

## Phase I/II Study of Irinotecan and UFT for Advanced or Metastatic Colorectal Cancer

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**Abstract.** The aim of this study was to determine the recommended dose of irinotecan in combination with the fixed dose of oral UFT as first-line therapy in patients with advanced or recurrent colorectal cancer, and to evaluate the response rate and overall survival as a phase II study. **Patients and Methods:** Thirteen patients were recruited into a phase I trial. Four doses of irinotecan ranging from 60 to 150 mg/m<sup>2</sup>/day were administered intravenously on day 1 and day 16 in combination with UFT given orally from day 2 to day 15. In a phase II study, 53 patients received at least one cycle of this therapy. **Results:** The recommended dose of this combination was determined as irinotecan 120 mg/m<sup>2</sup>/day and UFT 400 mg/m<sup>2</sup>/day. Dose-limiting toxicities were neutropenia and prolonged leucopenia. On an intent-to-treat analysis, the response rate in the phase II study was 24.5% (95% confidence interval 13.8% to 38.2%). The median overall survival time was 20.3 months (95% confidence interval, 15.0-22.8 months). Out of 20 patients with stable disease, 17 who received more than 4 cycles of the regimen lived longer than the other 3 patients who received fewer than 3 cycles ( $p=0.0353$ ). Hematological adverse events were mainly grade 3/4 neutropenia observed in 6 out of 53 patients. Grade 3 non-hematological toxicities, such as diarrhea, anorexia, nausea/vomiting and alopecia were observed in 6 patients. **Conclusion:** Irinotecan combined with

oral UFT was effective and well-tolerated. This regimen may be considered as a first-line therapy for advanced or metastatic colorectal cancer and may result in fairly long survival, even for patients with stable disease.

The greatest progress of systemic treatment for colorectal cancer has occurred since the introduction of irinotecan combined with fluorouracil-based drugs. The recent use of irinotecan-combined therapy prolonged survival and improved quality of life, but increased toxicity (1-5). The study of tegafur/uracil (UFT) combined with oral leucovorin (LV) resulted in a response rate and survival similar to parenteral administration of 5-fluorouracil (5-FU) and LV, and showed an advantage of the oral administration over parenteral administration (6-9). An oral administration of only UFT generated sufficient maximum and average concentrations of metabolic 5-FU compared to continuous 5-FU infusion (10). Oral chemotherapy with or without LV in an outpatient setting seems to have favorable convenience and lower toxicity profiles during chemotherapy, compared to intravenous administration (9, 11, 12).

Modulation of anticancer effects of 5-FU is obtained by the addition of uracil, LV and irinotecan. Various regimens of irinotecan-5-FU/LV or UFT/LV combinations have been investigated in the past. However, administration schedules of irinotecan and oral UFT, instead of infusional 5-FU, without LV were found in a few reports (13, 14). Alonso *et al.* (13) proposed a weekly irinotecan plus UFT schedule, using irinotecan at a dose of 110 mg/m<sup>2</sup> on days 1, 8, 15 every 28 days plus UFT 250 mg/m<sup>2</sup> on days 1 through 21 or irinotecan 100 mg/m<sup>2</sup> and UFT 300 mg/m<sup>2</sup>.

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Table I. Dose escalation schedule and toxicity in phase I study.

Dose level	Irinotecan (mg/m <sup>2</sup> )	UFT (mg/m <sup>2</sup> )	No. of patients	No. of PR	No. of HT		No. of NHT	
					Grade 3	4	Grade 3	4
1	60	400	3	0	0	0	1	0
2	90	400	3	0	0	0	0	0
3	120	400	3	3	0	0	1	0
4	150	400	4	2	0	1	2	0

PR, partial response; HT, hematological toxicity; NHT, non-hematological toxicity.

Here, a phase I/II study with irinotecan given on days 1 and 16, combined with UFT 400 mg/m<sup>2</sup>/day between day 2 and day 15 every 28 days was carried out in patients with advanced or recurrent colorectal cancer. The primary objective of this study was to determine a recommended dose of irinotecan combined with UFT 400 mg/m<sup>2</sup> by assessing the efficacy and toxicity. The second objective was to evaluate the feasibility of this regimen from the response rate and overall survival in patients with this regimen of chemotherapy.

