Results

Patient characteristics

A total of 20 patients were enrolled between January and October 2002 at the National Cancer Center Hospital. Table 1 shows the baseline characteristics of the patients. Only 1 patient had received adjuvant therapy with an oral fluoropyrimidine derivative 1 month before study entry.

There was a deviation from the protocol in one patient, who withdrew his consent during therapy. This patient had received a lower anterior resection for primary rectal cancer and had continuous mild anal bleeding. After cycle 1, he requested to be transferred to another other hospital for treatment of the anal bleeding and refused to continue chemotherapy (not considered DLT).

DLT and RD

Nine patients (six at level 1 and three at level 2) received at least two cycles of treatment for dose-finding. Adverse events occurring during the first two cycles of treatment, used to estimate the MTD, are shown in Tables 2 and 3.

Table 1. Patient characteristics

No. of patients	20
Male/female	15/5
Performance status (ECOG) 0/1	17/3
Age (years)	
Median	61
Range	32–71
Primary site	
Rectum	10
Colon	10
No. of metastatic sites 1/2/3	14/5/1
Metastatic sites	
Lung	10
Liver	9
Lymph nodes	6
Peritoneum	2
Pleura	1
Previous treatment	
Adjuvant oral fluoropyrimidine	1
None	19

ECOG, Eastern Cooperative Group

Three patients were treated at level 1 with 5-FU 400 mg/m^2. One of these patients had grade 4 neutropenia with fever on day 15 of cycle 1. This patient was a 54-year-old woman with multiple lung metastases and a performance status of 0. The results of physical examination, CBC, and chemistry profile were normal at entry, although the serum total bilirubin level 2 weeks before entry (1.2 mg/dl) had been slightly above the upper limit of normal. Chemotherapy was not given to this patient on day 8 of cycle 1 because of neutropenia. She received antibiotics and granulocyte colony-stimulating factor for the remainder of cycle 1. All adverse events resolved by day 1 of cycle 2, and the chemotherapy was resumed. However, the patient had grade 2 diarrhea on day 8 and grade 2 neutropenia on day 15 of cycle 2, indicating inability to tolerate irinotecan in combination with 5-FU and *l*-LV. Bolus 5-FU and *l*-LV were therefore given subsequently. Three additional patients were then assigned to receive level 1. The other five of the six patients given level 1 completed two cycles of treatment without severe toxicity.

The three patients who initially received level 2 (5-FU 500 mg/m^2) had no DLT. Level 2 was therefore designated as the RD. Eleven other patients received level 2 to confirm adverse events and efficacy. One of these patients had moderate hepatic dysfunction, probably related to a nutritional supplement. In this patient, treatment scheduled for day 1 of cycle 2 was postponed for 6 weeks. Apart from this deviation from protocol, no DLT occurred in any of the 14 patients given level 2.

Toxicity

Toxicity was recorded for all patients who received one to five cycles of chemotherapy (total, 75 cycles) (Table 4). The most common type of hematologic toxicity was neutropenia. All-grade neutropenia and grade 3/4 neutropenia, respectively, occurred in 42 (56%) and 7 (9%) of the 75 cycles administered. The hemoglobin level decreased slightly in 61 (81%) of the 75 cycles, with no grade 3/4 anemia. The baseline hemoglobin level in nearly all patients was grade 1 or the lower limit of normal before the start of treatment. Thrombocytopenia did not occur in any cycle.

The most frequent type of non-hematologic toxicity was fatigue. Grade 1/2 fatigue occurred in 45 (60%) of 75 cycles; no grade 3/4 fatigue was reported. Anorexia occurred in 24

Table 2. Hematologic toxicity in the first two cycles

	Grade 1	Grade 2	Grade 3	Grade 4	Grades 3, 4 (%)
Level 1 (n = 6)					
Leukopenia	1	2	1	0	17
Neutropenia	2	0	0	1	17
Hemoglobin decrease	4	1	0	0	0
Thrombocytopenia	0	0	0	0	0
Level 2 (n = 14)					
Leukopenia	5	1	2	0	14
Neutropenia	1	3	4	0	29
Hemoglobin decrease	10	1	0	0	0
Thrombocytopenia	0	0	0	0	0

(32%) and nausea in 22 (29%) of 75 cycles. Grade 1/2 mild diarrhea developed in 18 (24%) of 75 cycles. Stomatitis occurred in 8 (11%) of 75 cycles. Infection, with grade 4 neutropenia, occurred in 1 of 75 cycles. There was no treatment-related mortality. No patient who received up to five cycles of chemotherapy had to be hospitalized because of drug adverse reactions.

