicity was assessed according to the National Cancer Institute Common Toxicity Criteria, version 2.0.[18] Extramural reviewers were employed to determine the eligibility, assessability, and response of each patient.

Genotype analysis

DNA samples were extracted from peripheral blood, and genomic DNA was isolated from 77 patients who provided informed consent, using a DNA Purification Kit (QIAGEN Japan, Tokyo, Japan). Then, polymerase chain reaction (PCR) was done for amplification, and the PCR-direct DNA sequencing method was used to analyze the genotypes of *UGT1A1*6*, *UGT1A1 *27*, *UGT1A7,* and *UGT1A9*22*. In addition, *UGT1A1*28* was analyzed by polyacrylamide gel electrophoresis, and *UGT1A1*60* was analyzed by TaqMan® PCR. In this trial, we

considered both IP and IG to be the low-dose weekly irinotecan regimens, and we evaluated the relationship between *UGT* genotype and toxicities in both treatment groups combined.

Statistical analysis

The full analysis set (FAS) was defined as all patients who received treatment at least once and met all of the inclusion criteria. The per-protocol set (PPS) was defined as all patients who received treatment at least once and had no major protocol violations.

The primary end-point of this study was the overall response rate (ORR). The secondary end-points were progression-free survival (PFS), overall survival (OS), 1-year survival, 2-year survival, and toxicities. Assuming that the ORR would be 30% in the IP group and 45% in the IG group, we estimated that 35 patients per arm were required to give the study a power of 0.90 to detect a difference in response between the groups.[19] Thus, the target sample size was set as 80 patients (40 per group). PFS was defined as the time from the date of registration to the date of disease progression or death, and OS was defined as the time from the date of registration to the date of death. Survival was estimated by the Kaplan-Meier method. As an exploratory analysis, the association of UGT1A genotypes with toxicity or tumor response was assessed by Wald's test. All analyses were performed with SAS software (version 8.2; SAS Institute, Cary, NC).

The genotype frequencies for each single nucleotide polymorphism (SNP) were analyzed in an exploratory fashion to assess consistency between the observed

values and those expected from Hardy–Weinberg equilibrium, using Haploview version 3.32. Haploview based on the expectation-maximization method[20] was used to estimate haplotype frequencies, Lewontin's coefficients (D'),[21] and correlation coefficients (r^2).[22] The block structures and their haplotype frequencies were estimated using Haploview version 3.32.

This trial was registered with the Japan Pharmaceutical Information Center (JapicCTI-050111).

RESULTS

Patient characteristics

From January 2004 through April 2006, 80 patients were enrolled (40 in the IP group and 40 in the IG group). Two patients were not eligible (both in the IP group), because one had received surgery for a brain metastasis and the other had interstitial fibrosis of the lungs. Table 1 lists the baseline characteristics of the 78 assessable patients. The median number of treatment cycles was three in the IP group (range: 1 to 6 cycles) and four in the IG group (range: 1 to 9 cycles). The relative dose intensity was 100% for paclitaxel and 66.7% for irinotecan in the IP group (n=38), and 95.1% for gemcitabine and 94.0% for irinotecan in the IG group (n=40). The most common reason for stopping treatment was disease progression (52.6% in the IP group and 25.0% in the IG group). After this study, 89.7% of the patients received subsequent chemotherapy (36 patients in the IP group and 34 patients in the IG group). Cross-over administration was not performed in any patient.

Toxicity

Adverse events are listed in Table 2. Neutropenia of grades 3 and 4 was comparable in the IP and IG groups, but grade 4 neutropenia occurred in 36.8% of the patients in the IP group versus only 10.0% of those in the IG group. Grade 3 diarrhea and constipation were observed in 7.9% and 10.5% of patients in the IP group versus 5.0% and 5.0% of those in the IG group, respectively. All of the adverse events were tolerable, and there were no treatment-related deaths.

