Uracil with Ftorafur and Low Dose Oral Folinic Acid in Advanced Colorectal Cancer†

SURACHAT CHAKRAPEE-SIRISUK, M.D.*,
PAIROJ SINLARAT, M.D.*,
DARIN LOHSIRIWAT, M.D.**,
NARONG LERT-AKAYAMANEE, M.D.**,
THANYADEJ NIMMANWUDIPONG, M.D.**
VICHIEN SRIMUNINNIMIT, M.D.*,
VITHYA VATHANOPHAS, M.D.**,
PAIROACH ARCH-YAEMSUAN, M.D.**,
WIROON BOONNUCH, M.D.**,

Abstract

Background : Low dose oral Folinic acid was used together with uracil with ftorafur (UFT) producing some response with low toxicity in advanced colorectal cancer. However, the 28 day regimen produced 20 per cent severe (grade III, IV) diarrhea. This study required 21 days' treatment to evaluate the response rate and toxicity in advanced colorectal cancer.

Method : UFT 300 mg/m^2/day together with oral Folinic acid 7.5 mg/dose for 21 days with 7 days rest were required to treat 28 cases of recurrent or metastatic colorectal cancer.

Results : Partial response was seen in 13.6 per cent of 22 evaluable cases and minimal response seen in 18.2 per cent. The majority (77%) of these patients had previously been treated with 5-fluorouracil (5-FU). These results are comparable to other studies. Toxicity was low with 3.3 per cent grade III, IV diarrhea.

Conclusion : This regimen produced some activity in metastatic colorectal cancer with low toxicity.

Key word : UFT, Folinic Acid, Colorectal Cancer

CHAKRAPEE-SIRISUK S, SRIMUNINNIMIT V, SINLARAT P, et al
J Med Assoc Thai 2001; 84: 1142-1147

* Division of Medical Oncology, Department of Medicine,
** Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.
† Oral presentation at Bristol-Meyer Investigator Meeting. February 29, 2000, Peninsula Hotel, Bangkok, Thailand.

Colorectal cancer is one of the leading cancer in Thailand. In 1990, it was the third most common cancer in males (the annual average age standardized incidence rate was 8.9 per 100,000 population) and the fifth most common cancer in females (the annual average age standardized incidence rate was 5.9 per 100,000 population), with an estimated total of more than 3,054 new colorectal cancer patients in that year[1].

5-Fluorouracil (5-FU) and Folinic acid (FA) (Leucovorin, Citrovorum factor, 5-formyl-5, 6, 7, 8-tetrahydrofolic acid), are the standard drugs for advanced colorectal cancer.

Folinic acid modulates 5-FU by stabilization of the binding of FdUMP to thymidylate synthase. Randomized trials have demonstrated the advantage of FA + 5-FU over 5-FU alone[2]. Although the optimal dose, schedule and route of administration of FA remain unknown. Several clinical studies have suggested that a lower dose of FA offer efficacy comparable to a higher dose with lower cost and toxicity[3,4] and have shown that the oral administration of FA yields similar results to those obtained intravenously[5,6].

Some studies have shown that levels of FA obtained either by continuous IV infusion or per oral (PO) are comparable. Oral administration also produces a lower level of d-isomer[7]. This d-isomers may possibly compete with the cellular uptake of l-isomer, resulting in reduced efficacy of the modulation. Because the oral administration favors the selective absorption of l-isomer over d-isomer in a ratio of 5:1[8], oral administration may be more beneficial.

5-FU and FA have produced response rate in the range of 9.3 per cent-43 per cent[3,4,9]. Conventional regimens require intravenous injection weekly or 5-consecutive days per month, with significant toxicity including neutropenia, mucositis, diarrhea, dark vein, etc. Several investigators have suggested that prolonged low dose infusion of 5-FU may be superior to a shorter high dose exposure[10,11].