**Patients and Methods**

*Patients.* Between June 2000 and June 2002, eligible patients were recruited for the phase I trial from three centers and subsequently the phase II trial from ten centers. The main criteria for enrolment consisted of histologically-confirmed colorectal carcinoma, no prior chemotherapy for measurable disease, age between 20 and 75 years, a WHO performance status of 0 to 2, a life expectancy of more than three months, and adequate hematological and biochemical parameters: white blood cell count >3500/mm<sup>3</sup>, neutrophil count >2000/mm<sup>3</sup>, platelet count >100000/mm<sup>3</sup>, hemoglobin >9 g/dl, bilirubin <1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase <2 times of institutional upper limit of normal range and serum creatinine <1.5 mg/dl. Patients with diarrhea, intestinal obstruction and serious infectious diseases were excluded. All patients were informed of the purpose and conduct of this study and signed a written consent form.

*Study design and treatment.* The phase I trial was conducted as a non-randomized and dose-finding study using a dose escalation of irinotecan. Four dose levels of irinotecan ranging from 60 to 150 mg/m<sup>2</sup>/day were investigated in combination with a fixed dose of UFT 400 mg/m<sup>2</sup>/day (Table I).

All patients received antiemetic premedication with 5HT3 antagonists and dexamethasone prior to each dose of irinotecan. Initially, three patients were treated with the starting dose of irinotecan 60 mg/m<sup>2</sup> given as a 90-minute intravenous infusion on day 1 and day 16, and UFT 400 mg/m<sup>2</sup>/day given orally twice daily from day 2 to day 15. The patients had a rest period between day 17 and day 28. One cycle of irinotecan and UFT was administered every 28 days.

Dose escalation proceeded until dose-limiting toxicity (DLT) was encountered in the cycle. Toxicity grades were evaluated according to 2.0 version of National Cancer Institute Common Toxicity Criteria. DLT was defined as any of the following experienced during the cycle: grade 4 hematological toxicity, neutropenic fever, and grade 3 or 4 non-hematological toxicity except for alopecia, nausea or vomiting. If DLT was observed in any patient, an additional 3 patients were treated at that dose level. The maximum tolerated dose (MTD) was defined as being reached if 2 of 6 patients experienced DLT. The recommended dose was the dose level below MTD.

The phase II trial was conducted at ten centers. Pretreatment evaluation consisted of a medical history, physical examination, a complete blood count, serum chemistry profile and carcinoembryonic antigen measurement, a chest x-ray and a radiological tumor parameter assessment. A physical examination, complete blood count with differential and platelet count, and serum chemistry tests were performed to evaluate the toxicity before and during each course of therapy. Measurable tumors were reassessed by computed tomography and echography every two cycles. Complete response (CR) was defined as the complete disappearance of measurable lesions for at least 4 weeks, partial response (PR) as a decrease of at least 50% of measurable tumors, stable disease (SD) as a decrease of less than 50% or an increase of less than 25% of the disease, and progressive disease (PD) as an at least 25% increase in the tumor size or the appearance of new metastatic lesions. Treatment was discontinued for disease progression, unacceptable toxicity, a delay of >29 days in instituting the next cycle of therapy, or at investigators' discretion or patient's request. Based on previous cycle toxicity evaluated as grade 3 or 4, both doses were reduced by 25% in the subsequent treatment cycles.

The primary end-point of the phase II study was to evaluate the response rate and the secondary end-point was to assess the overall survival and adverse events.

*Statistical analysis.* Statistical analyses were performed using the JMP version 6.0.2 (SAS Institute Japan). Response rate and survival from the start of chemotherapy until death were calculated. The 95% confidence intervals (95%CI) were also calculated. The survival curve was obtained using the Kaplan-Meier method. The survival data between two groups were evaluated by the Mann-Whitney *U*-test and a *p*-value <0.05 was considered statistically significant.