Response and survival

In the IP group, there were 12 partial responses (PRs) for an overall response rate of 31.6% (95% confidence interval: 17.5% - 48.7%). In addition, 13 patients (34.2%) had stable disease (SD), and 12 patients (31.6%) had progressive disease (PD). In the IG group, there were 8 PRs for an overall response rate of 20.0% (95% confidence interval: 9.1% - 35.6%). There were 25 patients (65.8%) with SD and 6 patients (15.8%) with PD. One patient could not be assessed in each group. Median PFS was 86 days (95% CI: 78 days to 138 days) in the IP group and 145 days (95% CI: 109 days to 145 days) in the IG group (Fig. 1A). The MST, 1-year survival rate, and 2-year survival rate were 439 days (95% CI: 357 days to 608 days), 62.9% (95% CI: 47.4% to 78.3%), and 27.3% (95% CI: 12.9% to 41.7%) in the IP group versus 540 days (95% CI: 337 days to 670 days), 64.7% (95% CI: 49.7% to 79.6%), and 32.4% (95% CI: 17.5% to 47.4%) in the IG group, respectively (Fig. 1B).

Association of *UGT1A* genotype with study outcomes

The frequencies of UGT1A haplotypes and genotypes are listed in Table 3. No Hardy-Weinberg disequilibrium was observed (P>0.05). We constructed haplotypes using six polymorphisms (*UGT1A9*22*, *UGT1A7**, *UGT1A1*60*, *UGT1A1*28*, *UGT1A1*6*, and *UGT1A1*27*) to examine the effects of these key SNPs and found 10 haplotypes. The three most common haplotypes accounted for 78.3% of all haplotypes. This result was in agreement with findings previously reported for Asian patients [15]. The variants of *UGT1A1*, *UGT1A7,* and *UGT1A9* typed in this study are listed in Table 3. There were no patients homozygous for *UGT1A1*27*, and all of the patients heterozygous for *UGT1A1*27* were also heterozygous for *UGT1A1*28*. These results were also consistent with data previously reported for Asian patients [9, 14-16].

High linkage disequilibrium (LD) was observed among *UGT1A7* variants with D' values of 1, and r^2 values ranging from 0.485 to 1, which included *387T>G, 391C>A, 392G>A*, and *622T>C* (Fig. 2). We found a linkage association ($0.444<r^2<0.971$; $0.942<D'<1$) between *UGT1A7* variants and *UGT1A9*22*. *UGT1A7* (*622T>C*) and *UGT1A1*6* were also in high LD (D'=0. 854, r^2=0.423). On the other hand, a close association was not observed between *UGT1A1**28 and *UGT1A7*. We found a close linkage across *UGT1A1*28* and *UGT1A1*60* (D'=1, r^2=0.52). There was no *UGT1A7*4* in this study. Our results were similar to those of a study by Han and coworkers [15].

We examined the association of *UGT1A* genotypes with the toxicity profile in 77 assessable patients (one patient refused genotyping). Patients who were homozygous or heterozygous for *UGT1A1*6 and UGT1A1*27* had a higher

incidence of grade 4 neutropenia (P=0.020 and 0.033, respectively) (Table 4). In contrast, the other *UGT1A* genotypes were not significantly associated with neutropenia. None of the *UGT1A* genotypes analyzed in this study had a significant association with grade 3 diarrhea. Although homozygosity for *UGT1A1*28*, previously reported as showing the most significant association with irinotecan related-toxicity, was found in three patients, it was not associated with any adverse events during this trial.[9, 11] There were no significant differences in response, survival, or the delivered dose of irinotecan according to *UGT1A* genotype.

DISCUSSION

This randomized study showed that the IP group achieved a higher response rate than the IG group (31.6% vs. 20.0%, respectively). Although our sample size was small, the other efficacy data obtained in the IP group were comparable to the results for platinum-based regimens containing irinotecan or other third-generation anticancer drugs.[2] The paclitaxel dose used in this study (180 mg/m^2) was lower than that reported for other paclitaxel-containing regimens, but this dose was based on the results of a previous phase I study in chemotherapy-naïve Japanese patients.[7] Thus, patients in the IP group were considered to have received appropriate paclitaxel doses.