Tegafur (Ftorafur, Futraful, 1-(2 tetrahydrofuryl)-5- fluorouracil) is a pro-drug that is absorbed orally and metabolized *in vivo* to 5-fluorouracil (5-FU) with lower myelotoxicity, higher bio-availability than 5-FU tablet and prolonged half life (6-16 hours)[12]. Uracil increases intratumoral concentration and enhances antineoplastic action of 5-FU by inhibition of the catabolism of 5-FU[13,14]. UFT is an oral drug combination of Tegafur and Uracil in a molar ratio of 1:4. UFT increases the intratumoral concentration of 5-FU and enhances its antineoplastic action with a long half-life. UFT together with oral Folinic acid is an attractive alternative against intravenous 5-FU and Folinic acid.

In advanced colorectal cancer, phase I and phase II[15,16] studies of UFT plus Folinic acid using 500 mg/m^2 of FA (IV) for 2 hours on day 1, followed by oral UFT twice a day for 14 days. On day 2, the patients took oral FA, 15 mg/12h for 13 days repeated every 28 days for a minimum of 3 courses per patient. The maximum tolerated dose of UFT was established at 390 mg/m^2, producing an overall response of 39 per cent, and 9 per cent grade III, IV diarrhea.

Clinical studies using oral Folinic acid as low as 5 mg orally every 8 hours to modulate prolonged low dose 5-FU infusions have demonstrated marked biologic activity in terms of increased toxicity[17].

Saltz et al from the Memorial Sloan-Kettering Cancer Center[18], using UFT 350 mg/m^2/day divided every 8 hours and 5 mg tablet of Folinic acid every 8 hours concurrently for 28 consecutive days followed by a 7-day rest, suggested that UFT and low dose oral Folinic acid was well tolerated, with efficacy comparable to standard parenteral regimens. In addition, the cost of administration of an oral regimen would be expected to be lower than the more labor-intensive and equipment-intensive parenteral treatments, both in terms of direct costs of treatment administration and the indirect costs of lost work days of patients and families because of treatment visits. Oral administration is easier to use, so that the patient's quality of life can be improved. However, his 28 days regimen produced 20 per cent severe (grade III, IV) diarrhea.

Our study consisted of 21 days treatment to evaluate response rate and toxicity in advanced colorectal cancer.

Objective

This study aimed to evaluate response rate, response duration and toxicity of UFT plus oral Folinic acid in recurrent or metastatic colorectal cancer.

Eligibility

Patients had to have histologically documented colorectal cancer with recurrent or metastatic measurable lesion(s). Baseline blood tests had to

have a leukocyte count greater than $3x10^9$/L, platelets count greater than $100x10^9$/L, serum total bilirubin less than 5.0 mg/dl and serum creatinine less than 2.0 mg/dl. Age more than 14 years and performance status 0-3 ECOG criteria were required. Either untreated or previously treated patients, whether it was chemotherapy or radiation therapy or both, were included. The last treatment had to have stopped more than one month and had measurable lesion(s) outside the radiation field if previously radiated. Ethical committee approved and informed consent was obtained.

METHOD

Baseline evaluations included history taking, physical examination, body weight, performance status, blood chemistries: CBC, LFT, BUN, creatinine and CEA were completed. Appropriate radiological examinations: chest X-ray, computer tomography of upper abdomen (and/or ultrasonogram of upper abdomen if CT was not applicable), were obtained within 4 weeks of study entry.

Therapy was on an outpatient basis and consisted of: Folinic acid 7.5 mg (= half tablet of 15 mg) orally tid ac together with UFT 300 mg/m^2/day orally, rounded to the nearest 100 mg divided doses tid ac (UFT supplied in 100 mg capsules). If the three were not equal, the largest doses were taken earlier in the day (e.g. before breakfast, before lunch) on an empty stomach. Both Folinic acid and UFT were taken for 21 days with 7 days rest. Each patient was checked for drugs taken and drugs left on each treatment cycle. In patients experiencing dose limiting toxicity (grade III, IV), treatment was held until all toxicity had fully recovered, then restarted if clinically appropriate, with a reduction in the dose of UFT of 50 mg/m^2/day.

