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Oral Tegafur-uracil Plus Folinic Acid versus Intravenous 5-fluorouracil Plus Folinic Acid as Adjuvant Chemotherapy of Colon Cancer

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To compare, in terms of compliance, toxicity, quality of life (QOL) and efficacy, intravenous 5-fluorouracil plus folinic acid with oral tegafur-uracil plus folinic acid as postoperative adjuvant chemotherapy after curative resection in patients with Dukes' stage B2 and C2 colon cancer. Among all patients with adenocarcinoma of the colon operated on between July 1997 and June 1999, 122 with Dukes' stage B2 or C2 colon cancer were enrolled in this study. Fifty-three patients were treated with intravenous 5-fluorouracil plus folinic acid (5-FU group) and 69 with oral tegafur-uracil plus folinic acid (UFT group). Compliance, toxicity, QOL and efficacy were evaluated. Compared with the 5-FU group, patients in the UFT group experienced a lower incidence of grade 1 toxicity. The incidences of grade 2-4 toxicity were similar in the two treatment groups. However, severe toxicity (grade 3 or 4) was rare in both groups. A steady and significant increase of the QOL score, both during and after therapy, was evident in both groups suggesting that chemotherapy is quite tolerable and does not deteriorate the patients' QOL. At the median follow-up duration of 28 months, the survival rate and disease free survival rate for the UFT and 5-FU groups were 94.9% vs. 92.5% and 87.5% vs. 84.1%, respectively ($p>0.05$). These data suggest that oral tegafur-uracil modulated with oral folinic acid as an adjuvant chemotherapy in patients with Dukes' stage B2 and C2 colon cancer may be a good alternative to infusional 5- fluorouracil.

Key Words: 5-fluorouracil, tegafur-uracil, folinic acid, adjuvant chemotherapy, colon cancer

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INTRODUCTION

Colorectal cancer is frequently diagnosed at a stage when complete resection is possible. Therefore, surgery is the mainstay of treatment in Dukes' B and C colorectal cancer, but it is not curative in all patients. The risk of relapse and death is directly proportional to the depth of tumor invasion and/or the degree of regional lymph nodes metastasis. Postoperative adjuvant chemotherapy in high risk patients is therefore justified[1] and recent data demonstrated the clinical efficacy of 5-fluorouracil (5-FU), with its biochemical modulation using folinic acid (FA) or levamisole (LEV), in terms of survival prolongation.[2-9] Of these, FA modulation of 5-FU demonstrated a slightly more favorable survival benefit than LEV.[10] This advantage, in conjunction with an increased understanding of the mechanism of FA's biochemical modulation of 5-FU,[11-14] makes the regimen a logical choice for studies designed to further optimize and augment the clinical efficacy of chemotherapy for colon cancer.

Tegafur-uracil (UFT; Taiho Pharmaceuticals, Tokyo, Japan) is an oral drug formulation containing uracil and tegafur (ftorafur: 1-[2-tetrahydrofuryl]-5-fluorouracil) in a 4:1 molar ratio. Tegafur, a prodrug of 5-FU, undergoes metabolic activation by hepatic microsomal enzymes which may lead to a slow but sustained level of 5-FU mimicking protracted infusion of 5-FU. Oral coadministration of uracil with tegafur significantly increases blood and tissue 5-FU levels[15-17] by

competitive inhibition of 5-FU catabolizing dihydropyrimidine dehydrogenase.[18] Several recent studies have demonstrated the clinical efficacy of UFT in gastrointestinal, breast and lung cancer.[19-22] UFT is also effective as an adjuvant setting in non-small cell cancer of the lung after resection.[23,24] In addition, the demonstration of significant anti-tumor activity by the combination of oral UFT plus FA provides an excellent opportunity to optimize treatment with 5-FU plus FA.[25-28] The National Surgical Adjuvant Breast and Bowel Project (NSABP) has recently implemented a new clinical trial (Protocol C-06) comparing the efficacy of 5-FU plus FA with that of UFT plus FA in the treatment of patients with resected stage II or III colon cancer.[9]

Thus, development and evaluation of new treatment modalities with more effective drugs or drug combinations are needed to improve the outcome. Phase III, randomized, clinical trials have been designed primarily to answer questions of clinical efficacy. Although the primary outcome for most clinical trials is improved survival or disease free survival (DFS), recent studies have also compared the efficacy of treatments with no anticipated effects on survival but with different toxicities or rehabilitation outcomes. By identifying treatments with less morbidity, clinical trials have contributed to improving the quality of life (QOL) in cancer patients.[29] In addition, QOL assessment may contribute as an independent, potential prognostic variable for survival in cancer patients.[30-32] This would allow a more convenient and comfortable treatment strategy if the currently available positive data can be confirmed through ongoing studies.