This study showed that the IP and IG regiments were both well tolerated by patients with advanced NSCLC. The median numbers of treatment cycles administered in the IP and IG groups was three and four, respectively, which

were consistent with the study design. However, the delivered dose of irinotecan was lower in the IP group (dose intensity: 66.7%) because doses were skipped on days 8 and/or 15 (especially because of leukopenia). Although this was not a major problem in phase I trials, an increase in the deliverable dose of irinotecan in IP group may require modification of the timing for the administration of irinotecan in IP regimens, such as skipping treatment on day 8 or 15.

Recently, excision repair cross-complementation 1 (ERCC1) has been recognized as an invaluable biomarker for prediction of the clinical response to cisplatin-based chemotherapy in patients with NSCLC. Olaussen et al. have reported that patients with ERCC1-negative tumors appear to benefit from adjuvant cisplatin-based chemotherapy, whereas those with ERCC1-positive tumors do not.[23] A meta-analysis by Chen et al. has also shown that low or negative expression of ERCC1 is associated with a better objective response and longer median survival in patients with advanced NSCLC who receive platinum-based chemotherapy.[24] In that meta-analysis, patients with high/positive expression of ERCC1 who received platinum-based chemotherapy had an overall objective response rate of 28.4%. In the present study, the overall response rate in the IP group was 31.6%, suggesting that IP might be more effective for the patients with ERCC1-positive NSCLC. However, this must be confirmed in future clinical trials.

The ORR in the IP group was superior to that in the IG group, whereas PFS in the IP group was inferior to that in the IG group. A recent meta-analysis assessing the antitumor activities of third-generation drugs for the first-line treatment of advanced NSCLC reported that paclitaxel-based regimens are

associated with a significantly higher risk of earlier progression, despite having a response rate comparable to that of other third-generation regimens.[25] This finding is in accord with the results of our study. Although the primary end-point in our study design was ORR, the reasons for the discrepancy between ORR and PFS remain unknown. Moreover, Watanabe et al. showed in their meta-analysis that the disease control rate (CR, PR, and SD) is a more sensitive predictor of outcomes than the response rate (CR and PR) in patients with advanced NSCLC treated with platinum-based chemotherapy.[26] The disease control rate in the IP group and IG group were 67.7% and 84.6%, respectively. Further studies are required to clarify whether the optimal primary end-point of a phase II study is the response rate or disease control rate.

In this study, five patients had grade 1 or 2 pneumonitis in the IG group. All cases of pneumonitis were mild and controllable; however, the incidence was rather high. Recently, new molecular targeted drugs such as cetuximab or bevacizumab have been used in combination with cytotoxic drug regimens to treat advanced NSCLC. Regimens including molecular targeted drugs have been associated with a higher incidence of pneumonitis than combined treatment with cytotoxic drugs alone.[27] IP may be better suited for combined therapy with molecular targeted drugs because it has a low frequency of pneumonitis, a serious and potentially fatal toxic effect. IP might a better candidate for future clinical trials than non-platinum regimens in advanced NSCLC with low or negative expression of ERCC1.

UGT1A genotype analysis revealed that there was no relation between UGT polymorphisms and response; however, grade 4 neutropenia was significantly

associated with *UGT1A1*6* and **27*, but not with *28. In general, patients with *UGT1A1*27* also harbor *UGT1A1*28*, whereas those with *UGT1A1*28* do not necessarily harbor *UGT1A1*27*.[28] Both *UGT1A1*6* and **27* have only been identified in Asians, and *UGT1A1*6* has been reported to be associated with irinotecan-induced toxicities.[29, 30] On the other hand, *UGT1A1*27* is a rare polymorphism, and it remains unclear whether it is associated with irinotecan toxicity or not. Ando et al. reported that only 3 patients were heterozygous for *UGT1A1*27*, and all of them had severe neutropenia and/or diarrhea.[9] To the best of our knowledge, this is the first study that has demonstrated a significant association between *UGT1A1*27* polymorphism and neutropenia due to irinotecan-containing regimens. Hoskins et al. revealed that the risk of hematological toxicities among patients with a *UGT1A1*28* genotype did not significantly differ from that among patients with wild-type alleles in the subgroup of patients treated with low-dose weekly irinotecan ($\leq$100 mg/m^2).[31] Thus, evaluation of UGT1A1*27 genotype rather than UGT1A1*28 genotype may enhance the ability to predict toxicities in the clinical setting of low-dose weekly irinotecan chemotherapy.

