Multicenter Phase II Study of Irinotecan Plus Bolus Fluorouracil/*l*-Leucovorin for Metastasic Colorectal Cancer

HIDEYUKI MISHIMA[1], MASAKAZU IKENAGA[1], HIDEYUKI ISHIDA[2], SHIGENORI IWAMOTO[3], TAKASHI MORIMOTO[4], HIROYUKI NARAHARA[5], TAKESHI KATO[6], MASAKI TSUJIE[7], TOSHIYUKI KITAI[8], MUTSUMI FUKUNAGA[9], MASAYOSHI NAKANISHI[10], TOSHIMASA TSUJINAKA[1], HIROSHI FURUKAWA[9] and TETSUO TAGUCHI[1]; for the OSAKA GASTROINTESTINAL CANCER CHEMOTHERAPY STUDY GROUP

[1]Department of Gastroenterogical Surgery, Osaka National Hospital, Osaka 540-0006;
[2]Department of Surgery, Osaka Seamens Insurance Hospital, Osaka 552-0021;
[3]Department of Surgery, Kansai Medical University, Hirakata 573-1191;
[4]Department of Surgery, Yao City Hospital, Yao 581-0069;
[5]Department of Clinical Oncology, Graduate School of Biomedical Science, Hiroshima University, Hiroshima 734-8551;
[6]Department of Surgery, Mino City Hospital, Mino 562-8562;
[7]Department of Surgery, Hyogo Prefectural Nishinomiya Hospital, Nishinomiya 662-0918;
[8]Department of Surgery, Nara Shakaihoken Hospital, Yamatokoriyama-shi 639-1013;
[9]Department of Surgery, Sakai City Hospital, Sakai 590-0064;
[10]Department of Surgery, Matsushita Memorial Hospital, Moriguchi 570-8540;
[11]Japan Society for Cancer Chemotherapy, Osaka 550-0002, Japan

ANTICANCER RESEARCH *27*: 1003-1008 (2007)

Multicenter Phase II Study of Irinotecan Plus Bolus Fluorouracil/*l*-Leucovorin for Metastasic Colorectal Cancer

HIDEYUKI MISHIMA[1], MASAKAZU IKENAGA[1], HIDEYUKI ISHIDA[2], SHIGENORI IWAMOTO[3], TAKASHI MORIMOTO[4], HIROYUKI NARAHARA[5], TAKESHI KATO[6], MASAKI TSUJIE[7], TOSHIYUKI KITAI[8], MUTSUMI FUKUNAGA[9], MASAYOSHI NAKANISHI[10], TOSHIMASA TSUJINAKA[1], HIROSHI FURUKAWA[9] and TETSUO TAGUCHI[1]; for the OSAKA GASTROINTESTINAL CANCER CHEMOTHERAPY STUDY GROUP

[1]Department of Gastroenterogical Surgery, Osaka National Hospital, Osaka 540-0006;
[2]Department of Surgery, Osaka Seamens Insurance Hospital, Osaka 552-0021;
[3]Department of Surgery, Kansai Medical University, Hirakata 573-1191;
[4]Department of Surgery, Yao City Hospital, Yao 581-0069;
[5]Department of Clinical Oncology, Graduate School of Biomedical Science, Hiroshima University, Hiroshima 734-8551;
[6]Department of Surgery, Mino City Hospital, Mino 562-8562;
[7]Department of Surgery, Hyogo Prefectural Nishinomiya Hospital, Nishinomiya 662-0918;
[8]Department of Surgery, Nara Shakaihoken Hospital, Yamatokoriyama-shi 639-1013;
[9]Department of Surgery, Sakai City Hospital, Sakai 590-0064;
[10]Department of Surgery, Matsushita Memorial Hospital, Moriguchi 570-8540;
[11]Japan Society for Cancer Chemotherapy, Osaka 550-0002, Japan

