Efficacy of UFT Plus Oral Leucovorin in Advanced Colorectal Cancer : A Multicenter Study

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Abstract

Purpose : To evaluate the efficacy and toxicity of UFT plus oral leucovorin in advanced colorectal cancer.

Material and Method : Twenty cases of advanced colorectal cancer were entered into the study. All patients must have histologic proof and have measurable disease. Prior to the treatment all patients should have normal baseline hematology and normal liver and renal function, ECOG Performance status ≤ 2 and age 18-75 years. Chemotherapeutic drugs consisted of UFT 350 mg/m^2/day divided into 3 doses (8 hours apart) plus oral leucovorin 15 mg every 8 hours. Duration of treatment was 21 days per each cycle. Treatment was recycled every 28 days.

Results : Four cases (22.2%) had partial responses and six cases (33.3%) had stable disease. Duration of response was 4$^+$-7$^+$ months. Toxicity was darkened skin, mild diarrhea and mild alopecia.

Conclusion : UFT plus oral leucovorin was one of the active regimens in the treatment of advanced colorectal cancer.

Key word : Advanced Colorectal Cancer, UFT, Oral Leucovorin

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Tegafur and uracil (UFT) is composed of a 1:4 fixed molar ratio of Ftorafur (tegafur) and uracil. Tegafur is a fluorouracil (5-FU) prodrug, and uracil competes with 5-FU as a substrate for dihydropyrimidine dehydrogenase, an enzyme responsible for 5-FU catabolism. UFT may be administered orally with excellent gastrointestinal absorption, and therefore is potentially attractive as

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an alternative to 5-FU. When UFT was administered orally with the biochemical modulator leucovorin in a 28-consecutive-day schedule, response rates of 25 per cent to 43 per cent were observed in patients with previously untreated advanced colorectal cancer[1,2].

Patients with colorectal cancer who fail initial 5-FU-based therapy have limited therapeutic options. The camptothecin derivative irinotecan has shown a response rate of 15 per cent to 25 per cent in this setting[3-5]. A protracted venous infusion of 5-FU has also been reported to overcome resistance in a small subset of patients previously treated with bolus 5-FU[6,7]. Given the potential of daily oral UFT/leucovorin to mimic the pharmacology of a protracted venous infusion of 5-FU, we undertook a phase II trial of this therapy in patients with advanced colorectal cancer who had not received chemotherapy or had failed bolus 5-FU therapy.

PATIENTS AND METHOD

Patients eligible for this trial had histologically confirmed unresectable colorectal adenocarcinoma that was either metastatic or locally advanced and bidimensionally measurable. Patients must be at least 18 years old, with Eastern Cooperative Oncology Group performance status 0 to 2 and a life expectancy of at least 12 weeks. Patients who failed previous therapy with intravenous 5-FU plus lecovorin or interferon were eligible for the study. Study participation also required an absolute neutrophil count $\geq$ 1,500/μL, platelet count $\geq$ 100,000/μL, bilirubin $\leq$ 1.5 mg/dL.

Treatment Program

Patients were treated with UFT 350 mg/m^2/day plus leucovorin 45 mg/day in 3 divided doses every 8 hours for 21 consecutive days, followed by a 1-week rest period (1 cycle = 28 days). UFT was prepared as 100 mg capsule. If the number of daily capsules could not be evenly divided among the three daily administration times, the greater number of capsules were taken in the morning and afternoon, and the least number in the evening. One 15-mg oral leucovorin tablet was taken with each UFT dose.

Disease evaluations were repeated every two cycles and treatment was continued until disease progression was documented or it was no longer in the patient's best interests to continue.

RESULTS

Twenty cases of advanced colorectal cancer were entered to the study. Two cases were inevaluable due to protocol violation (Table 1). Of seven cases who had failed prior chemotherapy, four cases had received only one chemotherapeutic regimen, and three cases had received two or three chemotherapeutic regimens (Table 2). Duration from last chemotherapeutic treatment to this study was 2 to 7 months.

From 18 evaluable cases, four cases achieved partial response (22.2%), six cases achieved minor response plus stable disease (Table 3). Of note, two partial responders were previously treated with chemotherapy. Duration of partial response was 4^+ to 7^+ months.

Table 1. Patient's characteristics.

No of treatment	20	cases
No of evaluable	18	cases
Median age	63	yrs.
Range	29-70	yrs.
Sex M:F	13:7	
Site of diseases*		
Liver	9	cases
Lung	5	cases
L.N.	4	cases
Local tumor primary site	3	cases
Bone	1	cases
Prior chemotherapy	7	cases

*some patients had more than one site of disease
LN = Lymph Nodes

Table 2. Characteristics of patients with previous chemotherapy.

Previous chemotherapy		Time since last chemo.
Case 1	ldlv, fu, ifn	4 months.
Case 2	ldlv, fu, ifn	2 months.
Case 3	fu, leva	
	fu, ldlv	2 months.
Case 4	fu	
	fu, ldlv	2 months.
Case 5	fu, ldlv	not available
Case 6	fu, ifn	
	CDDP, fu, hai	
	Fu, ldlv	7 months.
Case 7	fu, ldlv	4 months.

Fu = 5-fluorouracil, ldlv = low dose leucovorin, ifn = interferon, CDDP = cis-platinum, hai = hepatic arterial infusion.

Table 3. Treatment outcomes (18 cases).

	Cases	(%)	Duration(mos)
Partial response (PR)	4	(22.2)	4+-7+
Minor response (MR)	4	(22.2)	5-7+
Stable disease (SD)	2	(11.1)	4+-9
Progression of disease (PD)	8	(44.4)	-

Toxicity : Darkened skin and nails were seen in all cases. Grade 2-3 alopecia was seen in all cases. Two-thirds of the patients had mild nausea and/or vomiting. A few patients had mild to moderate diarrhea, which recovered within four days after stopping UFT. There was no hematologic toxicity, except anemia grade 1-2.