Before each cycle, history taking, physical examination, measurement of physically measurable lesion(s), body weight, and performance status were done. CBC was checked every two weeks; bilirubin, SGOT, SGPT, Alk. Phos., CEA every month; and radiographic evaluation using CXR, CT scan (or ultrasonography) every two months.

Standard response criteria were used. Evaluation of response was done when at least 2 cycles of drugs had been taken. Patients with response continued the treatment until documented progression of disease, clinical deterioration, or unacceptable toxicity developed. Toxicity was graded and reported according to the National Cancer Institute common toxicity criteria. Patients were followed until progression of the disease.

Patients characteristics

From October 1996 to July 1998, twenty-eight patients were enrolled. Thirteen were male and 15 were female. Age ranged from 33 to 78, with a mean age of 58 years. Nineteen patients (67.9%) had ECOG performance status 1, 7 cases had performance status 0 and 2 cases had performance status 2.

Twenty cases had colon primary and 8 had rectal primary. Pathologic reports showed 75.0 per cent were moderately differentiated adenocarcinoma, 14.3 per cent were well differentiated, 3.6 per cent were poorly differentiated, differentiation was not known in 7.1 per cent.

Seven cases had prior adjuvant 5-FU and Levamisole, 10 had prior adjuvant 5-FU & Folinic acid, and 6 had prior 5-FU when they were radiated for their rectal primary cancer.

Six patients received less than two cycles of treatment and were not evaluable for response. Two were lost to follow-up after the first cycle. Disease progressed with spinal metastases requiring radiation therapy after one course of treatment in 1 case, 3 patients did not want to continue the drugs: two of them had partial gut obstruction and another one experienced diarrhea grade IV after the first cycle.

Computerized tomography was used to evaluate lesions in 81.5 per cent of all events. Compliance to administered drug schedule was good with only 1 course delayed due to compliance.

RESULTS

For the 22 cases that were evaluable for response, 3 cases (13.6%) had partial response, 4 cases (18.2%) had minimal response, 4 cases (18.2%) had stable disease and 11 cases (50.0%) had disease progression. The overall objective response (partial and minimal response) was 31.8 per cent. The best response was achieved after 2 cycles in 10 cases and after 4 cycles in 1 case. Duration of response ranged from 49 days to 16.8 months (mean 3.65 months $\pm$ 3.26 SD). For 5 patients who were chemonaive, 2 (40%) had minimal response and 2 (40%) had stable disease.

For 17 cases who had prior 5-FU, 3 (17.6%) had partial response, 2 (11.8%) had minimal response and 2 (11.8%) had stable disease. When considering

those who should be classified as 5-FU resistant (recurrence within 6 months after adjuvant 5-FU or progress within 2 months in chemo-naive) 1 PR, 1 MR, 1 SD were found in 9 patients of whom 3 were not evaluable for response.

In one particular case with lung and liver metastases, response was nearly complete with normalization of CEA. He received a total of 12 courses and his disease stabilized for almost 7 months after treatment was stopped.

Toxicity

Altogether, 92 out of 94 courses were evaluable for toxicity. Diarrhea grade I was found in 13.0 per cent, grade II in 7.6 per cent and grade III, IV in 3.3 per cent. Nausea-vomiting grade I occurred in 30.4 per cent, grade II 2.2 per cent and grade III, IV 1.1 per cent. However, these grade III & IV patients had partial gut obstruction at the onset of treatment. We did not see any grade 3, 4 diarrhea or vomiting after excluding partial gut obstruction from enrollment. Oral antiemetics were used in 37 per cent of cycles and 5HT3-receptor antagonist was never used.

Mucositis grade I was found in 3.3 per cent, grade II in 6.5 per cent and no grade III, IV mucositis. Hematological toxicity was almost negligible, with only 2.2 per cent of grade II neutropenia and 1.1 per cent of grade I thrombocytopenia and no grade III, IV hematological toxicity. Alopecia grade 1 was found in 5.4 per cent and no grade II alopecia. No patient experienced hand-foot syndrome. In the particular case with 12 courses of treatment, toxicity did not increase with time and the patient tolerated the treatment very well.

