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SHORT COMMUNICATION

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A pharmacological study of the weekday-on/weekend-off oral UFT schedule in colorectal cancer patients

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Abstract *Purpose:* The new weekday-on/weekend-off schedule for oral UFT administration consists of its administration for 5 consecutive days followed by 2 days off the drug. The intratumor 5-FU (5-fluorouracil) concentration has been reported to be correlated to the tumor response in patients treated with intravenous 5-FU. The aim of this study was to investigate the pharmacokinetics during the 2 days off the drug in cancer patients treated with the weekday-on/weekend-off schedule for oral UFT. *Methods:* The subjects were 24 colorectal cancer patients. They were divided into three groups, and were all given UFT, 600 mg/day, for 5 days before surgery. Surgery was performed 2, 24, or 48 h after the final dose of UFT. The 5-FU concentrations in the serum, tumor, and in the normal mucosa were measured. *Results:* The serum 5-FU concentrations after the final dose of UFT were: 23 ± 12 ng/ml (mean $\pm$ SD) at 2 h, 7 ± 3 ng/ml at 24 h, and 6 ± 3 ng/ml at 48 h. The intratumor 5-FU concentrations were: 113 ± 45 ng/g at 2 h, 54 ± 20 ng/ml at 24 h, and 54 ± 35 ng/ml at 48 h, and the concentrations in the normal mucosa were: 36 ± 15 ng/g (mean $\pm$ SD) at 2 h, 17 ± 6 ng/ml at 24 h, and 18 ± 6 ng/ml at 48 h after the final dose. While the serum 5-FU concentration decreased to very low levels by 24 h after the final dose of UFT, the intratumor 5-FU concentrations were maintained at more than 50 ng/g at least until 48 h after the final dose. The 5-FU concentrations in the normal mucosa were maintained at about one third of the intratumor concentrations at all time points. *Conclusion:* Although the weekday-on/weekend-off schedule for UFT administration included intermittent 2-day drug-off periods, this pharmacokinetic study revealed that the 5-FU concentrations in the tumor were maintained at much higher levels than in the serum throughout these periods.

Key words Intratumor concentration · Pharmacokinetics · UFT

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Introduction

Patients with advanced cancer have been reported to prefer orally administered anticancer agents to intravenous injections when equal efficacy can be offered [8]. The convenience, improvement in quality of life, and lower cost associated with oral anticancer agent administration have recently been recognized in western countries [3].

UFT is an oral anticancer agent which was developed in Japan. It is a combination drug consisting of a mixture of tegafur and uracil, with inhibitory activity on dihydrouracil dehydrogenase (DPD). It has therefore been classified as one of the DPD inhibitory fluoropyrimidines (DIFs) as proposed by Diasio [4]. A response rate of 25% has been reported for UFT administered alone for advanced colorectal cancer [12]. In the United States, combination therapy with UFT and leucovorin has been reported to have a survival effect equivalent to that of the conventional combination therapy with 5-FU and leucovorin, and furthermore, to be safer [2, 13]. UFT has usually been administered on a daily basis. When used as adjuvant chemotherapy for gastric cancer, UFT is reported to have a greater preventive effect on recurrence at a dose of 600 mg per day than at a dose of 400 mg per day [17]. However, when 600 mg of UFT was administered on consecutive days, the number of patients who stop taking the drug because of adverse reactions increased [9]. For this reason, it became necessary to modify the conventional consecutive-day administration schedule. We developed a new oral UFT schedule, the weekday-on/weekend-off schedule, in which 600 mg of UFT is administered for 5 consecutive days, followed by 2 days on which the drug is not administered. For the same

weekly dose of UFT, the new schedule provided a higher antitumor effect and better survival than the conventional daily administration schedule in tumor-bearing rats. There was no significant difference in body weight suppression between the two schedules [15]. In addition, we found that this weekday-on/weekend-off schedule for oral UFT was associated with good compliance and was feasible as adjuvant chemotherapy over a 1-year period in colorectal cancer patients [16].