We have developed a clinical trial comparing, in terms of compliance, toxicity, QOL and efficacy, intravenous 5-FU plus FA and oral UFT plus FA as postoperative treatments after curative resection in patients with Dukes' stage B2 and C2 colon cancer.

MATERIALS AND METHODS

Patients

Among all patients with adenocarcinoma of the colon operated on at Severance Hospital, Seoul, Korea, between July 1997 and June 1999, 122 with histologically confirmed adenocarcinoma of the colon, Dukes' stage B2 or C2, and life expectancy of more than 5 years were enrolled in this study. A colon tumor was defined as any lesion of the large bowel that did not require opening of the pelvic peritoneum to define the distal extent of the tumor or that was more than 15 cm above the anal verge on endoscopy. All patients had undergone a potentially curative resection, with neither gross nor microscopic evidence of residual disease, and were enrolled in the study no later than 21 days after the operation. Patients were ineligible if their Eastern Cooperative Oncology Group (ECOG) performance status score was greater than 2, their pretreatment leukocyte count was less than 4,000/mm^3, their platelet count was less than 100,000/mm^3, they showed evidence of abnormal renal or hepatic function (abnormal serum creatinine, alanine aminotransferase, aspartate aminotransferase, and total bilirubin), they were pregnant or lactating, or they had a concomitant or previous malignancy or a nonmalignant systemic disease precluding administration of the scheduled therapy. All patients signed written informed consent before enrollment.

Fifty-three patients received intravenous 5-FU plus FA (5-FU group) and 69 patients received oral UFT plus FA (UFT group). Initially, we tried a prospective, randomized, double blind study. However, the choice of regimen was not randomized because many of the patients wanted to make their own choice regarding therapeutic regimen.

Treatment

Patients in both groups received 12 cycles of therapy, each of 4-week duration. In the 5-FU group, 450 mg/m^2 of 5-FU and FA at a fixed dosage of 30 mg was administered as an IV bolus on days 1, 8 and 15 of the 4-week cycle followed by a rest period. In the UFT group, the 4-week cycle of therapy was defined as 21 consecutive days of treatment followed by a 7-day rest period. UFT at 300 mg/m^2/day and FA at 30 mg/day were administered alternately every 12 hours. Treatment was interrupted if the patient devel-

oped grade 3 or 4 toxicity as defined by World Health Organization (WHO) criteria[33] and reinstituted after recovery as defined by the same criteria.

Evaluation

All patients were examined clinically prior to enrollment into the study. Patients were evaluated at the beginning of every cycle for the occurrence of toxicity as graded by WHO criteria. Complete blood counts were obtained at the beginning of every cycle and carcinoembryonic antigen (CEA) levels at every 2 cycles. Radiologic evaluation of disease status was conducted at 6-month intervals. A multidimensional, QOL questionnaire (22 items) consisting of daily activity (6 items), physical function (5 items), psychological or emotional status (5 items), social status (5 items) and global assessment (1 item) measured patient QOL before adjuvant chemotherapy and every 3 months thereafter.[34]

Statistical analysis

The primary end points in this study were DFS and overall survival. For DFS, an event was defined as recurrence of colon cancer, secondary primary cancer, or death. For overall survival as the end point, death from any cause was considered an event. The overall survival and DFS curves were drawn using the Kaplan-Meier method and analyzed by the log-rank test. All data were reported as mean ± standard error of the mean. All ANOVAs, Student's t-tests, and Chi-square tests were performed by using $\alpha = 0.05$. All analyses were performed using SAS statistical software (version 6.12, SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient characteristics

Selected characteristics of the two treatment groups are presented in Table 1. The two groups were comparable in terms of age, sex, and performance status, as well as primary site, stage, size and histopathologic tumor type.