Dose intensity

Dose reduction was not required in any patient because of adverse events. At level 1, treatment had to be delayed for at least 1 week one time during five cycles in 3 of 6 patients, and 1 patient with DLT could not receive chemotherapy on day 8 of cycle 1. The total number of delayed cycles was 3 of 16 (19%). At level 2, treatment had to be delayed for 1 week at least one time in 9 of the 13 patients who received up to five cycles of chemotherapy, and 1 patient did not receive treatment on day 8 of cycle 5 because of fatigue. The total number of delayed cycles was 17 of 62 (27%). During five cycles at level 1, the mean dose intensities (DIs) of 5-FU and irinotecan were 242 mg/m^2 per week and 61 mg/m^2 per week, respectively. The relative DI was 91% of the initial dose for both drugs. During the first five cycles at level 2, the mean DIs of 5-FU and irinotecan were 287 mg/m^2 per week and 62 mg/m^2 per week, and the relative DIs at level 2 were 86% and 93%, respectively.

Table 3. Nonhematologic toxicity in the first two cycles

	Grade 1	Grade 2	Grade 3, 4
Level 1 (n = 6)			
Anorexia	4	0	0
Nausea	1	0	0
Vomiting	0	0	0
Diarrhea	1	1	0
Stomatitis	1	0	0
Fatigue	4	0	0
Level 2 (n = 14)			
Anorexia	8	2	0
Nausea	10	1	0
Vomiting	1	0	0
Diarrhea	3	1	0
Stomatitis	2	0	0
Fatigue	10	0	0

Table 4. Toxicity in all 75 cycles

	Grade 3	Grade 4	All grades (%)
Anorexia	0	0	24 (32)
Nausea	0	0	22 (29)
Vomiting	0	0	4 (5)
Diarrhea	0	0	18 (24)
Stomatitis	0	0	8 (11)
Fatigue	0	0	45 (60)
Febrile neutropenia	1	0	2 (3)
Leukopenia	2	0	35 (47)
Neutropenia	6	1	42 (56)
Hemoglobin decrease	0	0	61 (81)
Thrombocytopenia	0	0	0 (0)
Elevation of AST	0	0	1 (1)
Elevation of ALT	0	0	1 (1)

AST, aspartate aminotransferase; ALT, alanine aminotransferase

Efficacy

Response rates are shown in Table 5. Response was evaluated in 19 of 20 patients (excluding 1 patient in whom the tumor was not assessed after treatment, because of transfer to another hospital before evaluation of response). Two of 6 patients had a partial response at level 1 (33%). At level 2, 9 of 13 patients (69%) responded to treatment. The overall response rate was 58%. As of the time of this writing, all patients who received level 1, and 8 of the 13 patients who received level 2 had disease progression. The median TTP at the RD was 7.8 months.

Discussion

Irinotecan with 5-FU and LV has been shown to be effective for metastatic colorectal cancer in large randomized phase III trials.[4,5] This three-drug regimen is considered first-line treatment in western countries. However, toxicity associated with the original Saltz regimen (recommending treatment on days 1, 8, 15, and 22 every 6 weeks) often requires dosage modifications to decrease dose intensity.

Treatment for metastatic colorectal cancer must be safe and provide adequate tumor control. We therefore performed a phase I/II study to evaluate the safety and efficacy of a modified Saltz regimen and to confirm starting dose levels for Japanese patients with colorectal cancer. The MTD was not reached because the maximum approved weekly dose of irinotecan in Japan is 100 mg/m^2. We estimated level 2 (irinotecan 100 mg/m^2 with 5-FU 500 mg/m^2 and l-LV 10 mg/m^2) to be the RD. In practice, the administered weekly dose of irinotecan may slightly exceed 100 mg/m^2 in some patients given our RD. However,

Table 5. Response rates

	CR	PR	SD	PD	NE	Confirmed response rate
Overall (n = 19)	0	11	3	4	1	58%
Level 1 (n = 6)	0	2	1	3	0	33%
Level 2 (n = 13)	0	9	2	1	1	69%

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated

125 mg/m^2 or 150 mg/m^2 of irinotecan weekly would probably result in decreased dose intensity due to severe adverse events. Therefore, we firmly believe that our RD is adequate for Japanese patients.

