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ORIGINAL ARTICLE

Sotaro Sadahiro · Shigeru Ohki · Shigeki Yamaguchi
Toshiki Takahashi · Yoshimasa Otani
Satoshi Tsukikawa · Takuya Yamamura
Shoji Takemiya · Hideaki Nagasaki
Kiyoshi Nishiyama · Tsuneo Fukushima
Yoshiki Hiki · Susumu Yamaguchi · Kaoru Kumada
Hiroshi Shimada · Toshio Mitomi · Hiroyasu Makuuchi

Feasibility of a novel weekday-on/weekend-off oral UFT schedule as postoperative adjuvant chemotherapy for colorectal cancer

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Abstract *Purpose*: When oral anticancer agents are used for adjuvant chemotherapy of colorectal cancer, compliance and feasibility become issues because of the long treatment time. Appropriate studies of these issues are lacking. We investigated compliance and feasibility during a weekday-on/weekend-off schedule of oral UFT (uracil-tegafur) over a period of 1 year administered as adjuvant chemotherapy to patients with colorectal cancer. *Patients and methods*: A UFT dose of 600 mg/day was prescribed according to a weekday-on/weekend-off schedule to 87 patients after potentially curative resection. Compliance was investigated in three ways: physician interview, patient self-report, and chemical analysis of urine. The results were compared with the dose prescribed. Feasibility was evaluated on the basis of two indices: relative performance (RP), which was the ratio of the actual total dose taken to the total dose planned, and individual dose intensity (IDI), which was the ratio of the actual dose taken to the dose planned during a given period. *Results*: The compliance assessed by physician interview and by patient self-report conformed well with the prescribed dose, the rate of agreement among the three compliance measures being more than 94%. Chemical analysis of urine in 38 of the patients revealed that they were actually taking the drug. The RP was 0.72, and the IDI was 0.8. *Conclusion*: From these results, the feasibility of the weekday-on/weekend-off schedule was judged to be good. It is suggested that the feasibility would be even better if the dose of UFT was set according to body surface area.

Key words UFT · Compliance · Adjuvant chemotherapy · Colorectal cancer

S. Sadahiro (✉)[1] · S. Ohki · S. Yamaguchi · T. Takahashi
Y. Otani · S. Tsukikawa · T. Yamamura · S. Takemiya
H. Nagasaki · K. Nishiyama · T. Fukushima · Y. Hiki
S. Yamaguchi · K. Kumada · H. Shimada · T. Mitomi
H. Makuuchi
UFT Compliance Study Group, Kanagawa, Japan

Contact Address:
[1] Department of Surgery,
Tokai University, School of Medicine,
Kanagawa, Japan, Bohseidai Isehara-shi,
Kanagawa 259-1193, Japan
Tel.: +81-463-931121, Fax: +81-463-965577

Introduction

Many cancer patients prefer to be treated with orally administered anticancer agents providing equal efficacy can be maintained [9]. Oral agents are suitable for postoperative adjuvant chemotherapy in colorectal cancer in terms of patient convenience and cost savings [2]. However, when patients are given the responsibility to take medications that sometimes produce undesirable effects, questions of compliance arise.

Oral fluoropyrimidines have been widely used in Japan, and their efficacy has been shown by meta-analysis [20]. One of the newer drugs in this class is UFT, which is a combination of tegafur and uracil in a 1:4 molar ratio. In advanced colorectal cancer, a response rate of 25% has been reported for UFT alone [17] and a response rate of 25% or 42% when it is used in combination with leucovorin [18, 21]. Although it has been reported that better disease-free survival is obtained with UFT as adjuvant chemotherapy for colorectal cancer [13], its efficacy needs to be increased even further.

When used as adjuvant chemotherapy for gastric cancer, UFT has been reported to have a greater preventive effect on recurrence at a dose of 600 mg/day than at a dose of 400 mg/day [22]. Similarly, a better survival rate has been obtained with UFT as adjuvant chemotherapy for gastric cancer in patients with good compliance than in patients with poor compliance [12].