Abstract. *Treatment of metastatic colorectal cancer remains inadequate. Patients and Methods: In a multicentre Phase II study, irinotecan (100 mg/m^2), 5-fluorouracil (5-FU) (500 mg/m^2), and l-leucovorin (l-LV) (250 mg/m^2) were administered on days 1, 8, and 15 of a five-week cycle. Forty-five patients were enrolled. Results: The objective response rate was 26.7%. The median survival time was 21.8 months and the one-year survival rate was 73.3%. The median number of cycles was 4.0, with a median relative dose intensity of 83.3% for both irinotecan and 5-FU. Grade 3 or 4 haematological toxicities were anaemia in four patients, leukopaenia in six patients, and neutropaenia in 15 patients, while non-haematological toxicities were diarrhoea in three patients, and nausea, vomiting, anorexia and increased transaminases in two patients each. No treatment-related deaths occurred. Conclusion: Irinotecan plus 5-FU/l-LV can be used to treat metastatic colorectal cancer on an outpatient basis.*

Correspondence to: Hideyuki Mishima, MD, Department of Gastroenterogical Surgery, Osaka National Hospital, 2-1-14, Hoenzaka, Chuo-ku, Osaka 540-0006, Japan. Tel: +81 6 6942 1331, Fax: +81 6 6946 5660, e-mail: hmishima@onh.go.jp

Key Words: Irinotecan, bolus 5-FU/*l*-LV, colorectal cancer.

In Japan, approximately 40, 000 people die of colorectal cancer annually and mortality due to this cancer is still rising. In 2004, colorectal cancer became the chief cause of death from malignancy among Japanese women (1).

Combinations of 5-fluorouracil (5-FU) as the base drug with irinotecan or oxaliplatin (FOLFIRI or FOLFOX) have been the standard chemotherapy regimens for colorectal cancer.

Irinotecan is an anticancer agent that inhibits topoisomerase I (2), and it has come into widespread use combined with 5-FU+leucovorin (5FU/LV) for metastatic colorectal cancer since an additive effect of this combination was demonstrated in patients with colorectal cancer (3, 4).

In Japan, continuous infusion of 5-FU/LV was approved in February 2005 and oxaliplatin was approved in April 2005. The previously approved 5-FU/LV regimen was once-weekly administration of a combination of "bolus 5-FU + high dose LV" (RPMI regimen), while irinotecan was approved for use at a dose of 100 mg/m^2 once weekly or 150 mg/m^2 every two weeks. Accordingly, the regimens of combined therapy with irinotecan plus 5-FU/LV established by Douillard *et al.* (3) and Saltz *et al.* (4) were outside the coverage of the Japanese national health insurance scheme. It was therefore necessary to establish a Japanese version of combined therapy with irinotecan plus 5-FU/LV.

A phase I clinical study was started in May 2000 with a fixed dosage of 5-FU/*l*-LV (RPMI regimen) (500/250 mg/m^2)

Table I. *Criteria for dose reduction or discontinuation.*

Criteria (toxicity in the previous course)	Irinotecan and 5-FU
- Grade 3/4 leucopaenia, neutropaenia, thrombocytopaenia - Grade 3/4 non-haematologic toxicity (excluding nausea, vomiting, anorexia and alopecia) - Increase of PS to 2 - Administration ommitted twice in succession during the previous course	Dose reduction by 1 level
- Grade 3-4 increase of ALT/AST - Increase of PS to 3 or more	Discontinuation
- When toxicity meeting the dose reduction criteria occurred again after an initial dose reduction	- Reduction of both drugs again by 1 level or discontinuation when dose reduction was not possible

PS: Performance status (Eastern Cooperative Oncology Group).

and escalating doses of irinotecan. According to a modified version of the schedule devised by Saltz *et al.* (4), irinotecan plus 5-FU/*l*-LV were administered on days 1, 8, and 15 of a five-week cycle. The dose of irinotecan was increased from level 1 (50 mg/m^2) to level 6 (100 mg/m^2) in 10 mg/m^2 increments. With the exception of one patient in whom grade 4 diarrhoea occurred at dose level 1, no dose-limiting toxicity (DLT) was detected and the maximum tolerated dose (MTD) was not reached, even at level 6. For the phase II study, the recommended dose of irinotecan was set at 100 mg/m^2. The relative dose intensity of irinotecan and 5-FU/*l*-LV was 90% or more regardless of the dose level or cycle number, suggesting that this regimen was safe (5).