DISCUSSION

Although the US recommended UFT 300 mg/m^2/day with oral leucovorin 25-30 mg every 8 hours for 28 days followed by 7 days rest, the optimal dose and schedule for UFT and FA remain unknown. Studies using UFT ranged from 300-400 mg/m^2/day administered daily with Folinic acid ranged from 15-150 mg/day for 14-28 days have been reported[19]. Direct comparison of UFT alone *versus* UFT with low dose or high dose Folinic acid has not been clinically performed[20].

In the University of Southern California Medical Center and Memorial Sloan-Kettering Cancer Center study[18], 5 major objective responses (25%: 1 complete and 4 partial) were observed in 20 evaluable patients. No major response was seen in patients who had prior adjuvant therapy with 5-FU.

In the Pazdur et al multicenter phase III study[21], the overall response rate was 12 per cent with UFT 300 mg/m^2/day and FA 75-90 mg/day for 28 days every 35 days. In the Carmichael et al randomized study[22], using UFT 300 mg/m^2/day and FA 90 mg/day for 28 days every 35 days, the overall response rate was 11 per cent, the median time to progression was 3.4 months.

In the present study, with 21 instead of 28 days regimen, the major response rate (partial response) was 13.6 per cent. Objective responses (partial response and minimal response) were observed in 31.8 per cent. Duration of response ranged from 49 days to 16.8 months (mean 3.65 months $\pm$ 3.26 SD).

However, in Saltz's study, most of the patients (16/21, 76%) were chemo-naïve, no major response was seen in patients who had prior adjuvant therapy with 5-FU. In the present study, most of the patients (17/22) had prior 5-FU treatment. In this prior treated group, 3 (17.6%) major (partial) response and 29.4 per cent objective responses (3 partial response and 2 minimal response) were observed.

In Saltz's study, diarrhea was found to be the dose limiting toxicity with 3 patients having grade III diarrhea, and 1 patient with grade IV diarrhea (20% grade III, IV). Two patients (10%) experienced dose-limiting mucositis and no dose-limiting myelosuppression. In Pazdur et al[21], and Carmichael et al[22] studies, grade III, IV diarrhea were found in 21 per cent and 18 per cent; grade III, IV nausea/vomiting in 13 per cent and 9 per cent; grade III, IV mucositis in 1 per cent and 2 per cent, respectively.

The present study resulted in less toxicity and there was less grade III, IV diarrhea (3.3%), nausea-vomiting grade III, IV in only 1.1 per cent, no dose-limiting mucositis and no dose-limiting myelosuppression. This difference, may be due to the schedule, ethnic difference, or uracil's saturation of hepatic dihydropyrimidine dehydrogenase (the rate limiting enzyme in 5-FU catabolism)[23] and is worthy of further investigation.

In conclusion, this was a very well tolerated regimen. It produced some response, even after prior bolus 5-FU, with minimal toxicity.

ACKNOWLEDGEMENT

The authors wish to thank Taiho Pharmaceutical Co., Tokyo, Japan for partially supporting the drug UFT. We also wish to thank Ms. Jarunee Janjaruporn R.N., and Ms. Sunee Thanakhumtorn R.N. for their very helpful data management.

(Received for publication on October 4, 2000)