Nevertheless, it has been reported that when consecutive daily doses of 600 mg UFT are administered, the number of patients who stop taking the drug because of adverse reactions increases as the dose per unit of body weight increases [10]. Thus, there is a need to modify the conventional consecutive daily administration schedule.

We developed a new administration schedule for oral UFT, the weekday-on/weekend-off schedule, in which UFT is administered for five consecutive days and not administered on the next 2 days. This schedule provides a higher antitumor effect and better survival in tumor-bearing rats than the conventional daily administration schedule when the weekly doses of UFT are the same, with no difference in toxicity [19]. On the other hand, compliance and feasibility are important factors for adjuvant chemotherapy, especially with oral anticancer agents because treatment continues for a long period. Noncompliance by a significant number of cancer patients could actually invalidate the results of a clinical trial [8]. Because there have been no appropriate reports on these issues for adjuvant chemotherapy with oral agents in colorectal cancer, it was necessary to clarify compliance and feasibility for this schedule before proceeding to a phase III study to confirm effectiveness. The aim of this study was to evaluate the compliance and feasibility of the new oral UFT schedule, the weekday-on/weekend-off schedule, over a period of 1 year as adjuvant chemotherapy for colorectal cancer.

Patients and methods

Eligibility, registration, and follow-up

Patients were eligible if they were 15 to 75 years old with a body weight of at least 40 kg, had undergone potentially curative resection for surgical stage II or III colorectal cancer, had a performance status of 0–2, had no history of other malignancy, and were not being scheduled for radiation. The exclusion criteria were a white blood cell count below 4000/μl, a hemoglobin value below 8 g/dl, a platelet count less than 100,000/μl, or an aspartate transaminase (AST) or an alanine transaminase (ALT) value more than twice the upper limit of normal at that institution. Written informed consent was obtained from every patient.

Between March 1995 and July 1997, patients from the 11 institutions participating in the UFT Compliance Study Group (Table 1) were registered by fax at the center established at the Department of Surgery of Tokai University. If a patient was judged to be eligible, the registration center instructed the physicians regarding the investigation of drug compliance, symptoms and signs, and clinical laboratory studies and collected and compiled these data. Blood chemistry findings were examined before surgery, before UFT administration started, 8 weeks after surgery, and every 2 months thereafter through 12 months. In principle, the physician saw the patient once every 2 weeks and prescribed the medication. Adverse reactions were evaluated according to the criteria of the Japan Society for Cancer Therapy [4].

All 91 registered patients, 60 men and 31 women aged 27 to 75 years (mean 57.5 years), were eligible for the trial. However, four patients did not receive UFT, either because consent was withdrawn ($n = 1$) or because of postoperative complications ($n = 3$). The remaining 87 patients constituted the population for this study.

Table 1 UFT Compliance Study Group, Kanagawa, Japan

Department of Surgery, Tokai University School of Medicine
Department of Surgery II, Yokohama City University School of Medicine
Department of Surgery II, Urafune Hospital, Yokohama City University
Department of Surgery, National Sagamihara Hospital
Department of Surgery, East Hospital, Kitasato University
Department of Surgery I, St. Marianna University School of Medicine
Department of Surgery I, Toyoko Hospital, St. Marianna University
Department of Surgery, Kanagawa Cancer Center Hospital
Department of Surgery, Fujigaoka Hospital, Showa University
Department of Surgery, Yokohama National Hospital
Department of Surgery, Yokohama Municipal Citizens Hospital
Department of Surgery, Tokai University (registration center)

Chemotherapy schedule

Beginning 2 weeks after surgery, patients were given oral UFT 600 mg/day in three portions Monday through Friday. Whenever grade 2 gastrointestinal symptoms, liver or kidney function abnormalities, or myelosuppression occurred according to the Criteria of the Japan Society for Cancer Therapy [4], the UFT dosage was reduced 50% (300 mg/day). If the adverse reactions reached grade 3 or more, drug administration was suspended until after recovery. Whenever grade 2 or more neurotoxicity occurred, drug administration was suspended. If recurrence of the disease was confirmed, administration of UFT was discontinued, with no restrictions being placed on subsequent treatment.