In conclusion, the response rate achieved in the IP group was higher than that in the IG group, while the toxicities of both regimens were controllable. The *UGT1A1*6* and **27* genotypes might be useful for predicting grade 4 neutropenia due to low-dose weekly irinotecan regimens. To confirm the findings of this study, further prospective studies are needed in an independent data set.

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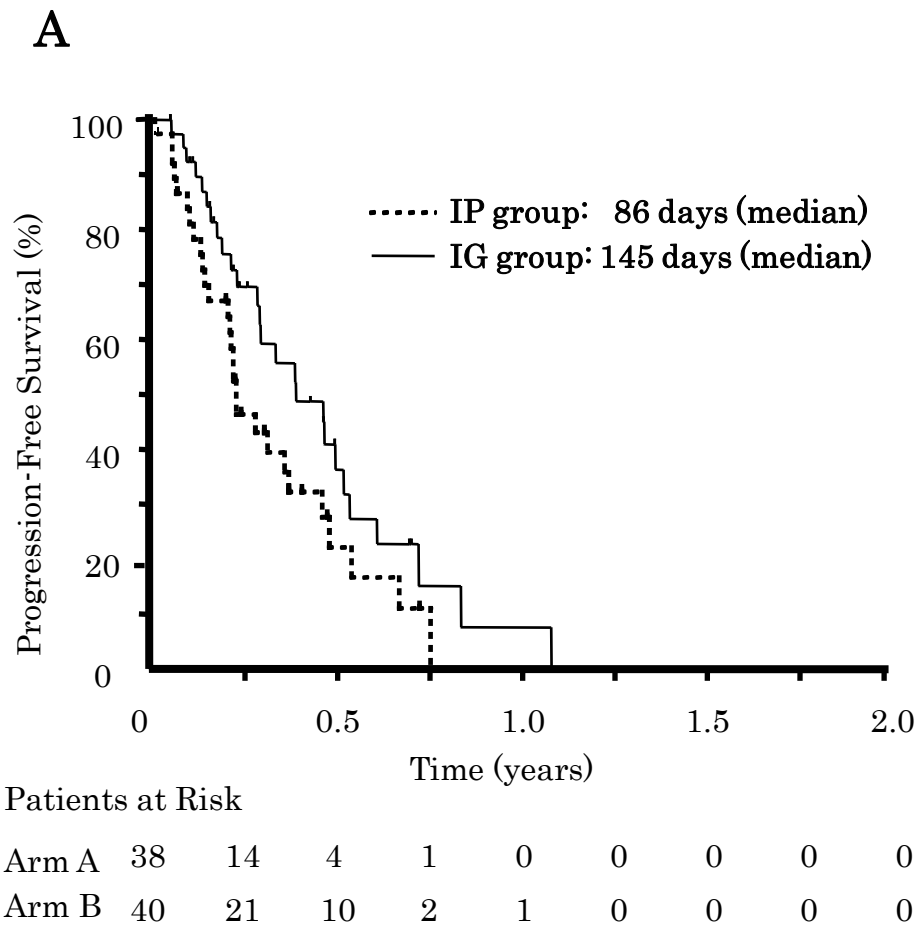
FIGURE LEGENDS

Figure 1. Kaplan-Meier curves for (A) progression-free survival and (B) overall survival.

Figure 2. Linkage disequilibrium analysis for UGT1A1, UGT1A7, UGT1A9 single nucleotide polymorphisms. D' (upper, red) and r^2 (lower, blue) values are shown for each square.