**Results**

*Patient characteristics.* Thirteen patients with measurable tumors and good performance status participated in the phase I trial. The demographic characteristics of patients are presented in Table II. A total of 53 patients were enrolled in the phase II trial. Their characteristics are also given in Table II.

*Efficacy and adverse events in phase I study.* Responses were not observed at level 1 and 2. A partial response was obtained in 3 patients at level 3 and 2 patients at level 4. Toxicity was generally mild at level 1, 2 and 3 (Table I). One patient treated with the fourth dose level developed grade 4 neutropenia. Non-hematological toxicity included one grade

Table II. Patient characteristics.

	Phase I	Phase II
No. of patients	13	53
Median age (range; years)	52(46-71)	63(37-73)
Gender		
Female	7	18
Male	6	35
WHO performance status (grade)		
0	10	45
1	2	8
2	1	0
Primary site		
Colon	2	24
Rectum	11	29
Indication		
Advanced disease	4	9
Recurrence	9	44
Metastatic site		
Lung	5	22
Liver	4	24
Lymph node	4	10
Local	3	11
Others	5	3

3 alopecia at level 1, one grade 3 anorexia and nausea/vomiting at level 3, and one grade 3 anorexia and one grade 3 alopecia at level 4. DLT was experienced in 2 of 4 patients at level 4. One patient developed grade 4 neutropenia and the other could not start the next cycle of therapy more than 29 days after the first cycle due to prolongation of leucopenia. Recommended doses from the present study are irinotecan 120 mg/m<sup>2</sup>/day and UFT 400 mg/m<sup>2</sup>/day.

**Efficacy in phase II study.** A total of 53 eligible patients underwent this therapy and were evaluated for response. Four patients could not receive the full course of the first cycle, 3 could not be examined with CT scan according to the protocol schedule and 1 was lost to follow-up. All patients were assessed for safety and tolerance. A mean of 5.9 (1-33) cycles were administered in evaluated patients. The median follow-up time was 546 (136-1596) days in these patients. One complete response and 12 partial responses were observed. Stable disease was recorded in 20 patients and progressive disease in 12 patients. On an intent-to-treat analysis, the overall response rate was 24.5% (95%CI, 13.8%-38.2%). The responses were observed in 50% of lymph node metastasis, 33% of local recurrence, 22% of lung metastasis and 17% of liver metastasis. The median overall survival time was 20.3 months (95%CI, 15.0-22.8 months). The two-year overall survival rate was 28.3%. Of 20 patients with stable disease 17 received more than 4

Table III. Adverse events in phase II study.

Adverse event	NCI-CTC grade (53 patients)			
	1	2	3	4
<b>Hematological</b>				
Anemia	6	3	0	0
Leucopenia	9	12	1	0
Neutropenia	10	8	5	1
Thrombocytopenia	1	0	0	0
<b>Non-hematological</b>				
Liver dysfunction	1	0	0	0
Renal dysfunction	0	1	0	0
Anorexia	10	7	2	0
Nausea/vomiting	13	4	2	0
Diarrhea	6	2	2	0
Eruption	1	0	0	0
Alopecia	8	4	0	0
General fatigue	2	1	0	0
Fever	0	1	0	0
Abdominal pain	0	2	0	0
Malaise	1	0	0	0

NCI-CTC, National Cancer Institute Common Toxicity Criteria.

cycles of this regimen and lived for 19.2 months, while the other 3 patients received lower than 3 cycles and lived for 5.7 months. The former survival time was significantly longer than the latter ( $p=0.0353$ ).

**Safety.** All 53 patients who received at least one dose of the study medication were evaluated for safety. At the 120 mg/m<sup>2</sup> starting dose of irinotecan, 3 patients had a dose reduction in the second course. Adverse events of a total of 53 patients are summarized in Table III.