Against this background, an open-label, multicenter phase II clinical study (OGSG0201) was conducted to evaluate the efficacy and safety of irinotecan + 5-FU/*l*-LV (weekly IFL regimen) for metastatic colorectal cancer. Since marked individual differences of the adverse reactions to irinotecan are known to occur (6, 7), dose reduction criteria were established with two lower dose levels (75 mg/m^2 and 50 mg/m^2) of this drug in consideration of safety. The minimum dose of irinotecan was set at 50 mg/m^2 because some subjects responded at this dose level in the phase I study.

Patients and Methods

Patient eligibility. Patients with metastatic colorectal cancer were eligible for enrollment in the study. Other eligibility criteria were as follows: histologically or cytologically confirmed advanced colorectal cancer or postoperative recurrent cancer with metastasis to other organs (liver, lung, lymph nodes, *etc.*); at least one measurable lesion (at least twice the slice thickness and with a maximum diameter ≥20 mm on CT or ≥10 mm on spiral CT); no prior chemotherapy (patients receiving postoperative chemotherapy with oral fluorinated pyrimidines or 5-FU/LV were acceptable if recurrence occurred at least 26 weeks after the completion of such therapy); no prior radiotherapy (except to a region other than the target lesion of the present study); age between 20 and 75 years; an Eastern Cooperative Oncology Group performance status of 0-1; a life expectancy ≥13 weeks from the start of treatment; acceptable major organ function (white blood cell count between 4,000/mm^3 and 12,000/mm^3, neutrophil count ≥2,000/mm^3, platelet count ≥100,000/mm^3, haemoglobin ≥8.0 g/dL, serum AST/ALT <2.5 times the institutional upper limit of normal (ULN), serum total bilirubin <1.5 times the ULN, serum creatinine ≤ULN and normal electrocardiogram) and written informed consent provided by the patient.

Chemotherapy schedule. On days 1, 8, and 15, irinotecan (100 mg/m^2) was administered as a 90-minute intravenous infusion, followed by l-LV (250 mg/m^2) as a 2-hour infusion. After one hour of *l*-LV infusion, 5-FU (500 mg/m^2) was given as an intravenous bolus. Treatment was repeated every five weeks until unacceptable toxicity occurred, consent was withdrawn, or disease progression was noted. Patients then received second-line therapy based on the preference of their attending physician.

Treatment criteria. Prior (on the same day or previous day) to receiving treatment on days 8 and 15, each patient was screened to ensure that the white blood cell count was ≥3,000/mm^3; the neutrophil count was ≥1,500/mm^3; the platelet count was ≥100,000/mm^3; the temperature was <38˚C with no detectable infection and that no diarrhoea or other toxicities >grade 2 (except nausea, vomiting, alopecia, anorexia, or malaise), as assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2 (8) were apparent. The scheduled dose was not administered when any of the criteria described above were not fulfilled. Even if a dose was omitted, the subsequent cycle was started as scheduled on day 36. Similar checks were made before the second or subsequent cycles to ensure that the above criteria and the serum creatinine level of ≤1.5 mg/dL were fulfilled. If any of these criteria were not met, treatment was suspended until the patient recovered. However, if the administration criteria were not fulfilled until five weeks or more had elapsed since the last day (day 1, 8, or 15) of the preceding cycle, the patient was removed from the study.

Dose modification criteria. Patients were checked for toxicity during each cycle and the doses of irinotecan and 5-FU were reduced according to the dose modification criteria (Table I) and dose reduction schedule (Table II). When a patient experienced similar

Table II. *Dose modification.*

	Irinotecan	5-FU	*l*-LV
Starting dose	100 mg/m^2	500 mg/m^2	
Level 1	75 mg/m^2	400 mg/m^2	250 mg/m^2
Level 2	50 mg/m^2	300 mg/m^2	

Table III. *Clinical characteristics of the patients.*

No. of patients	45	Tumour	
Gender			
Male	27	Primary	31
Female	18	Recurrent	14
Median age (range)			
	64 yr (40-75)	Histology	
		Adenocarcinoma	42
PS			
0	24	Mucinous	3
1	21	Sites of metastasis:	
		Lymph nodes	7
Prior treatment			
None	8	Liver	26
Surgery	33	Lungs	14
Surgery + Adjuvant	4	Others	7
		T-Bil value at registration	
		1≤	2
		1>	43

PS: Performance status (Eastern Cooperative Oncology Group). T-Bil: total bilirubin.

toxicity again after dose reduction, the doses of both irinotecan and 5-FU were reduced once more. When a patient experienced toxicity again after a second dose reduction that patient was withdrawn from the study. After dose reduction, the dose was not increased again.