In our study, only one patient had grade 3 febrile neutropenia as the DLT. This patient had a slightly abnormal bilirubin level 1 week before study entry. The investigator in charge enrolled this patient because the serum bilirubin level had returned to normal at the time of entry. Knight et al.[9] analyzed predictors of toxicity in patients given the original Saltz regimen. Their logistic regression analysis showed that only an elevated bilirubin level predicted a higher incidence of grade 4 neutropenia (P = 0.03). They concluded that dose attenuation was most rapid in patients with performance status 2 and abnormal baseline bilirubin. In patients with mildly elevated bilirubin levels, systemic exposure to irinotecan and SN-38 increases the levels considerably, because the pharmacokinetics of irinotecan depend on liver function; dose reduction is therefore required.[12-14] Wasserman et al.[14] reported that patients with Gilbert's syndrome were at increased risk for irinotecan-related toxicity because of deficient UGT*1.1 activity. We recommend that treatment with irinotecan is started at a dose of 100 mg/m^2 in patients with good performance status and normal bilirubin levels. The dose should be reduced in patients with abnormal bilirubin levels.

The most common toxic effect in our study was fatigue, reported in 45 of 75 cycles in eligible patients receiving up to five cycles each. Although not severe, fatigue was a major cause of delayed treatment and occurred frequently after three cycles of chemotherapy. When required, treatment was discontinued for at least 1 week in patients with fatigue. This rest led to recovery in nearly all patients. Postponement of subsequent cycles of chemotherapy also promoted recovery from nausea and anorexia, two other common toxic effects. Neutropenia was another important reason for delaying treatment, and occurred in 42 of 75 cycles, including 7 with grade 3/4 neutropenia. Excluding the patient with DLT, neutropenia usually did not resolve after 1 week of rest. At the RD, the mean absolute DIs of 5-FU and irinotecan were 287 mg/m^2 per week and 62 mg/m^2 per week, and the relative DIs were 86% and 93%, respectively. Differences between the scheduled and administered doses were caused by temporary discontinuation of treatment and dose reduction. On the basis of our experience, we recommend that treatment be suspended for at least 1 week in patients with adverse events.

Our regimen was highly active, with a response rate of 69% in patients receiving the RD. Our overall response rate of 58% is similar to that in previous studies of irinotecan with 5-FU and LV. We conclude that a combination of irinotecan, 5-FU, and *l*-LV is safe, effective, and clinically feasible, and this regimen could be one of the standard first-line treatments for metastatic colorectal cancer in Japan.

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V．健康危険情報

健康危険情報

本試験開始後に確認された有害事象のうち、2004 年 9 月のモニタリングレポートより Grade4 の非血液毒性、JCOG 効果安全死恵評価委員会へ報告された有害事象、およびその他の有害事象を以下にまとめる。

1）Grade4 の非血液毒性

症例	治療群	有害事象	発生時期	関連性
27	B（UFT/LV）	GOT/GPT 上昇	4 コース day15	definite
74	B	GPT 上昇	1 コース day21	definite（未報告）
152	B	GPT 上昇	1 コース day35	definite

2）JCOG 効果安全性評価委員会へ報告された有害事象

症例	治療群	有害事象	発生時期	関連性
9	B（UFT/LV）	下痢、悪心、食欲低下 G3	1 コース day31	probable
28	B	GPT G3	1 コース day35	definite
32	B	GOT/GPT G3	1 コース day32	definite
78	B	GPT G3	1 コース day34	definite
172	B	GOT/GPT G3	1 コース day35	definite
178	B	GOT/GPT G3	1 コース day40	definite
198	B	GPT G3	1 コース day35	definite

3）その他の有害事象

症例	治療群	有害事象	発生時期	関連性
12	B	心臓虚血	1 コース day6	possible（既知）
18	A	子宮溜膿腫	3 コース中	unlikely（未報告）
61	A	帯状疱疹	1 コース day19	possible（未知、未報）
74	B	血球貪食症候群	1 コース day21	possible（未知、未報）
		DIC G3	1 コース day23	possible（未知、未報）

術後補助療法として実施した UFT/LV に関して、一施設で肝機能障害が頻発した。これについては厚生労働省、企業、院内に報告している。他の施設でも散発性に発症があるが、頻度は必ずしも高くなく、既知の有害事象として取り扱われている。今後、集計によりその頻度や、発生様式について検討する予定である。