Hematological adverse events were mainly grade 3/4 neutropenia and leucopenia. Grade 3/4 neutropenia occurred in 6 (11%) out of 53 patients. No patients experienced febrile neutropenia, severe anemia or severe thrombocytopenia. Non-hematological adverse events consisted of anorexia, nausea/vomiting, diarrhea and alopecia. Grade 4 non-hematological adverse events did not occur. Grade 3 diarrhea was observed in 2 (2%) patients and grade 3 anorexia in 2 (2%) patients, grade 3 nausea/vomiting in 2 (4%) patients and grade 3 alopecia in one (2%) patient. No patients experienced the hand-foot syndrome. Overall, anorexia was reported in 36% of all patients, nausea/vomiting in 36%, diarrhea in 19% and alopecia in 23%.

## Discussion

The present study has established the safety and effective regimen of combining irinotecan and UFT as first-line treatment for advanced or metastatic colorectal cancer

when irinotecan is administered on days 1 and 16 in combination with UFT on days 2-15 every 28 days. DLTs consisted of grade 4 neutropenia and prolongation of leucopenia. The phase 1 trial of this study determined the recommended dose of irinotecan to be 120 mg/m<sup>2</sup>/day in combination with oral UFT 400 mg/m<sup>2</sup>/day. Alonso *et al.* (13) demonstrated that recommended doses of this combination were irinotecan 110 mg/m<sup>2</sup> on days 1, 8 and 15, and UFT 250 mg/m<sup>2</sup> on days 1-21 every 28 days or irinotecan 100 mg/m<sup>2</sup> and UFT 300 mg/m<sup>2</sup>. The total dose of UFT per course is similar to that reached in the current study although the administration schedule and dose of irinotecan is different. Kono *et al.* (14) administered UFT 400 mg/m<sup>2</sup>/day on days 1-14 but reduced the recommended level of irinotecan 100 mg/m<sup>2</sup>/day to 30 mg/m<sup>2</sup>/day for outpatient control of grade 3/4 fatigue. In the present trial, all the patients were admitted to receive the first administration of irinotecan for observation of safety. Thereafter, patients were treated in an outpatient setting or on admission according to the adverse events during the first or subsequent cycles. Patients receiving two cycles of the treatment well tolerated the outpatient administration. The current phase II trial revealed a response rate of 24.5%. This response rate is superior to the 11.7% response rate of an oral UFT/LV regimen (6) and irinotecan plus UFT/LV regimens (15, 16). Other phase II regimens of irinotecan plus UFT revealed a slightly higher response rate of 33.4% and 34.5% over our regimen (17, 18). The regimens of FOLFIRI with infusion of high dose 5-FU for 1 or 2 days obtained 49% and 56% response rates (19, 20). Addition of 5-FU infusion regimens such as FOLFOX 6 and FOLFIRI or administration of oral UFT from day 1 may be needed to improve the response rate.

The mean overall survival time achieved in the present trial was 20.3 months, which was similar to the data of FOLFOX 6 or FOLFIRI (20). Other regimens using irinotecan plus UFT with LV or without LV offered a slightly shorter survival time of 16 to 18 months (15-18). The present study suggested that overall survival was compatible to the combination of infusional 5-FU/LV and irinotecan although a higher dose of UFT was needed. In patients with stable disease, patients receiving more than 4 courses achieved prolongation of survival time. This regimen may contribute to retaining a state of tumor dormancy.

The current regimen offered lower toxicity. The phase I trial of this combination has established the recommended dose in consideration of DLTs such as grade 4 neutropenia and prolongation of leucocytopenia. Grade 3/4 toxicity of leucopenia and neutropenia was observed in 11% of the total patients, which is consistent with previous reports (16, 18). A high dose of irinotecan may easily generate leucopenia and neutropenia (15, 19, 20). The incidence of

grade 3 non-hematological adverse events was 11%. Life threatening neutropenia and the hand-foot syndrome were not experienced. These findings resulted from a higher dose of UFT and lower dose of irinotecan than other previous reports and proved the safety of this regimen.

## Conclusion

Our findings suggest that the current combination of irinotecan and UFT, even without LV, is as effective as FOLFIRI and FOLFOX 6 with regard to survival, and is well-tolerated with lower incidences of hematological and non-hematological adverse events. This regimen may be used as a first-line therapy for advanced or metastatic colorectal cancer in the outpatient setting and may prolong survival, even for patients with stable disease.

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