Compliance of treatment

Treatment status is displayed in Table 2. Both groups received comparable cycles of treatment. Mean numbers of therapy cycles administered in the 5-FU and UFT groups were 9.9 ± 3.6 and 10.1 ± 3.4, respectively. Thirty nine of the 53 (73.6%) in the 5-FU group and 50 out of the 69 (72.5%) in the UFT group were compliant patients; defined as subjects who received more than 80% of scheduled therapy. Fourteen (26.4%) patients in the 5-FU group and 19 (27.5%) in the UFT group discontinued the treatment. Reasons for premature termination of treatment in the 5-FU group consisted of 2 cases of toxicity, 7 of patient refusal, 3 of recurrence and 2 of difficulty in IV injection. In the UFT group, there were 4 cases of toxicity, 11 of patient refusal, 2 of recurrence, 1 of pulmonary tuberculosis and 1 of financial hardship. Of the remaining compliant patients, 8 (20.5%) patients in the 5-FU group and 16 (32.0%) in the UFT group required dose adjustment or treatment delay due to toxicities.

Toxicity

The 53 patients in the 5-FU group received 522 cycles of chemotherapy and the 69 in the UFT group received 695 cycles. The side effects associated with treatment are listed and analyzed in Tables 3 and 4. Table 3 depicts the frequency of treatment-related adverse reactions per total number of cycles at each grade. Compared with the 5-FU group, patients in the UFT group experienced a lower incidence of grade 1 toxicity (340 of 522 cycles, 65.1%, for the 5-FU group vs. 304 of 695 cycles, 43.7%, for the UFT group, $p < 0.001$). The incidences of grade 2 - 4 toxicity were similar in the two treatment groups (8.8% vs. 8.6%, respectively).

Table 4 lists the number of worst toxicities per patient for any grade of adverse reactions. The most frequent side effects in both groups were gastrointestinal symptoms, such as diarrhea, nausea and vomiting, followed by hematologic complications such as leukopenia. There was no instance of leukopenia-related sepsis or thrombo-

Table 1. Patient Characteristics

Characteristics		No. of patients		
		5-FU group*(n=53)	UFT group†(n=69)	*p* value
Sex	Male	27	43	0.21
	Female	26	26	
Age	Mean (years)	55.7 ± 10.2	56.2 ± 11.9	0.79
	Range (years)	34 - 73	23 - 80	
ECOG performance status				0.43
0		30	47	
1		22	21	
2		1	1	
Primary tumor site				0.47
Ascending colon		22	35	
Transverse colon		6	3	
Descending colon		6	6	
Sigmoid colon		19	25	
Dukes' Stage				0.97
B2		34	44	
C2		19	25	
Tumor				
Size (cm)		6.2 ± 2.2	6.6 ± 3.2	0.39
Circumference (%)		79.7 ± 19.2	80.1 ± 21.0	0.92
Length (cm)		4.7 ± 2.5	4.9 ± 1.9	0.73
Histopathologic type				0.59
Papillary adenocarcinoma		0	1	
Tubular adenocarcinoma				
Well differentiated		7	6	
Moderately differentiated		38	54	
Poorly differentiated		3	5	
Mucinous adenocarcinoma		5	3	

*5-FU group, intravenous 5-FU plus FA group.
†UFT group, oral UFT plus FA group.

cytopenic bleeding. The incidence and grade of toxicity in both groups were comparable. Forty-four (83.0%) in the 5-FU group and 49 (71.0%) in the UFT group experienced mild toxicity of grade 1 or 2. Severe toxicity (grade 3 or 4), although rare in both groups, was somewhat higher (not statistically significant) in the UFT group than in the 5-FU group (10 of 69 patients, 15.9% vs. 3 of 53 patients, 5.7%, respectively, Chi-square test, p=0.077), and all cases were gastrointestinal toxicities.