Assessment of compliance

In principle, the physician saw and interviewed each patient once every 2 weeks. Based on these interview records, every 3 months the physician evaluated patient compliance on the following three-grade scale: A – taking the drug, i.e. omission of no more than three doses per week; B – inability to take the drug because of adverse effects; or C – forgetting to take the drug three or more times per week.

Drug compliance was also evaluated on a three-grade scale at 3-month intervals on the basis of patient self-reports: A – taking the drug; B – forgetting to take the drug fewer than three times a week; or C – forgetting to take the drug three times a week or more. To prevent the self-reports from being influenced by physician statements, the reports were filled out and collected at a different site.

As an objective evaluation of compliance, the urine of randomly selected patients was collected under the instruction of the registration center at 3, 6, and 9 months after the start of treatment. Urine tegafur concentrations ≥3500 ng/ml were considered evidence of compliance [14, 15].

Indices of feasibility

Relative performance (RP) [11] and individual dose intensity (IDI) [1] were used as feasibility indices. The RP was the ratio of the actual total dose taken to the total dose planned and was the fixed value obtained as the product of the daily dose and the dosage period stipulated in the protocol. It was calculated when the treatment period had been completed. The value was 1.0 when a patient actually took the total dose planned and decreased when a patient discontinued taking the drug or received a reduced dose. The IDI was the ratio of the actual dose taken to the stipulated dose at a certain time-point. Because it was calculated for each period, it could be evaluated at any time-point. This property of the IDI was utilized for patients who stopped taking UFT for reasons other than adverse reactions. In these cases, IDI was calculated at

the time when the patient stopped taking UFT, and the patient was regarded as a censored case thereafter.

The difference between the RP and the IDI lay in the handling of censored cases. The RP was an index of feasibility that included adverse reactions, recurrences, and all other cases of discontinuation, whereas IDI focused only on discontinuation because of adverse reactions to the drug.

Results

Drug administration

There were 30 patients (35%) in whom UFT was discontinued and not restarted, and in 18 of them (21% of the series), the drug was stopped because of adverse reactions. The other reasons for stopping UFT were disease recurrence in seven patients, change of physician in two, and surgical complications, patient request unassociated with adverse reactions, and failure to follow-up in one patient each. There were 17 patients (20%) who stopped taking the drug temporarily, and there were 11 patients (12.6%) whose dose was reduced.

Toxicity

The principal adverse reactions were upper gastrointestinal symptoms and signs, including anorexia, nausea and vomiting, and liver dysfunction (Table 2). The overall rate of occurrence of adverse reactions was 35%, and the rate for reactions of grade 2 or worse was 16%. Hematologic toxicity (thrombocytopenia) occurred in just one patient. Neurotoxicity was observed in seven patients as taste abnormalities in two and other nonserious reactions in the others. The two skin lesions were mild dermatitis; no cases of hand-foot syndrome were observed. Grade 3 anorexia and diarrhea were observed in one patient, who recovered by day 14 after discontinuing the drug. No serious adverse reactions were observed.

Table 2 Toxicities

Toxicity (n = 87)	n	%	Grade[a]			
			1	2	3	4
Leukopenia	0	0.0	0	0	0	0
Thrombocytopenia	1	1.1	1	0	0	0
Liver dysfunction	7	8.0	3	4	0	0
Nausea	10	11.5	5	5	0	0
Vomiting	4	4.6	1	3	0	0
Diarrhea	6	6.9	3	2	1	0
Stomatitis	2	2.3	1	1	0	0
Pigmentation	5	5.7	5	0	0	0
Alopecia	1	1.1	1	0	0	0
Skin	2	2.3	1	1	0	0
Neurotoxicity	7	8.0	5	2	0	0
Others	3	3.4	2	1	0	0