REFERENCES

1. Vatanasapt V, Martin N, Sriplung H, et al. Cancer in Thailand 1988-1991. IARC Technical Report. Lyon, France, 1993; 16: 59-64.
2. Arbuck SBG. Overview of clinical trials using 5-fluorouracil and leucovorin for the treatment of colorectal cancer. Cancer 1989; 63: 1036-44.
3. Poon MA, O'Connell MJ, Wieand HS, et al. Biochemical modulation of fluorouracil with leucovorin: Confirmatory evidence of improved therapeutic efficacy in advanced colorectal cancer. J Clin Oncol 1991; 9: 1967-72.
4. Buroker TR, O' Connell MJ, Wieand HS, et al. Randomized comparison of two schedules of fluorouracil and leucovorin in the treatment of advanced colorectal cancer. J Clin Oncol 1994; 12: 14-20.
5. Brenckman WD, Laufman LR, Morgan ED, et al. Pilot trial of 5-FU with high doses oral leucovorin tablets in advanced colorectal carcinoma. Proc Am Soc Clin Oncol 1988; 7: A376.
6. Hines JD, Aldelstein DJ, Spies JL, Giroski P, Carter SG. Efficacy of high-dose oral leucovorin and 5-fluorouracil in advanced colorectal carcinoma. Plasma and tissue pharmacokinetics. Cancer 1989; 63: 1022-5.
7. Schilsky RL, Choi KE, Vokes EE, et al. Clinical pharmacology of the stereo-isomers of leucovorin during repeated oral dosing. Cancer 1989; 63: 1018-21.
8. Straw J, Szapary D, Wynn WT. Pharmacokinetics of the diasteroisomers of leucovorin after intravenous and oral administration to normal subjects. Cancer Res 1984; 44: 3114-9.
9. Labianca R, Pessi MA, Pancera G, Luporini G. Modulation of 5-fluorouracil with folinic acid: High or low dose? In: Bleiberg H, Rougier P, Wilke HJ. Management of colorectal cancer. London: Martin Dunitz Ltd, 1998: 239-48.
10 Lokich JJ, Ahlgren JD, Gullo JJ, Philips JA, Frver JG. A prospective randomized comparison of continuous infusion fluorouracil with conventional bolus schedule in metastatic colorectal cancer: a Mid-Atlantic Oncology Program study. J Clin Oncol 1989; 7: 425-32.
11. Leichman CG, Lickman L, Spears CP, Rosen PJ, Jeffers S, Groshen S. Prolonged continuous infusion of fluorouracil with weekly bolus leucovorin: A phase II study in patients with disseminated colorectal cancer. J Natl Cancer Inst 1993; 85: 41-4.
12. Malik STA, Talbot D, Clarke P, et al. Phase II trial of UFT in advanced colorectal and gastric cancer. Br J Cancer 1990; 62: 1023-5.
13. Fujii S, Ikenaka K, Fukushima M, Shirasak T. Effect of Uracil and its derivatives on antitumor activity of clinical doses of 1-(2-tetrahydrofurly)-5 fluorouracil, Gann 1978; 69: 763-72.
14. Fujii S, Kitano S, Ikenaka K, Shirasak T. Effect of co-administration of uracil or cytosine on the antitumor activity of clinical doses of 1-(2-tetrahydrofuryl)-5-fluorouracil and level of 5-fluorouracil in rodents. Gann 1979; 70: 209-14.
15. Gonzalezbaron M, Feliu J, Ordonez A, et al. Phase I study of UFT plus leucovorin in advanced colorectal cancer: A double modulation proposal. Anticancer Research 1993; 13: 759-62.
16. Gonzalez-Baron M, Feliu J, De la Gandara I, et al. Efficacy of oral Tegafur modulation by uracil and leucovorin in advanced colorectal cancer: A phase II study. Eur J Cancer 1995; 31A: 2215-9.
17. Hansen R, Beatty P, Quebbeman E, Anderson T. Continuous 5-fluorouracil infusion and oral calcium leucovorin: A phase I trial. Proc Am Soc Clin Oncol 1991; 10: 157.
18. Saltz LB, Leichman CG, Young CW, et al. A fixed-ratio combination of uracil and ftorafur (UFT) with low dose leucovorin. An active oral regimen for advanced colorectal cancer. Cancer 1995; 75: 782-5.
19. Hoff PM, Pazdur R, Benner SE, Canetta R. UFT and leucovorin: a review of its clinical development and therapeutic potential in the oral treatment of cancer. Anti-Cancer Drugs 1998; 9: 479-90.
20. Sulkes AA, Benner SE, Canetta RM. Uracil-Ftorafur: an oral fluoropyrimidine active in colorectal cancer. Review article. J Clin Oncol 1998; 16: 3461-75.
21. Pazdur R, Douillard JY, Skillings JR, et al. Multi-

center phase III study of 5-fluorouracil (5-FU) or UFT in combination with leucovorin (LV) in patients with metastatic colorectal cancer. Proc Am Soc Clin Oncol 1999; 18: 263a.
22. Carmichael J, Popiela T, Radstone D, et al. Randomized comparative study of Orzel (oral Uracil/Tegafur (UFT) plus leucovorin (LV)) *versus* parenteral 5-fluorouracil (5-FU) plus LV in patients with metastatic colorectal cancer. Proc Am Soc Clin Oncol 1999; 18: 264a.
23. Keyomarsi K, Moran RG. Folinic acid augmentation of the effects of fluoropyrimidines on murine and human leukemic cells. Cancer Res 1986; 46: 5229-35.