Table 2. Patient Compliance

	5-FU group* (n=53)	UFT group† (n=69)	*p* value
Mean number of treatment cycles	9.9 ± 3.6	10.1 ± 3.4	0.73
Compliant patients	39	50	0.89
Dose adjustment or delay of treatment due to toxicities	9	16	0.35
Non-compliance	14	19	
Toxicity	2[1)]	4[2)]	
Refusal	7	11	
Recurrence	3	2	
Others	2[3)]	2[4)]	

*5-FU group, intravenous 5-FU plus FA group.
†UFT group, oral UFT plus FA group.
[1)]One case of vomiting and 1 of leukopenia.
[2)]One case of stomatitis, 2 of diarrhea and 1 of hand-foot syndrome.
[3)]Two cases of difficulty in IV injection.
[4)]One case of pulmonary tuberculosis and one of financial hardship.

Quality of life (QOL)

QOL before treatment was excellent in both groups. The mean total QOL score before treatment was higher in the UFT group than in the 5-FU group (91.9 ± 9.8 vs. 86.5 ± 13.5, respectively, p=0.016), probably due to selection bias by non-randomization. A steady and significant increase of QOL score, both during and after therapy, was evident in both groups ($p < 0.05$, repeated measures ANOVA), and did not differ between the two groups (Table 5).

Survival, disease free survival and recurrence rate

The median duration of follow-up for the patients was 28 months (5 - 45 months), and the median survival duration had not been reached by the time of writing, April 2001. Until then, there were no significant differences in the survival rate, DFS rate, or recurrence rate between the two groups. The following results were recorded for the 5-FU and UFT groups, respectively: survival rate, 92.5% and 94.9% (Fig. 1); DFS rate, 84.1% and 87.5% (Fig. 2); recurrence rate, 15.1% (8/53 patients) and 11.6% (8/69 patients); recurrence rate at the anastomotic site, 3.8% (2/53 patients) and 1.4% (1/69 patients); and distant metastasis rate, 11.3% (6/53 patients) and 10.1% (7/69 patients). The most common site of distant metastasis was the liver (data not shown).

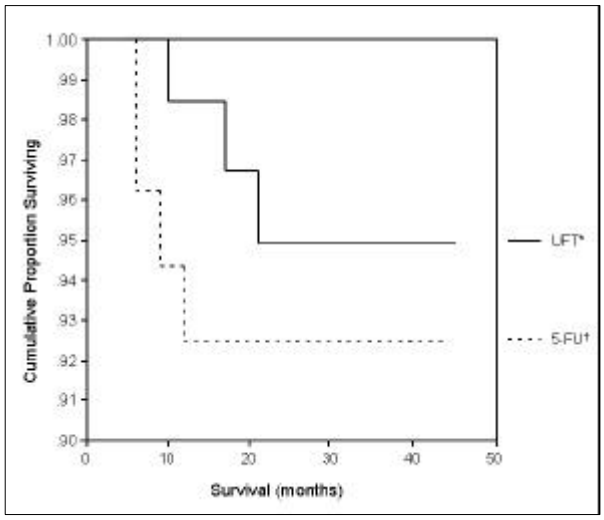

Fig. 1. Overall survival curve. *UFT, oral UFT plus FA group. †5-FU, intravenous 5-FU plus FA group.

DISCUSSION

Oral fluoropyrimidine has been used clinically for 30 years. Tegafur (tetrahydrofuranyl-5-fluorouracil), synthesized by Hiller, et al. in 1967,[35]

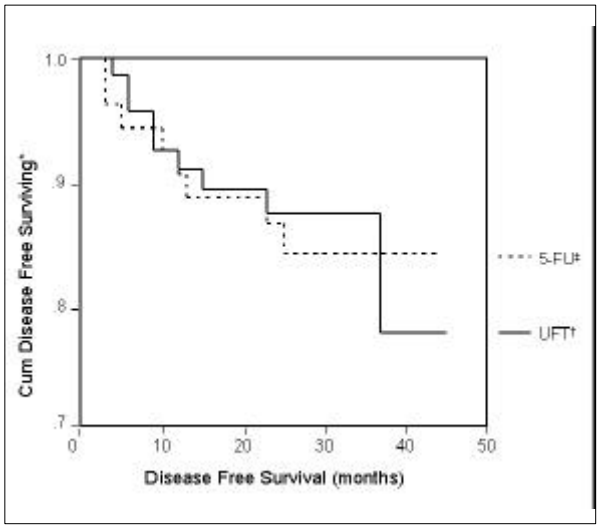

Fig. 2. Disease free survival curve. *Cum Disease Free Surviving, Cumulative Proportion Disease Free Surviving. †UFT, oral UFT plus FA group. ‡5-FU, intravenous 5-FU plus FA group.