The uptake and retention of the anticancer agent by the tumor has been reported to be correlated with the tumor response in patients treated with 5-FU [1, 5, 7, 11, 14]. The weekday-on/weekend-off schedule for UFT consists of its administration for 5 consecutive days followed by 2 days off the drug. Because the pharmacokinetics during the drug-off period had been unclear, we studied it by administering UFT to colorectal cancer patients for 5 consecutive days and analyzing its pharmacokinetics during the 2 drug-off days following the final dose in this study.

Patients and methods

All of the patients were registered at the Department of Surgery of Tokai University. The eligibility criteria were the following: patients with histologically proven, potentially resectable colorectal cancer, aged 20 years or older, body weight 40 kg or above, performance status (Eastern Cooperative Oncology Group) 0 to 2, and no history of administration of 5-FU or 5-FU derivatives during at least 2 weeks prior to the study. The hematological criteria for registration into the study were as follows: leukocyte count, 4000/mm^3 or more; platelet count, 100,000/mm^3 or more; hemoglobin, 8.0 g/dl or more; GOT and GPT values no more than twice the upper limit of normal; serum creatinine value no greater than 1.5 mg/dl. All of the patients gave their informed consent. A total of 24 patients were registered, and were randomly assigned to one of three groups of eight patients each. There were no disparities in background factors, that is, gender, age, or body weight, between the groups (Table 1).

Administration schedule

Each patient was given 200 mg UFT, three times a day, for 5 days. In one group, UFT administration was started at noon 5 days before surgery, and the final dose was given on the day of surgery, 2 h before the operation. In the second group, UFT administration was started at noon, 6 days before surgery, and the final dose was given on the day before surgery, 24 h before the operation. In the third group, UFT administration was started at noon, 7 days before surgery, and the final dose was given two days before surgery, 48 h before the operation. Thus, the intervals between the final dose and the operation were 2 h, 24 h, and 48 h.

Table 1 Patient characteristics

	Time between final UFT administration and surgery		
	2 h	24 h	48 h
No of male/female patients	5/3	8/0	4/4
Age [y; mean (range)]	64 (53–78)	59 (41–85)	64 (46–78)
Body weight, mean (kg)	57.4	60.6	56.5

Specimen collection

Peripheral blood samples were collected at the time of the resection of the tumor. The serum was separated and the samples were stored at –80 °C. Approximately 1 g each of the tumor and of grossly normal mucosa from at least 5 cm away from the tumor were collected from the surgical specimen immediately after the resection, and stored at –80 °C. The 5-FU concentration was measured by GLC–mass spectrometry (GLC, gas–liquid chromatography) according to the method of Marunaka et al. [10].

Results

The tumor was removed at approximately the scheduled time in all the 24 patients registered. UFT had been administered for 5 days in every patient and no adverse reactions had been observed. The serum, intratumor, and normal mucosal concentrations of 5-FU at 2, 24, and 48 h after the final dose are shown in Table 2. The 5-FU concentrations in the normal mucosa were below the limit of detection (10 ng/g-tissue) 24 h after the final dose in two cases, and 48 h after the final dose in one case. The serum 5-FU concentration was below the limit of detection (2 ng/ml-serum) at 48 h in one case.

While the serum 5-FU concentration had decreased to very low levels by 24 h after the final dose of UFT, the intratumor concentration of 5-FU had decreased to only about half, that is, 54 ng/g 24 h after the final dose of UFT, and this level was maintained at least until 48 h after the final dose. The concentration of 5-FU in the normal mucosa 2 h after the final dose was approximately one third of the intratumor concentration, and had decreased by almost a half within 24 h, and was maintained at this levels until 48 h after the final dose.