ยูราซิล และโตราเฟอร์ ใช้ร่วมกับโฟลินิกแอซิดขนาดต่ำ ในมะเร็งลำไส้ใหญ่ระยะท้าย

สุรชาติ จักรภีร์ศิริสุข, พ.บ., วิเชียร ศรีมุนินทร์นิมิต, พ.บ.*, ไพโรจน์ สินลารัตน์, พ.บ.*, วิทยา วัฒโนภาส, พ.บ.**, ดรินทร์ โล่ห์สิริวัฒน์, พ.บ.**, ไพโรจน์ อาจแย้มสรวล, พ.บ.**, ณรงค์ เลิศอรรฆยมณี, พ.บ.**, วิรุณ บุญนุช, พ.บ.**, ธัญเดช นิมมานวุฒิพงษ์, พ.บ.***

ยูราซิล และโตราเฟอร์ (ยูเอฟที) เมื่อใช้ร่วมกับโฟลินิกแอซิดขนาดต่ำ ในการรักษามะเร็งลำไส้ใหญ่ระยะท้าย มีรายงานว่าได้ผล โดยมีผลข้างเคียงไม่มาก ยกเว้นมีอุจจาระร่วงรุนแรง (ระดับ 3, 4) ถึง 20% ในการศึกษานี้ ได้ใช้ยูเอฟที 300 มิลลิกรัมต่อตารางเมตรของพื้นผิวร่างกายต่อวัน แบ่งเป็น 3 เวลา รับประทานก่อนอาหาร ร่วมกับโฟลินิกแอซิด 7.5 มิลลิกรัม (โฟลินิกแอซิด 15 มิลลิกรัม ครึ่งเม็ด) ต่อครั้ง ติดต่อกัน 21 วัน เว้น 7 วัน พบว่า จากผู้ป่วย 22 รายที่สามารถประเมินผลการตอบสนองได้ 13.6% มีการตอบสนองต่อการรักษาบางส่วน (Partial Response), 18.2% ตอบสนองในระดับน้อย (minimal response) โดยที่ส่วนใหญ่ของผู้ป่วย (77%) เคยได้รับการรักษาด้วย 5-FU มาแล้ว ซึ่งได้ผลใกล้เคียงกับการศึกษาอื่น ๆ ส่วนผลข้างเคียงประเมินจากการใช้ยา 92 ชุด พบว่ามีอุจจาระร่วงรุนแรง (ระดับ 3, 4) 3.3%, คลื่นไส้อาเจียนรุนแรง (ระดับ 3, 4) 1.1% เกิดขึ้นในผู้ป่วยที่มีการตีบของลำไส้บางส่วนอยู่เดิม นอกนั้นไม่พบผลข้างเคียงที่รุนแรง

สรุป การใช้ยาตำรับนี้รักษามะเร็งลำไส้ใหญ่ระยะท้าย พบว่าได้ผลบ้าง โดยมีผลข้างเคียงน้อยมาก

คำสำคัญ : ยูเอฟที, โฟลินิกแอซิด, มะเร็งลำไส้ใหญ่

สุรชาติ จักรภีร์ศิริสุข, วิเชียร ศรีมุนินทร์นิมิต, ไพโรจน์ สินลารัตน์, และคณะ
จดหมายเหตุทางแพทย์ ฯ 2544; 84: 1142-1147

* สาขาวิชาเคมีบำบัด, ภาควิชาอายุรศาสตร์,
** ภาควิชาศัลยศาสตร์, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10700