becomes effective through its gradual conversion to 5-FU, by the liver enzyme P-450 mainly, thymidine phosphorylase, and spontaneously. Tegafur has a modest anticancer effect with oral administration as a single agent.[36] However, it has neurological side effects such as lethargy and coma in addition to the side effects of its metabolite, 5-FU.[37] Especially in Japan, where an oral agent with a mild toxicity profile was highly valued, the drug has become commonly used.[38] The combination of uracil and tegafur (UFT),[39] in a molar ratio of 4:1, produces an enhanced intra-tumoral concentration of fluoropyrimidine, one which is 5 to 10 times greater than that achieved with tegafur alone.[16,18] Approximately 85% of 5-FU is catabolized to fluoro-β-alanine by the enzyme dihydropyrimidine dehydrogenase. Uracil competitively inhibits the degradation of 5-FU by this enzyme, which thus increases the

Table 3. Toxicities per Cycle

Toxicity	5-FU group* (n=522 cycles)					UFT group† (n=695 cycles)				
	WHO grade					WHO grade				
	1	2	3	4	Total	1	2	3	4	Total
Hematologic toxicity	93	20	0	0	113	114	15	0	0	129
Leukopenia	56	18	0	0	74	44	7	0	0	51
Thrombocytopenia	0	2	0	0	2	0	0	0	0	0
Anemia	37	0	0	0	37	70	8	0	0	78
Bleeding	0	0	0	0	0	0	0	0	0	0
Gastrointestinal toxicity	244	21	4	1	270	188	30	10	5	233
Diarrhea	23	4	1	1	29	37	12	5	3	57
Nausea	157	9	1	0	167	113	11	2	1	127
Vomiting	52	5	2	0	59	18	4	1	1	24
Stomatitis	6	0	0	0	6	18	3	1	0	22
Abnormal LFT	6	3	0	0	9	2	0	1	0	3
Other toxicity	3	0	0	0	3	2	0	0	0	2
Nephrotoxicity	0	0	0	0	0	0	0	0	0	0
Respiratory toxicity	0	0	0	0	0	0	0	0	0	0
Cardiac toxicity	0	0	0	0	0	0	0	0	0	0
Neurologic toxicity	3	0	0	0	3	0	0	0	0	0
Infection	0	0	0	0	0	2	0	0	0	2
Any toxicity	340‡	41	4	1	386	304‡	45	10	5	364

*5-FU group, intravenous 5-FU plus FA group.
†UFT group, oral UFT plus FA group.
‡Chi-square test, $p<0.001$.

Table 4. Worst Toxicity per Patient

Toxicity	5-FU group* (n=53)					UFT group† (n=69)				
	WHO grade					WHO grade				
	1	2	3	4	Total	1	2	3	4	Total
Hematologic toxicity[1)]	23	7	0	0	30	27	9	0	0	36
Leukopenia	16	7	0	0	23	14	4	0	0	18
Thrombocytopenia	1	0	0	0	1	0	0	0	0	0
Anemia	16	0	0	0	16	25	6	0	0	31
Bleeding	0	0	0	0	0	0	0	0	0	0
Gastrointestinal toxicity[2)]	29	10	2	1	42	37	6	6	4	53
Diarrhea	9	4	1	1	15	14	5	4	3	26
Nausea	31	4	1	0	36	33	5	2	1	41
Vomiting	15	2	2	0	19	7	2	1	1	11
Stomatitis	5	0	0	0	5	10	2	1	0	13
Abnormal LFT	1	3	0	0	4	2	0	1	0	3
Other toxicity[3)]	2	0	0	0	2	2	0	0	0	2
Nephrotoxicity	0	0	0	0	0	0	0	0	0	0
Respiratory toxicity	0	0	0	0	0	0	0	0	0	0
Cardiac toxicity	0	0	0	0	0	0	0	0	0	0
Neurologic toxicity	2	0	0	0	2	0	0	0	0	0
Infection	0	0	0	0	0	2	0	0	0	2
Any toxicity[4)]	30	14	2	1	47	38	11	6	4	59

