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Short report

A pharmacological pilot study: application of an intermittent schedule of oral uracil and ftorafur (UFT) for hepatocellular carcinoma patients

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Patients with hepatocellular carcinoma (HCC) are highly compromised by failing liver function. To retain good compliance in the administration of uracil and ftorafur (UFT) in such patients, an intermittent schedule for oral administration of UFT was expected to have the same effect as daily continuous use without affecting liver function. A pharmacological pilot study was carried out to confirm the efficacy of this schedule. Sixteen patients with HCC who underwent hepatectomy were given UFT 200 mg b.i.d. for five consecutive days. Blood samples were drawn before the last administration of UFT and at the operation (2 days after the last administration of UFT), and the tumor and adjacent liver tissue were collected. The concentration of ftorafur (FT), 5-fluorouracil (FUra) and uracil (Ura) in serum and liver tissue were measured. Oral administration of UFT 200 mg b.i.d. resulted in a trough level of FT, FUra and Ura in serum of 9.4 μg/ml, 13.3 ng/ml and 64.2 ng/ml, respectively. At the operation, FT and FUra in serum had decreased significantly. However, FUra in tissue was still higher than that in serum, in contrast to the results for FT and Ura. There was no difference in the concentration of FUra between the tumors and adjacent liver tissues. No side effect was noted in any of the patients. These results indicated that an intermittent schedule for the administration of oral UFT is not only tolerable but also effective because a sufficient concentration of FUra in the liver tissue is reached and maintained.

Key words: Hepatocellular carcinoma, pharmacokinetics, UFT.

Introduction

Recently, through progress in diagnostic techniques, HCC has become detectable in its early phase.[1,2] The number of resections of small tumors has increased, but recurrence rates are still high after operation.[1,3,4] Although the majority of recurrences occur in the remnant livers, extra-hepatic metastases were also found in a study of hepatectomized cases.[4] This indicates that HCC had already developed occult metastases or micrometastases at the time of diagnosis. Furthermore, multiple occurrences should be considered because of the high potential of tumorigenicity of a liver compromised by chronic viral infections.[5] In these cases, not only the residual liver but the foci of extra-hepatic micrometastases should be targeted. This indicates that systemic chemotherapy should be given postoperatively.

Oral UFT (Taiho Pharmaceutical Co. Ltd, Tokyo, Japan) is a combination of uracil (Ura) and ftorafur (FT) in a 4:1 molar ratio. Ura inhibits competitively dihydropyrimidine dehydrogenase (DPD), the rate limiting enzyme in 5-fluorouracil (FUra) catabolism.[6] FT is metabolized to FUra in the liver.[7,8] Co-administration of Ura increased the intracellular level of FUra and enhanced the antitumor activity of FT in rodents.[9] However, because the majority of HCC patients have liver cirrhosis as a complication, there is a suspicion that continuous administration of oral UFT adversely affects remnant liver function.[10] Therefore careful attention must be paid to the permissible schedule for the administration of a drug.

We designed an intermittent schedule for oral administration of UFT, with 2 days of rest after 5 days of administration to allow for wash-out of the drugs. This pilot study was performed to confirm if this administrative design was valid.

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Patients and methods

Sixteen patients with HCC who underwent hepatectomy in our department between December 1993 and May 1995 were enrolled into this study after giving informed consent. The patients consisted of 12 males and four females ranging from 19 to 71 years of age, with an average age of 56 years. The patients were given UFT 200 mg b.i.d. (FT equivalent) for five consecutive days. The hepatic resections were performed 2 days after the last administration of UFT.

To determine the trough levels, blood was drawn before the last administration of UFT and again at the operation. The blood samples were centrifuged and serum was stored at −80°C until analysis. The serum concentration of FT was determined with HPLC, FUra as FT's metabolite and Ura concentrations were determined with gas chromatography/mass spectroscopy. The tumor and adjacent tissue were collected from the hepatectomy specimen, and the concentrations of the drugs were determined by the same methods as described above. The determinations were performed according to the method described by Marunaka *et al.*[11] The clearance of FT was calculated by the formula: (trough level − level after rest period)/trough level.