[a] Adverse drug reaction criteria of the Japan Society of Clinical Oncology

Compliance

The prescribed dose, the compliance based on the physician interviews, and the compliance based on the patient self-reports are compared in Table 3. On the basis of the physician interviews, it was judged that the drug was not being taken by 4 of 72 patients (6%) at 3 months, 3 of 66 (5%) at 6 months, 1 of 61 (2%) at 9 months, and 3 of 57 (6%) at 12 months. There were no instances in which the physician's judgment that the patient was taking the drug was contradicted by the patient's self-report. The rate of consistency between the compliance assessed by physician interview and self-report at 3, 6, 9, and 12 months was 94%, 99%, 99%, and 94%, respectively. Assuming that none of the patients who failed to respond by self-report was actually taking the drug, the rates of noncompliance were 11% (8/72) at 3 months, 9% (6/66) at 6 months, 7% (4/61) at 9 months, and 9% (5/57) at 12 months.

The urine tegafur concentration was within the expected range in 36 of the 38 patients tested. One of the two patients in whom it was negative had stopped taking UFT, and in the other, the urine specimen was collected from the patient on Monday, more than 2 days after the final dose for the preceding week. Ogasawara et al. have reported that the drug concentration decreases below the limit of detection beginning approximately 36 h after the final dose in more than 80% of patients [14].

Feasibility of the drug administration schedule

The RP and IDI values calculated for the 87 patients are shown in Fig. 1. The mean RP value was 0.72. The mean IDI was 0.94 at 3 months and 0.83, 0.79, and 0.76 at 6, 9, and 12 months, respectively, with a mean overall value of 0.80. The IDI value at the time of discontinuation was used for the 12 patients in whom the drug was stopped for reasons other than adverse reactions.

Discussion

Self-reports, pill counts, electronic monitoring devices, and chemical analysis of blood and urine have been used for evaluating drug compliance [5–8, 15, 23]. High compliance values – 90% or more – have been reported for oral anticancer drugs [5–7, 23], and in this series, the compliance as determined by physician assessment and patient self-report were nearly identical, with values of more than 90%. The urine tegafur concentration was judged to show drug ingestion in all of the patients studied in this way, and it was confirmed that the dose prescribed almost matched the dose actually taken.

Compliance with drug administration has been reported to improve as a result of patient education [8]. In this study, compliance with the UFT schedule appeared to be good because the patients had been informed that they had malignancies, which is not always done in

Table 3 Relationship between the prescription records, the physician interview, and patient self-report

	3 months		6 months		9 months		12 months	
No. of cases prescribed	72		66		61		57	
Drug not taken during the period	15		21		26		30	
The investigation of compliance	Interview	Self-report	Interview	Self-report	Interview	Self-report	Interview	Self-report
Taking the drug	68	68	63	61	60	58	54	54
Unable to take the drug[a]	4	0	3	2	1	0	3	0
Unknown	0	4	0	3	0	3	0	3

[a] Did not take the drug three or more times a week

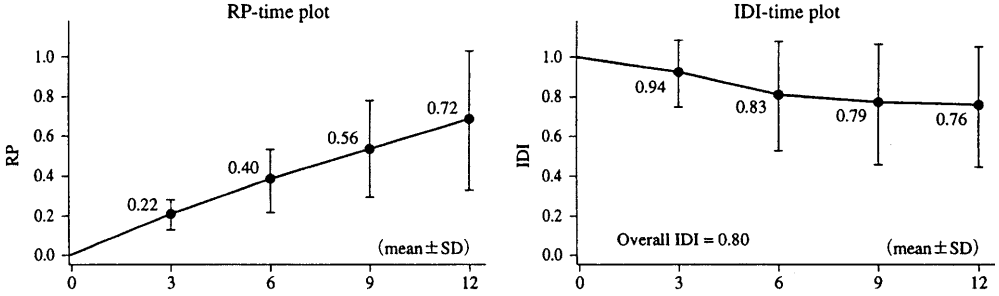

Fig. 1 Changes in mean relative performance and individual dose intensity values over time ($n = 87$)

Japan, and had been thoroughly instructed on how to take the drug, that is, to take it on weekdays but not on weekends.