Discussion

The principal aim of systemic cancer chemotherapy is the selective killing of the tumor cells; accumulation of a high concentration of the anticancer agent in the tumor

Table 2 5-FU concentration in the serum, tumor, and normal mucosa at various intervals after the final dose of UFT

Interval after the final dose of UFT	n[a]	5-FU concentration (mean ± SD)		
		Serum (ng/ml)	Tumor tissue (ng/g)	Healthy colorectal tissue (ng/g)
2 h	8	23 ± 12	113 ± 45	36 ± 15
24 h	8	7 ± 3	54 ± 20	19 ± 8[b]
48 h	8	6 ± 3[c]	54 ± 35	19 ± 8[d]

[a] n, no of patients
[b] $n = 6$: 5-FU concentration below the limit of detection (10 ng/g tissue) in two cases
[c] $n = 7$: 5-FU concentration below the limit of detection (2 ng/ml serum) in one case
[d] $n = 7$: 5-FU concentration below the limit of detection (10 ng/g tissue) in one case

cells is therefore a prerequisite for attaining this goal [1]. Dimitrakopoulou-Strauss et al. investigated drug distribution in the case of liver metastases from colorectal cancer by positron emission computed tomography with ^{18}F-labeled fluorouracil. They reported that the lesions that trapped higher concentrations of fluorouracil had a lower growth rate, and that the survival time was longer in these patients [5]. Presant et al. used ^{19}F magnetic resonance spectroscopy to measure the half-life of 5-FU in cancer lesions, and reported that the response rate was higher in lesions in which the drug was trapped and its half-life was prolonged [14]. Findlay et al. measured the serum and intratumor 5-FU concentrations during prolonged 5-FU administration. They reported that neither the serum nor the intratumor 5-FU concentrations were correlated with the tumor response, but that the serum 5-FU concentrations were related to the drug toxicity [6].

5-FU is metabolized inside the tumor cells to fluorinated nucleotides which exert an antitumor action. Its chief mechanism of action, inhibition of DNA synthesis, is time-dependent. Therefore, selectively maintaining a higher intratumor concentration of 5-FU for prolonged periods is thought to be important for the drug sensitivity. We thought it necessary to investigate the drug pharmacokinetics over a period of several days during oral anticancer drug chemotherapy, such as with UFT. The 7-day weekday-on/weekend-off cycle for UFT includes 2 drug-off days, to ensure adequate tolerance and to maintain the daily dose of UFT at 600 mg/day, which is the maximum allowable dose of the drug. For the same weekly dose in a tumor-bearing rat model, the antitumor effect of this schedule was significantly better than that with conventional consecutive daily administration. These results suggested that a higher daily dose of UFT provided a better antitumor effect and that a 2-day drug-off period did not reduce this effect. However, this had not been verified in humans. In the present study, the intratumor concentration of 5-FU 24 h after the final dose of UFT was found to have decreased to approximately half the concentration at 2 h after the final dose, but a concentration of more than 50 ng/g was still maintained until at least 48 h after the final dose. The intratumor concentration of 5-FU required for TS inhibition is, however, not known. It will therefore be necessary to investigate the antitumor efficacy of the weekday-on/weekday-off UFT schedule in a prospective study. The maintenance of the relatively high intratumor 5-FU concentrations could be attributable in part to the trapping of 5-FU by the tumor; this was observed after a single injection of 5-FU. In addition, it has been shown that even greater amounts of 5-FU are trapped with prolonged UFT administration, because uracil, one of its constituents, inhibits DPD, a rate-limiting enzyme of 5-FU degradation in the tumor [18]. Furthermore, in this study the 5-FU concentrations in the normal mucosa did not increase more than approximately one third of the levels in the tumor.

Our results that the serum 5-FU concentrations decreased to very low levels within 24 h after the final dose and that these low levels were maintained until 48 h after the final dose suggest that the two drug-off days in this schedule reduce the adverse reactions to the drug and improve drug tolerance. The results of this study suggest that the weekday-on/weekend-off schedule of oral UFT administration can be used as one arm of a randomized controlled study of adjuvant chemotherapy for colorectal cancer, which necessitates long-term administration.

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