Endpoints and evaluation criteria. The antitumor effect of therapy (response rate) was selected as the primary endpoint and was evaluated by extramural review according to the response evaluation criteria in solid tumors (RECIST) (9). The secondary endpoints consisted of safety (incidence and grade of adverse events), overall survival and relative dose intensity. For grading of adverse events, NCI-CTC version 2.0 (8) was used. The relative dose intensity was calculated for each drug and cycle using the following equation:
Relative dose intensity (%) = (actual dosage/planned dosage) x (35/actual no. of days per cycle) x100. Overall survival was calculated by the Kaplan-Meier method (10).

Sample size. In other Japanese studies, irinotecan monotherapy achieved a response rate of 27% in patients with advanced/recurrent colorectal cancer (including those with prior chemotherapy) (11), while 5-FU/*l*-LV has achieved response rates of 28% and 32% in patients receiving initial chemotherapy (12, 13).

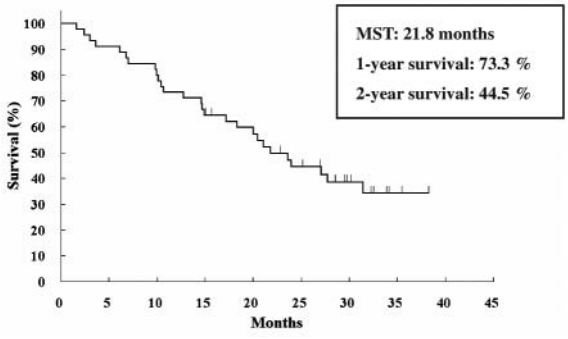

Figure 1. *Overall survival. MST: median survival time.*

Saltz *et al.* (4) reported that the response rate to irinotecan plus 5-FU/*l*-LV (IFL regimen) as first-line chemotherapy was 39%, while the response rates for 5-FU/*l*-LV or irinotecan alone were 21% and 18%, respectively. Accordingly, 40% was taken as the expected response rate and ±15% as the 95% confidence interval, so the required number of patients was estimated to be 41. Therefore, the target number of patients was set at 45 to allow for some exclusions from analysis.

Results

Patient characteristics. Between July 2002 and October 2003, 45 patients with metastatic colorectal cancer were enrolled at 11 institutions and all of them were eligible for analysis. Thirty-one patients had initial tumours and 14 had a recurrence. Twenty-seven patients were men and 18 were women. The median age was 64 years (range: 40-75 years). Twenty-four patients had an initial performance status of 0 and the remaining 21 had a performance status of 1. Among the 45 patients, 8, 33, and 4 had received no prior therapy, surgery alone, or a combination of surgery and adjuvant chemotherapy, respectively. The histological diagnosis was adenocarcinoma in 42 patients and mucinous carcinoma in 3 patients. The sites of metastasis were the liver in 26 patients, the lungs in 14 patients, lymph nodes in 7 patients, and other organs in 7 patients. The patients' clinical characteristics are shown in Table III.

Tumor response and survival. The objective response rate was 26.7% (96% CI: 14.6%-41.9%). There was a complete response (CR) in one patient, partial response (PR) in 11 patients, stable disease (SD) in 28 patients, and progressive disease (PD) in five patients (according to RECIST) (9). The tumour stabilization rate (including SD) was 88.9%. The median survival time (MST) was 21.8 months and the median follow-up time was 20.5 months (range: 1.6-38.3 months). Furthermore, the 1-year survival rate was 73.3% and the 2-year survival rate was 44.5% (Figure 1).