Figure. 1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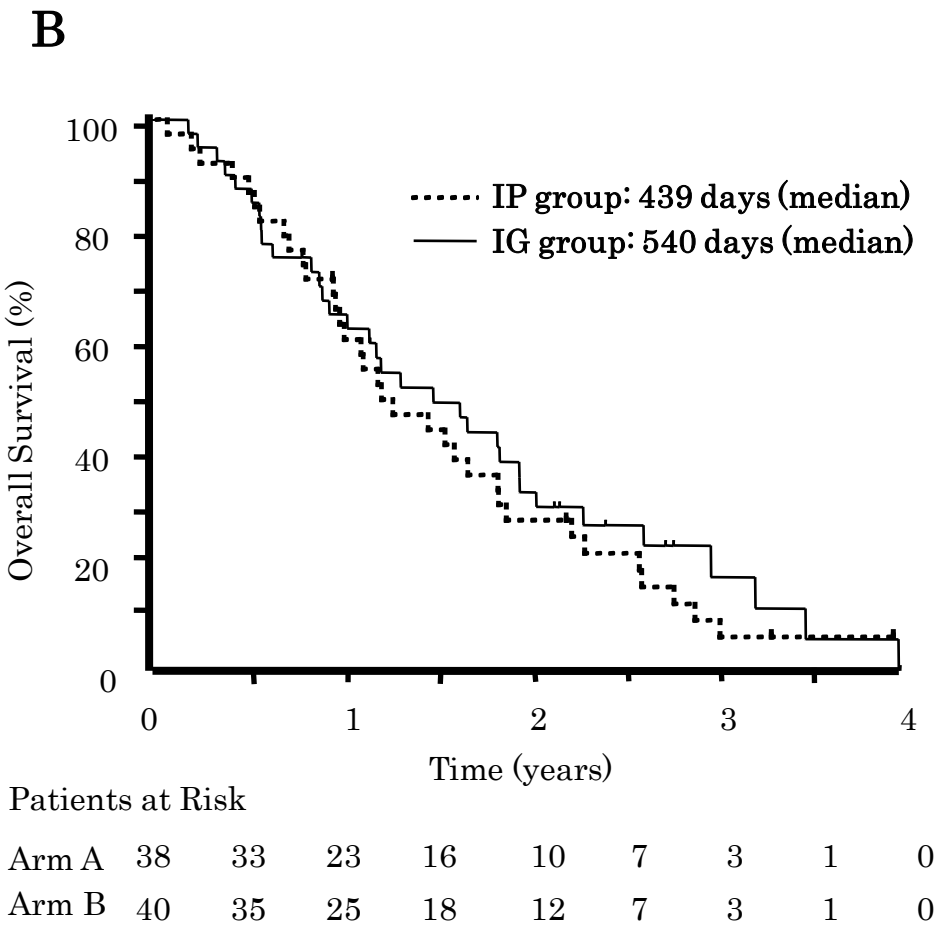
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60
40
20
0
Overall Survival (%)
IP group: 439 days (median)
IG group: 540 days (median)
0
1
2
3
4
Time (years)
Patients at Risk
Arm A 38 33 23 16 10 7 3 1 0
Arm B 40 35 25 18 12 7 3 1 0

Figure. 2

	-118(T)9>10	N129K	R131RQK	R131RQK	W208R	-3297T>G	-53(TA)6>7	211G>A	686C>A
-118(T)10>9		1	1	1	0.942	0.537	0.355	0.706	1
N129K	0.971		1	1	1	0.529	0.343	0.799	1
R131RQK	0.971	1		1	1	0.529	0.343	0.799	1
R131RQK	0.971	1	1		1	0.529	0.343	0.799	1
W208R	0.444	0.485	0.485	0.485		0.059	0.155	0.854	0.173
-3297T>G	0.202	0.191	0.191	0.191	0.002		1	1	1
-53(TA)6>7	0.046	0.041	0.041	0.041	0.017	0.515		1	1
211G>A	0.144	0.18	0.18	0.18	0.423	0.051	0.026		0.338
686C>A	0.055	0.053	0.053	0.053	0.003	0.078	0.151	0.022	

r2

0.9-1
0.8-0.9
0.7-0.8
0.6-0.7
<0.6

D'

0.9-1
0.8-0.9
0.7-0.8
0.6-0.7
<0.6

Table 1. Patient Characteristics

	IP group (Irinotecan/Paclitaxel)	IG group (Irinotecan/Gemcitabine)
No. of patients evaluated	38	40
Male/Female	26/12	28/12
Age<65	20	24
65≤	18	16
Stage IIIB/IV	7/31	8/32
PS 0/1	10/28	11/29
Histology		
Adenocarcinoma	30	31
Squamous	7	6
Others	1	3