DISCUSSION

Phase II studies have shown that oral UFT/leucovorin is an active and well-tolerated regimen in patients with previously untreated colorectal cancer[1,2]. There is a paucity of effective second-line therapies for the treatment of advanced colorectal cancer. It has been reported that some patients who fail bolus 5-FU therapy respond to continuous 5-FU infusions. A prior pharmacokinetic analysis has suggested that 5-FU plasma levels with oral UFT/leucovorin are similar to those obtained with protracted venous infusions of 5-FU[7].

Therefore, we undertook the current study to determine the response rates and toxicity of daily oral UFT/leucovorin in advanced colorectal cancer patients. The regimen of UFT plus oral leucovorin in our study is unique in that it provides protracted delivery of 5-FU with continuous dosing of leucovorin over a 21 day period. Our results suggest that an effective oral chemotherapy regimen (UFT plus leucovorin) for patients with metastatic colorectal carcinoma is well tolerated. Response rates were somewhat lower than those achieved with intravenous schedules of 5-FU plus leucovorin. The response rate of 22.2 per cent and 33.3 per cent with stable disease reported in this study was lower than the response rates reported by the North Central Cancer Treatment Group (NCCTG) using an intensive course 5-FU regimen with low-dose leucovorin (42%), the weekly high-dose leucovorin regimen studied by the Gastrointestinal Tumor Study Group (30.3%), and a protracted-infusion schedule of 5-FU plus weekly intravenous leucovorin recently reported by the Southwest Oncology Group (26%)[8-10]. Median durations of response was 4+-7+ months and our patients had minimal toxic reactions and disruption in their daily living offered by a completely oral regimen.

The serious toxic effects, including neutropenia and severe oral mucositis, often associated with these intravenous regimens[8,11] were not observed with the oral regimen reported here. Intravenous regimens have resulted in toxicity-related hospitalization rates of 20 per cent to 30 per cent[11]. We did not observe either acral erythema (described in patients who received protracted 5-FU infusions) or neurotoxicity (described in studies of intravenous tegafur).

Oral treatment regimens for colorectal cancer have been explored by several investigators. Use of tegafur alone at a dose for 1000 mg/m^2/day for 14 consecutive days yielded a 17 per cent major response rate in 18 patients with colorectal cancer. Neurologic toxicity (dizziness, headache, insomnia, lethargy) that was not dose limiting was experienced by 25 per cent of these patients[11]. The neurologic toxicties of tegafur are thought to be attributable in part to the formation of butyrolactone, a metabolite produced during the activation of tegafur[12]. By potentiating the 5-FU derived from tegafur, uracil permits a lower total dose of tegafur to be used. This most likely accounts for the absence of neurologic toxicity encountered with UFT.

Other investigators have reported in abstract form their evaluations of UFT in colorectal cancer on different treatment schedules. In these preliminary reports, UFT with higher doses of leucovorin (leucovorin 50 mg orally every 8 hours with UFT for 28 days)[13] and UFT with oral and parenteral leucovorin (leucovorin 500 mg intravenously on day 1 then 15 mg orally every 12 hours on days 2-14 with UFT given days 1-14)[8] also have demonstrated activity in patients with colorectal cancer. In the absence of direct randomized comparisons of these regimens against each other and against the one we report here it is impossible to determine the superiority of one regimen over another.

SUMMARY

Oral UFT and leucovorin regimen is convenient for patients with minimal toxic reaction though the major response rate was only 22 per cent. The median duration of response is comparable to other studies.

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ประสิทธิภาพของยูเอฟทีและลิวโควอรินชนิดรับประทานในการรักษามะเร็งลำไส้ใหญ่ระยะแพร่กระจาย

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ผู้ป่วยมะเร็งลำไส้ใหญ่ระยะแพร่กระจายจำนวน 20 ราย ซึ่งก่อนรักษาได้พิสูจน์แล้วว่าเป็นมะเร็งลำไส้ใหญ่และมีรอยโรคซึ่งสามารถวัดผลได้ ผู้ป่วยจะได้รับยาเคมีบำบัด UFT ขนาด 350 มิลลิกรัมต่อตารางเมตรต่อวันแบ่งให้ผู้ป่วยรับประทานวันละ 3 เวลา (ห่างกัน 8 ชั่วโมง) และยา calcium leucovorin ขนาด 15 มิลลิกรัม รับประทานวันละ 3 เวลา (ห่างกัน 8 ชั่วโมง) ให้ผู้ป่วยรับประทานติดต่อกัน 21 วัน โดยจะซ้ำยาชุดต่อไปเมื่อครบ 28 วัน ผลการรักษาพบว่าผู้ป่วย 4 ราย (22%) ตอบสนองต่อการรักษาแบบชั่วคราว (partial response) ผู้ป่วย 6 ราย (33.3%) โรคไม่เปลี่ยนแปลง ระยะเวลาตอบสนองเท่ากับ 4^{+}–7^{+} เดือน ผลข้างเคียงคือ ผิวสีคล้ำ ท้องเดินและผมร่วง ผลการรักษานี้พบว่ายา UFT กับ leucovorin เป็นยาที่มีประสิทธิภาพพอควรในการรักษามะเร็งลำไส้ใหญ่

คำสำคัญ : มะเร็งลำไส้ใหญ่ระยะแพร่กระจาย, ยายูเอฟที, ยาลิวโควอรินชนิดรับประทาน

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