Table IV. *Haematological toxicity.*

	Grade				≥ Grade 3	Total
	1	2	3	4		
Anaemia	21	12	2	2	4 (8.9%)	37 (82.2%)
Leucopaenia	15	13	5	1	6 (13.3%)	34 (75.6%)
Neutropaenia	3	13	12	3	15 (33.3%)	31 (68.9%)
Thrombocytopaenia	4	0	0	0	0 (0%)	4 (8.9%)

Table V. *Non-haematological toxicity.*

	Grade				≥ Grade 3	Total
	1	2	3	4		
Diarrhoea	4	7	2	1	3 (6.7%)	14 (31.1%)
Abdominal pain	3	0	0	0	0 (0%)	3 (6.7%)
Nausea	10	7	2	-	2 (4.4%)	19 (42.2%)
Vomiting	10	5	2	0	2 (4.4%)	17 (37.8%)
Anorexia	9	6	2	0	2 (4.4%)	17 (37.8%)
Constipation	3	0	0	0	0 (0%)	3 (7.7%)
Alopecia	15	8	-	-	-	23 (51.1%)
Fatigue	11	2	0	0	0 (0%)	13 (28.9%)
Stomatitis	2	0	0	0	0 (0%)	2 (4.4%)
Back pain	1	0	0	0	0 (0%)	1 (2.2%)
Numbness	1	0	0	0	0 (0%)	1 (2.2%)
Pigmentation	1	1	0	0	0 (0%)	2 (4.4%)
↑ T-Bil	4	2	0	0	0 (0%)	6 (13.3%)
↑ AST/ALT	3	0	1	1	2 (4.4%)	5 (11.1%)
↑ ALP	2	0	0	1	1 (2.2%)	3 (8.9%)

Toxicity. A high incidence of haematological toxicity occurred, as shown in Table IV, but the therapy was regarded as tolerable and all of the toxicities were controllable. The main non-haematological toxicities were diarrhoea in 14 patients (31.1%), nausea in 19 patients (42.2%), vomiting in 17 patients (37.8%), anorexia in 17 patients (37.8%), alopecia in 23 patients (51.1%), fatigue in 13 patients (28.9%), increased total bilirubin in six patients (13.3%), and increased AST/ALT in five patients (11.1%). The main non-haematological toxicities of grades 3-4 were diarrhoea in three patients (6.7%), nausea in two patients (4.4%), vomiting in two patients (4.4%), anorexia in two patients (4.4%), and increased AST/ALT in 2 patients (4.4%). None of these toxicities became serious and all were controllable (Table V). Furthermore, no treatment-related deaths occurred within 60 days of starting this therapy.

Relative dose intensity. The median number of cycles completed was 4.0 (range: 1-11), with a mean of 4.3. The median relative dose intensity was 83.3% (range: 33.3%-100%) for both irinotecan and 5-FU, while the mean relative dose intensity was 81.1% for irinotecan and 82.5% for 5-FU. The median relative dose intensity for each cycle ranged from 43.8% to 97.2% and the mean relative dose intensity for each cycle was 43.8% to 85.8% (Table VI).

Table VI. *Relative dose intensity.*

	Irinotecan		5-FU	
	Median	Mean	Median	Mean
1st cycle (n=45)	97.2%	85.8%	97.2%	85.1%
2nd cycle (n=42)	83.3%	81.9%	83.3%	83.7%
3rd cycle (n=33)	83.3%	82.3%	84.8%	84.7%
4th cycle (n=23)	78.6%	82.2%	83.3%	84.5%
5th cycle (n=15)	74.5%	79.9%	80.0%	80.6%
6th cycle (n=13)	78.6%	78.2%	83.3%	79.8%
7th cycle (n=9)	71.4%	70.0%	83.3%	74.2%
8th cycle (n=8)	71.4%	70.6%	71.4%	73.6%
9th cycle (n=3)	83.3%	77.8%	83.3%	77.8%
10th cycle (n=2)	69.4%	69.4%	69.4%	69.4%
11th cycle (n=1)	43.8%	43.8%	43.8%	43.8%
Total	83.3%	81.1%	83.3%	82.5%

No. of cycles	
Median	4.0 cycles
Mean	4.3 cycles
Range	1-11

Relative dose intensity (%) = (actual dose / planned dose) x (35 / actual days of cycle) x100.

Discussion

The chemotherapy regimen used in the present study, unlike the IFL regimen of Saltz *et al.* (4), was based on the RPMI regimen (bolus 5-FU + high dose LV) in combination with irinotecan given weekly.