*5-FU group, intravenous 5-FU plus FA group.
†UFT group, oral UFT plus FA group.
[1)]Indicates the sum of the highest toxicity of all hematologic toxicities which each patient experienced.
[2)]Indicates the sum of the highest toxicity of all GI toxicities which each patient experienced.
[3)]Indicates the sum of the highest toxicity of all other toxicities except skin toxicities which each patient experienced.
[4)]Indicates the sum of the highest toxicity of all cycles which each patient received.

amount of 5-FU available for its anabolic pathways and ultimately results in either RNA dysfunction or DNA deprivation.[10] Tumors have both higher levels of thymidylate phosphorylase and substantially lower amounts of dihydropyrimidine dehydrogenase, which leads to the highest concentration of 5-FU occurring within the tumor. For example, in a series of patients with head and neck cancer who were treated with UFT, the concentration of 5-FU in tumor tissue was two to 6.3 times greater than in non-tumoral tissues, and reached about 17 times its plasmatic levels.[40,41]

FA (L.5-formyl tetra-hydrofolate, leucovorin) is the prototype biomodulator of 5-FU. Use of 5-FU in combination with FA in the treatment of colon cancer has consistently resulted in higher response rates when compared with 5-FU alone.[42] Some randomized trials that compared 5-FU with and without FA have also demonstrated a survival advantage for the FA-containing regimen.[43,44] Effective intratumoral concentrations of FA ($>1\mu$ mol/L)[45] can be achieved by nonparenteral and oral administration. Pharmacokinetic studies of oral FA have shown that single doses up to 50 mg

Table 5. Quality of Life Before and During Therapy

	5-FU group*	UFT group†	*p* value
Before treatment	(n=50)	(n=63)	
Total score	86.5 ± 13.5	91.9 ± 9.8	0.016‡
Daily activity	26.2 ± 4.8	27.5 ± 3.0	NS
Physical function	23.0 ± 4.1	24.8 ± 3.0	0.009‡
Psychological status	19.0 ± 4.0	20.0 ± 3.1	NS
Social status	14.8 ± 3.5	16.1 ± 3.1	0.040‡
Global assessment	3.93 ± 0.61	4.18 ± 0.45	NS
3 months later	(n=47)	(n=62)	
Total score	93.4 ± 11.0	95.5 ± 9.0	
Daily activity	28.0 ± 2.8	28.5 ± 2.0	
Physical function	25.4 ± 3.4	25.4 ± 3.2	
Psychological status	19.9 ± 3.9	20.9 ± 3.9	
Social status	16.4 ± 3.3	17.2 ± 3.0	
Global assessment	4.25 ± 0.50	4.34 ± 0.41	
6 months later	(n=45)	(n=57)	
Total score	95.2 ± 7.5	95.3 ± 8.8	
Daily activity	28.9 ± 1.8	28.3 ± 2.1	
Physical function	25.4 ± 2.7	26.3 ± 3.3	
Psychological status	20.2 ± 2.8	24.1 ± 3.8	
Social status	17.0 ± 2.7	16.6 ± 3.4	
Global assessment	4.34 ± 0.34	4.33 ± 0.40	
12 months later	(n=37)	(n=46)	
Total score	97.1 ± 8.0	97.6 ± 8.6	
Daily activity	28.7 ± 1.8	27.9 ± 4.1	
Physical function	27.0 ± 2.9	26.9 ± 3.3	
Psychological status	21.0 ± 3.2	21.3 ± 3.3	
Social status	16.6 ± 3.3	17.2 ± 3.0	
Global assessment	4.41 ± 0.36	4.44 ± 0.39	
18 - 24 months later	(n=19)	(n=29)	
Total score	94.0 ± 9.4	98.8 ± 7.3	
Daily activity	27.6 ± 2.3	27.4 ± 4.9	
Physical function	25.7 ± 3.7	27.1 ± 1.4	
Psychological status	19.6 ± 3.4	21.2 ± 3.5	
Social status	17.4 ± 2.3	18.2 ± 2.5	
Global assessment	4.27 ± 0.43	4.49 ± 0.33	