Table 2. Toxicities

		No. of Patients					
		G0	G1	G2	G3	G4	≥G3 (%)
Leukopenia	IP group	3	9	15	10	1	28.9
	IG group	5	5	21	9	0	22.5
Neutropenia	IP group	2	4	2	16	14	78.9
	IG group	5	2	13	16	4	50.0
Febrile Neutropenia	IP group	33	0	3	2	0	5.3
	IG group	28	5	3	4	0	10.0
Diarrhea	IP group	22	10	3	3	0	7.9
	IG group	19	13	6	2	0	5.0
Constipation	IP group	26	2	6	4	0	10.5
	IG group	21	7	10	2	0	5.0
Neruopathy	IP group	13	22	3	0	0	0
	IG group	39	1	0	0	0	0
Pneumonitis	IP group	37	0	1	0	0	0
	IG group	35	2	3	0	0	0

Abbreviation: G, grade.

Table 3. Frequency of UGT1A Haplotypes and Genotypes

Haplotype	UGT1A9*22	UGT1A7(*)†	UGT1A1*60	UGT1A1*28	UGT1A1*6	UGT1A1*2 7	Frequency
	-118(T)$_{10}$>(T)$_9$	*387T>G, 391C>A, 392G>A, 622T>C*	-3279 T > G	-53(TA)$_{6>7}$	211G>A	686C>A	(%)
1	10	TCGT(*1)	T	6	G	C	57.0
2	9	GAAC(*3)	T	6	A	C	10.6
3	9	GAAT(*2)	G	6	G	C	10.7
4	10	TCGT(*1)	G	7	G	C	7.6
5	9	GAAC(*3)	T	6	G	C	4.3
6	10	TCGT(*1)	T	6	A	C	1.4
7	9	GAAC(*3)	G	7	G	C	4.4
8	9	GAAT(*2)	G	7	G	C	0.7
9	10	GAAC(*3)	T	6	A	C	0.7
10	9	GAAT(*2)	G	7	G	A	2.7

UGT1A Genotype	Wild type	Hetero	Homo	NA
*UGT1A1*28*	6/6	6/7	7/7	-
n	58	16	3	0
*UGT1A1*6*	G/G	G/A	A/A	-
n	58	17	2	0
*UGT1A1*27*	C/C	C/A	A/A	-
n	73	4	0	0
*UGT1A1*60*	T/T	T/G	G/G	-
n	43	22	8	4
*UGT1A7 (*1,*2,*3,*4)*	*1/*1, *1/*2, *1/*3	*2/*3	*2/2, *3/3	-
n	64	6	3	4
*UGT1A9*22*	10/10	10/9	9/9	-
n	34	30	9	4

Abbreviations: NA, Not analysed. Hetero, Heterozygous. Homo, Homozygous.

† *UGT1A7*1: TCGT, UGT1A7*2: GAAT, UGT1A7*3: GAAC, UGT1A7*4: TCGC*

Table 4. UGT Genotypes and Neutropenia

		Grade 4/All	%	OR	*P* value
*UGT1A1*28*	Wild type	12/58	20.7	1.369	0.609
	Hetero/Homo	5/19	26.3		
*UGT1A1*6*	Wild type	9/58	15.5	3.960	0.020
	Hetero/Homo	8/19	42.1		
*UGT1A1*27*	Wild type	14/73	19.2	12.643	0.033
	Hetero/Homo	3/4	75.0		
*UGT1A1*60*	Wild type	8/43	18.6	1.591	0.415
	Hetero/Homo	8/30	26.7		
UGT1A7	Wild type	12/64	18.8	3.467	0.094
	Hetero/Homo	4/9	44.4		
*UGT1A9*22*	Wild type	4/34	11.8	3.333	0.058
	Hetero/Homo	12/39	30.8		

Abbreviations: OR, odds ratio. Hetero/Homo, Heterozygous/Homozygous.