Although the objective response rate was not very high (26.7%), the tumour stabilization rate was 88.9%, while the MST was 21.8 months and the 1-year survival rate was 73.3%. These results were superior to other published data (4, 14, 15) and were similar to the results (MST of 20.3 months and 1-year survival rate of 74.3%) obtained by addition of bevacizumab to IFL, as reported by Hurwitz *et al.* (16). Goto *et al.* also conducted phase I and II studies using the modified IFL regimen of Saltz *et al.* (17), which was CPT-11 (100 mg/m^2), *l*-LV (10 mg/m^2), and 5-FU (500 mg/m^2) on days 1 and 8 with the duration of one cycle being set at 21 days. They reported an overall response rate of 58% (11/19), while the relative dose intensity of CPT-11 and 5-FU was about 90%. Although the response rate was higher than in the present study, the incidence of grade 3-4 adverse reactions was also higher

(leucopenia in 47%, neutropenia in 56%, decreased hemoglobin in 81%, fatigue in 60%, anorexia in 32%, nausea in 29%, and diarrhoea in 24%), indicating that their regimen caused more severe toxicity than ours (17).

In the present study, unlike other reports, all of the haematological and non-haematological toxicities (including gastrointestinal toxicities) were controllable. During two phase III clinical trials (N9741 and C89803) conducted in the United States, the IFL group showed more than twice the mortality of the control group within 60 days (18), so an analysis of early deaths was conducted. As a result, reduction of the dose to 100 mg/m^2 for irinotecan and 400 mg/m^2 for 5-FU was recommended for the first cycle only. Eventually, the Oncologic Drugs Advisory Committee demonstrated that careful patient selection is needed for the safe administration of IFL (19, 20).

Since the toxicity of irinotecan is known to show marked individual variations (6, 7), two dose reduction levels were established for the present study. As a result, the median relative dose intensity of both irinotecan and 5-FU was 83.3% and the mean relative dose intensity was more than 80%. This suggests that appropriate postponement of therapy and dose reduction could alleviate serious toxicity and improve the delivery of this therapy at general hospitals in Japan.

The recent package insert for irinotecan states that the dosage should be reduced in *UGT1A1*28* homozygous individuals. In addition, the NCCN Guideline 2006 (version 2) states that irinotecan should not be used in patients with a high total bilirubin level (20, 21). In the present study, total bilirubin was elevated in two patients, but the remaining patients had levels in the normal range. Although the initial dose of irinotecan was lower with the present regimen than with the IFL regimen of Saltz *et al.* (4), the relative dose intensity was similar for the two regimens and no serious adverse events occurred in our study. This was considered to be partly attributable to the low percentage of patients with high total bilirubin levels. In addition, infusion of 5-FU over three min or less and the criteria for postponing treatment with this regimen are considered to be other factors contributing to the lack of serious adverse reactions.

Idelevich *et al.* conducted a multicenter phase II study of 138 patients treated with IFL and reported that toxicity was manageable and the dose intensity was appropriate, suggesting that the regimen may be a good option as first-line treatment for metastatic colorectal cancer (15).

The main problem with our weekly regimen is the duration of administration. Although this therapy can be given on an outpatient basis, four hours are required for treatment (including premedication), because a 90-minute infusion of irinotecan is followed by a 120-minute infusion of *l*-LV. This problem might be solved by simultaneous administration of irinotean and *l*-LV which would reduce the time required to about two hours.

In recent years, FOLFIRI and FOLFOX have been widely used as first- and second-line treatments for metastatic colorectal cancer. On the other hand, concomitant administration of bevacizumab is recommended in the NCCN Guideline 2006 (version 2) (20, 21). However, bevacizumab and cetuximab have not been approved for use in Japan and most chemotherapy for colorectal cancer is delivered at general hospitals, rather than specialist hospitals. Among the 45 patients in the present study, 43 were enrolled by general surgeons rather than by oncologists. In consideration of this situation, it is necessary to develop a simple and effective regimen for colorectal cancer treatment (*e.g.*, concomitant use of an oral drug or the RPMI regimen).

Our weekly regimen is easy to administer on an outpatient basis and does not require a central venous catheter.

Acknowledgements

This study was conducted by the Osaka Gastrointestinal Cancer Chemotherapy Study Group.

References

1 Vital Statistics of Japan. Statistics and Information Dept., Minister's Secretariat, Ministry of Health, Labour and Welfare. Health and Welfare Statistics Association. Tokyo, 2006.