The rate of adverse reactions during postoperative adjuvant chemotherapy with consecutive daily administration of UFT at a dose of 400 mg has been reported to be 54% at 1 year [16]. When the drug is given for 2 years, the rates of particular reactions have been reported to be 33% for leukopenia, 4% for thrombocytopenia, 19% for AST elevation, 21% for GPT elevation, 5% for nausea and vomiting, and 4% for diarrhea [21]. Similar results have also been obtained on this new administration schedule. Thus, there were no increases in adverse reactions even though the daily dose was raised.

In the weekday-on/weekend-off schedule, the daily dose was set at 600 mg to increase the dose intensity. Because the dose of UFT in most phase II studies has been 600 mg [17], and because large variations in the pharmacodynamics of 5-FU were expected in view of the individual differences in the activity of dihydropyrimidine dehydrogenase [3], we thought that setting the daily dose at 600 mg and adjusting it according to toxicity was the best method.

The mean value of RP was 0.72, meaning that 72% of the total dose of UFT planned in the protocol was given. The mean value of the other index of feasibility, IDI, tended to decrease as the dosage period grew longer, but the overall mean value was 0.80. This figure means that only 20% of the planned dose was not administered because of adverse reactions. An RP of 0.62 and an IDI of 0.77 have been reported for a schedule in which UFT 300 mg was administered on consecutive days after treatment with MMC and 5-FU as adjuvant chemotherapy for gastric cancer [22]. Although the subjects and the dosage schedule were different in our trial, the oral UFT weekday-on/weekend-off schedule was judged to have good feasibility and to be a useful schedule on the basis of the RP and IDI values.

We analyzed the relationship between both RP and IDI and body surface area, and in the next step we set the daily dose of UFT on the basis of body surface area.

The results of this study suggest that the weekday-on/weekend-off method of oral UFT administration could be used as one arm of a randomized controlled study in the adjuvant chemotherapy for colorectal cancer.

References

1. Coppin CML (1987) The description of chemotherapy delivery: option and pitfalls. Semin Oncol 14 [Suppl 4]: 34
2. DeMario MD, Ratain MJ (1998) Oral chemotherapy: rationale and future directions. J Clin Oncol 16: 2557
3. Grem JL, Yee LK, Venzon DJ, Tkimoto CH, Allegra CJ (1997) Inter- and intraindividual variation in dihydropyrimidine dehydrogenase activity in peripheral blood mononuclear cells. Cancer Chemother Pharmacol 40: 117
4. Japan Society for Cancer Therapy (1993) Criteria for the evaluation of the clinical effects of solid cancer chemotherapy. J Jpn Soc Cancer Ther 28: 101
5. Lee CR, Nicholson PW, Souhami RL, Deshmukh AA (1992) Patient compliance with oral chemotherapy as assessed by a novel electronic technique. J Clin Oncol 10: 1007
6. Lee CR, Nicholson PW, Souhami RL, Slevin ML, Hall MR, Deshmukh AA (1993) Patient compliance with prolonged low-dose oral etoposide for small cell lung cancer. Br J Cancer 67: 630
7. Lee CR, Nicholson PW, Ledermann JA, Rustin GJS (1996) Patient compliance with prolonged oral altretamine treatment in relapsed ovarian cancer. Eur J Gynaecol Oncol 17: 99
8. Levine AM, Richardson JL, Marks G, Chan K, Graham J, Selser JN, Kishbough C, Shelton DR, Johnson CA (1987)