*5-FU group, intravenous 5-FU plus FA group.
†UFT group, oral UFT plus FA group.
‡Student's t-tests.

have a 100% bioavailability with absorption complete at 2 hours.[46] The development of UFT as a convenient oral drug for long-term administration has to be credited to the efforts of Japanese investigators. UFT and oral FA offer the advantage of a nonparenteral regimen for patients with advanced colorectal cancer, as opposed to currently prescribed programs of bolus 5-FU and FA[47] or even to the better tolerated and more effective, prolonged infusional schedules that require central catheters and portable pump technologies.[48] Thus, a UFT plus oral FA regimen may be more comfortable, avoid hospitalization, and reduce costs, while at the same time increase patient compliance.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) has recently implemented a new clinical trial (Protocol C-06) comparing the efficacy of 5-FU plus FA with that of UFT plus FA in the treatment of patients with resected stage II or III colon cancer.[9] For the present study we have also developed a clinical trial comparing intravenous 5-FU plus FA treatment and oral UFT plus FA treatment, after curative resection in patients with Dukes' stage B2 and C2 colon cancer; in terms of compliance, complication, QOL and efficacy. As noted in the materials section, we were unable to complete a prospective, randomized, double blind study because many of our patients wanted to make their own choice regarding therapeutic regimen. The overall number of randomized patients was 10 (18.9%) in the 5-FU group and 13 in the UFT group (18.8%). Nevertheless, all surgical procedures, postoperative chemotherapy courses and follow up examinations were performed by the same surgeon and gastroenterologist, thus avoiding any bias due to differential treatment policy or follow up.

The overall degree of compliance was similar in both treatment groups. The most common toxicities, which decreased compliance, were vomiting and leukopenia in the 5-FU group, and diarrhea, stomatitis and hand-foot syndrome in the UFT group.

Mild toxicity (grade 1 or 2) was more frequent in the 5-FU group, while severe toxicity (grade 3 or 4) was somewhat more frequent (not statistically significant) in the UFT group. The most common toxicities in both groups were gastrointestinal toxicities such as nausea, vomiting, diarrhea and stomatitis, and all of the grade 3 and 4 toxicities were also gastrointestinal forms. These results are in partial agreement with those of the phase II study by Pazdur,[26] in which none of the patients experienced significant hematologic toxicity or significant stomatitis. However, in our study, stomatitis or mild hematologic toxicity was reported in 13 (18.84%) and 36 patients (52.17%), respectively, in the UFT group. The reason for this may be due to the relatively small body mass of oriental patients. Our treatment protocol followed the method suggested by research in western countries, which may not in fact be the most appropriate to our patients. Nevertheless, the degree of hematologic toxicity in our study was acceptable.

Nowadays consideration for the effects of treatment on QOL is increasing and it has become a very important factor in choosing treatment modality. A steady and significant increase of QOL score, both during and after therapy, was evident in both groups suggesting that chemotherapy is quite tolerable and does not deteriorate the patients' QOL.

Although the 5-year survival rate has not yet been determined for the two treatment courses studied here, both the survival rate and the DFS rate were somewhat higher in the UFT group, although not to a statistically significant degree. However, this is only a preliminary report investigating compliance, toxicity, QOL and efficacy. The patient follow up component of this study, to analyze survival and recurrence rates, remains on-going.

In conclusion, our experience suggests that treatment consisting of oral UFT combined with oral FA is well tolerated, convenient and produces little toxicity. A final analysis, from the on-going component of this study based on comparison of toxicity profiles, demonstrating that UFT plus FA treatment offers overall survival benefits similar to or greater than those provided by 5-FU plus FA, will confirm that UFT modulated with oral FA as an adjuvant chemotherapy after curative resection in patients with Dukes' stage B2 and C2 colon cancer is a better alternative to infusional 5-FU plus FA.

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