The staging of the patients and histopathological classification of the tumor were performed according to the classification of the Liver Cancer Study Group of Japan.[12]

Paired *t*-test was used for the statistical analysis.

Results

Six patients were stage II, five were stage IVA and one was stage IVB. Six patients were HBsAg positive and eight were HCV antibody positive. Histological cirrhoses of the liver were observed in four cases (25%). Seven patients were treated preoperatively with arterial infusion of lipiodol and anticancer drugs. Histopathological differentiation of tumors showed that 12 (75%) were moderately differentiated HCC. The average tumor size was 5.4 cm. Capsular formation was found in 12 cases (75%). The average indocyanine excretion rate in 15 min (ICG R_{15}) was 13.9% (Table 1).

The patients were given a daily dose of 254 mg/m^2 of UFT (range 224.4–300.7). Oral administration of UFT 200 mg b.i.d. for 5 days resulted in a trough level of FT, FUra and Ura in serum of 9.4 μg/ml (range 4.0–17.8), 13.3 ng/ml (range 4.4–34.8) and 64.2 ng/ml (range 17.2–248.9), respectively. At the operation, blood and the tissue samples were collected at 32–47 h (mean 42.8 h) after completion of administration of UFT. During the 2 days rest, the concentration of FUra in serum decreased to 3.9 ng/ml, close to the lowest measurable level (1.0 ng/ml) (Figure 1). There was no correlation between the function of liver (ICG R_{15}) or kidney (Ccr) and the clearance of FT (Figure 2).

Three patients were excluded from the determination of drug concentrations because of the small tumor specimens. More than 20 times higher concentrations of FUra were found in the tumor and

Table 1. Backgrounds of the patients

Stage (TNM)		Edmondson Steiner	I	4
I	2	classification	II	8
II	6		III	1
III	2		IV	1
IV-A	5	Fc	+	12
IV-B	1			
HBs antigen				4
positive	6			
negative	10	tumor size (mm)		54 ± 40 (10–160)
HCV antibody				
positive	8	ICG R_{15} (%)		13.9 ± 4.3 (5.5–21.5)
negative	8			
Liver cirrhosis		albumin (g/dl)		3.8 ± 0.5 (3.0–4.2)
yes	4	bilirubin (mg/dl)		0.7 ± 0.2 (0.3–1.2)
no	12			
Prior lipiodol		GOT (U/l)		78.9 ± 72.3 (15–308)
chemotherapy		GOT (U/l)		88.1 ± 96.0 (20–404)
yes	7	platelet ($\times 10^4$ mm^{-3})		15.6 ± 6.0 (3.6–25.3)
no	9	prothrombin time (%)		91.0 ± 9.0 (78.2–115.3)

Mean ± SD (range).

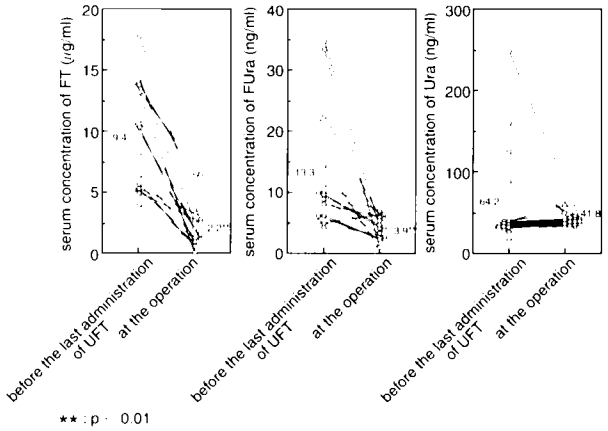

Figure 1. Changes of serum concentrations of drugs before the last administration of UFT and at the operation.