2 Kawato Y, Aonuma M, Hirota Y, Kuga H and Sato K: Intracellular roles of SN-38, a metabolite of the camptothecin derivative CPT-11, in the antitumor effect of CPT-11. Cancer Res *51*: 4187-4191, 1991.

3 Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M and Gruia G: Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer. Lancet *355*: 1041-1047, 2000.

4 Saltz LB, Cox JV, Blanke CB, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, Elfring GL and Miller LL: Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med *343*: 905-914, 2000.

5 Hideyuki M, Toshimasa T, Kazumasa F, Hiroshi F and Tetsuo T: Optimal dosing schedule of irinotecan plus fluorouracil and high dose l-leucovorin: Phase I study for metastatic colorectal cancer. Proc ASCO *22*: 338 (abstr), 2003.

6 Innocenti F, Undevia SD, Iyer L, Chen PX, Das S, Kocherginsky M, Karrison T, Janisch L, Ramirez J, Rudin CM, Vokes EE and Ratain MJ: Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol *22*: 1382-1388, 2004.

7 Marsh S and McLeod H: Pharmacogenetics of irinotecan toxicity. Pharmacogenomics *5*: 835-843, 2004.

8 NCI Common Toxicity Criteria Version 2.0. Bethesda, National Cancer Institute, Division of Cancer Treatment, 1999.

9 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst *92*: 205-216, 2000.

10 Shimada Y, Yoshino M, Wakui A, Nakao I, Futatsuki K, Sakata Y, Kambe M, Taguchi T and Ogawa N: Phase II study of CPT-11, a new camptothecin derivative, in metastatic colorectal cancer. CPT-11 Gastrointestinal Cancer Study Group. J Clin Oncol *11*: 909-913, 1993.
11 Kaplan EL and Meier P: Nonparametric estimation from incomplete observations. Amer Stat Assoc J *53*: 457-481, 1958.
12 Yoshino M, Ota K, Kurihara M, Akazawa S, Tominaga T, Sasaki T, Konishi T, Kodaira S, Kumai K, Sugano K, Ogawa M, Ariyoshi Y and Murakami M: Late phase II trial of high-dose l-leucovorin and 5-fluorouracil in advanced colorectal carcinoma. Jpn J Cancer Chemother *22*: 785-792, 1995.
13 Konishi K, Yabushita K, Taguchi T, Ota J, Takashima S, Abe T, Kikkawa N, Yasutomi M, Sowa M, Maehara Y, Arima S, Isomoto H, Kurihara M, Ohtani T, Hirabayashi N and Nakano S: A late phase II trial of l-leucovorin and 5-fluorouracil in advanced colorectal cancer. Jpn J Cancer Chemother *22*: 925-932, 1995.
14 Goto A, Yamada Y, Hosokawa A, Ura T, Arai T, Hamaguchi T, Muro K, Shimada Y and Shirao K: Phase I/II study of irinotecan, 5-fluorouracil, and l-leucovorin combination therapy (modified Saltz regimen) in patients with metastatic colorectal cancer. Int J Clin Oncol *9*: 364-368, 2004.
15 Idelevich E, Man S, Lavrenkov K, Gluzman A, Geffen DB and Shani A: Irinotecan combined with bolus 5-fluorouracil and folic acid for metastatic colorectal cancer: Is this really a dangerous treatment? J Chemother *16*: 487-490, 2004.
16 Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R and Kabbinavar F: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med *350*: 2335-2342, 2004.
17 Goto A, Yamada Y, Hosokawa A, Ura T, Arai T, Hamaguchi T, Muro K, Shimada Y and Shirao K: Phase I/II study of irinotecan, 5-fluorouracil, and l-leucovorin combination therapy (modified Saltz regimen) in patients with metastatic colorectal cancer. Int J Clin Oncol *9*: 364-368, 2004
18 Sargent DJ, Niedzwiecki D, O'Connell MJ and Schilsky RL: Recommendation for caution with irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med *12*: 144-145, 2001.
19 FDA panel says Camptosar death rates not excessive. Scrip: Dec 07, 2001 (20011207).
20 National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology, Colon Cancer – Version 2. 2006. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp?button=I+Agree
21 National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology, Rectal Cancer – Version 2. 2006. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp?button=I+Agree

Received July 31, 2006
Revised February 7, 2007
Accepted February 8, 2007