Compliance with oral drug therapy in patients with hematologic malignancy. J Clin Oncol 5: 1469
9. Liu G, Franssen E, Fitch MI, Warner E (1997) Patient preferences for oral versus intravenous palliative chemotherapy. J Clin Oncol 15: 110
10. Maehara Y, Sugimachi K, Kikuchi K, Inokuchi K, Komi N, Hattori T, Taguchi T, Kondo T, Abe O, Uchino J, Ogawa N (1993) Cooperative study of surgical adjuvant chemotherapy for colorectal cancer (fourth report): five-year results after surgery. Jpn J Cancer Chemother 20: 109
11. Nakajima T, Okabayashi K, Nakazato H, Iwanaga G, Ota K, Kito T, Yamatsuma Y, Furaukawa H, Hiratsuka M (1989) Individual dose intensity and relative performance as indices for assessing the quality of clinical cancer chemotherapy and their effect on therapeutic results. Oncologia 22: 100
12. Nakajima T, Okabayashi K, Nakazato H, Iwanaga G, Ota K, Kinoshita T, Kito T, Yamamura Y, Furukawa H, Hiratsuka M (1994) Adjuvant chemotherapy with MFC-related regimens for patients with gastric cancer after curative gastrectomy. J Jpn Soc Cancer Ther 29: 654
13. Nakazato H, Koike A, Saji S, Suzuki H, Takagi H, Nimura Y, Hasumi A, Baba S, Manabe T, Maruta M, Miura K, Yamaguchi A, Kato Ohashi Y (1997) Efficacy of oral UFT as adjuvant chemotherapy to curative resection of colorectal cancer: a prospective randomized clinical trial (abstract). Proc Am Soc Clin Oncol 16: 279
14. Ogasawara H, Horiuchi M, Tsukuda M, Kaneko S, Komiyama S, Sugita M, Miyake H (1990) Usage of urine FT level for medication compliance in head and neck cancer patients with administration of UFT. Jpn J Cancer Chemother 17: 1221
15. Ohsawa S, Kondo Y, Shiroto H, Masuko H, Fukushima T, Kataoka A, Ohmori K, Sawaguchi Y, Baba E, Takahashi T, Sawada Y, Hashimoto I, Uchino J (1992) A study of urinary tegafur, 5-fluorouracil and uracil concentrations in the case of gastric carcinoma for the confirmation of drug-taking compliance after UFT oral administration. Jpn J Cancer Chezmother 19: 2189
16. Okuda M, Teramoto T, Watanabe M, Utsunomiya T, Kodaira S, Kitajima M (1995) Adjuvant chemotherapy with mitomycin C, tegafur and UFT for colorectal cancer. J Jpn Soc Coloproctol 48: 120
17. Ota K, Taguchi T, Kimura K (1987) Report on nationwide pooled data and cohort investigation in UFT phase II study. Jpn J Cancer Chemother 14: 2746
18. Pazdur R, Lassere Y, Rhodes V, Ajani JA, Sugarman SM, Patt YZ, Jonse DV, Markowitz AB, Abbruzzese JL, Bready B, Levin B (1994) Phase II trial of uracil and tegafur plus oral leucovorin: an effective oral regimen in the treatment of metastatic colorectal carcinoma. J Clin Oncol 12: 2296
19. Sadahiro S, Mukai M, Tokunaga N, Tajima T, Makuuchi H, Yoshida M, Okabe H, Uchida J, Takeda S, Unemi N (1998) Preliminary study on the optimal dosage schedule for oral tegafur/uracil (UFT) chemotherapy. Int J Clin Oncol 3: 7
20. Sakamoto J, Hamada C, Kodaira S, Nakazato H, Ohashi Y (1997) A meta-analysis of adjuvant therapy using oral fluoropyrimidines in patients with curatively resected colorectal carcinoma (abstract). Proc Am Soc Clin Oncol 16: 266
21. Saltz LB, Leichman CG, Young CW, Muggia FM, Conti JA, Spiess T, Jeffers S, Leichman LP (1995) A fixed-ratio combination of uracil and ftorafur (UFT) with low dose leucovorin. Cancer 75: 782
22. Sugimachi K, Maehara Y, Ogawa M, Kakegawa T, Tomita M (1997) Dose intensity of uracil and tegafur in postoperative chemotherapy for patients with poorly differentiated gastric cancer. Cancer Chemother Pharmacol 40: 233
23. Waterhouse DM, Calzone KA, Mele C, Brenner DE (1993) Adherence to oral tamoxifen: a comparison of patient self-report, pill counts, and microelectronic monitoring. J Clin Oncol 11: 1189