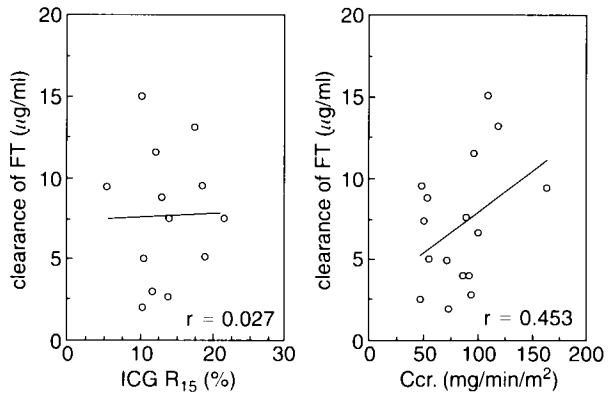

Figure 2. Correlation between the function of liver or kidney and the clearance of FT.

adjacent liver tissue than in the serum. In contrast to that of FUra, the concentrations of FT and Ura in the tissues were about equal to that in the serum. The tissue uptake of FT was not correlated with the degree of the liver cirrhosis, the volume of the tumor or any other factor (Figure 3).

No side effect was noted in any of the patients.

Discussion

Most of the patients with HCC experienced hepatic relapse or developed metastasis within a few years postoperatively.[1,13] This may be caused by circulating cancer cells in HCC patients.[14] For this reason, various modes of adjuvant therapies were given postoperatively,[15,16] including oral administration of UFT.[10] UFT is a combination of the drugs Ura and

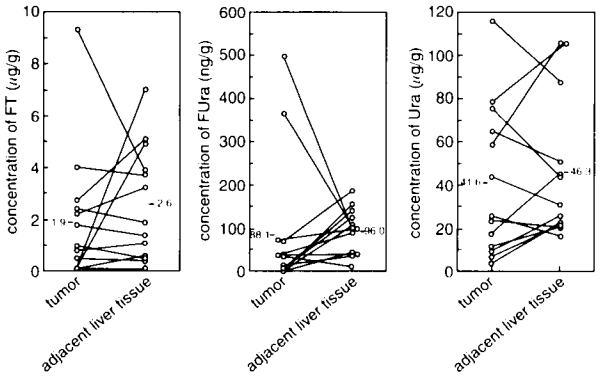

Figure 3. Concentrations of drugs in the tumor and adjacent liver tissue.

FT, and is the only approved oral drug for the treatment of patients with HCC in Japan.[5] UFT for HCC patients has been almost exclusively used as an adjuvant following hepatectomy, chemoembolization[10] or ethanol injection. One of the problems in oral anticancer adjuvant drug therapy is that patients with HCC are frequently compromised by cirrhosis of the liver.[1,2] FT is metabolized to FUra in the liver.[7,8] Therefore, there is a suspicion that continuous administration of oral UFT adversely affects the function of the remaining liver. Furthermore, poor liver function in HCC patients affects the excretion of the drugs. The present study was conducted to investigate the adequacy of an intermittent schedule for oral administration of UFT in patients with HCC. We have previously reported a higher concentration of FUra in tumor tissue than in non-cancerous liver tissue in patients with HCC compromised by cirrhosis.[17] Nevertheless, the time period required to achieve an adequate drug level was still not clear. The present study confirmed an adequate concentration of FUra in the liver tumor tissue 43 h after the final administration of UFT.

There was no correlation between the clearance of FT and liver function or any other factors of the liver. This means that the serum level of FT was not influenced by the liver function. Ccr showed a slight correlation with the serum concentration of FT, suggesting poor clearance of FT in patients with renal dysfunction. There was no clinical side effect nor any postoperative liver failure. These results of an intermittent schedule of administration of oral UFT gave a long-lasting adequate concentration of FUra without affecting the remnant liver function. Nevertheless, the concentrations of drugs in the tumor tissue and in the non-cancerous liver tissue were different in each case. Further study is neces-

sary to elucidate whether this intermittent schedule of oral UFT administration in HCC patients is tolerable in all patients who have various degrees of liver disorders.

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