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Clinical paper

A crossover study of oral administration of UFT in chronic liver disease: comparison of continuous and intermittent schedules

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This study was aimed at evaluating the tolerance to an intermittently administered oral UFT for hepatocellular carcinoma (HCC) with chronic liver disease (CLD). Ten patients who had received curative therapy for HCC with CLD (Child's classification A or B) were randomly assigned either an intermittent schedule (IS), oral administration of UFT (130 mg/m^2/b.i.d.) with 2 days rest a week, or a continuous schedule (CS), consecutive administration of UFT with the same dose. On day 12, the serum concentration of 5-fluorouracil (5-FU) was measured. After 2 weeks rest, the patients were switched to the other schedule for 10 weeks and the concentration of 5-FU was measured on day 12. The median values of the area under the curve (AUC) and maximum concentration (C_{max}) of 5-FU in IS and CS were 187.7 and 263.2 ng/ml/h, 57.1 and 93.0 ng/ml, respectively. Both the AUC and C_{max} for IS were significantly lower than those for CS. One IS patient had tolerable diarrhea, while three of the CS patients had intolerable nausea and one had hemorrhagic gastritis. IS seemed to be a suitable measure for CLD. [© 1998 Lippicott-Raven Publishers.]

Key words: Chronic liver disease, continuous administration, crossover trial, hepatocellular carcinoma, intermittent administration, UFT.

Introduction

Recent advances in the treatment of hepatocellular carcinoma (HCC) have provided useful therapeutic options, such as percutaneous ethanol injection, transcatheter arterial embolization, microwave coagulation therapy, intra-arterial infusion chemotherapy and radioimmunotherapy.[1-8] The prognosis for HCC remains poor, however, because of its frequent recurrence.[9] The multicentric carcinogenesis of HCC and tumor spread via the portal vein are reportedly related to its recurrence, resulting in a low survival rate.[10] Extrahepatic metastases were also found in a study of hepatectomized cases.[11] This fact suggests that HCC had already developed systemic micrometastases at the time of diagnosis. Malignant tumors were reported to be susceptible to drug-induced cure when they were in an early stage of development.[12] Effective adjuvant measures against the recurrence of HCC are therefore necessary in order to achieve a good prognosis.

UFT is an oral anticancer agent composed of uracil and ftorafur [precursor of 5-fluorouracil (5-FU)] at a molar ratio of 4:1. It has been used extensively over the past decade.[13-18] Recently, UFT has been developed in Western countries.[19] Oral administration of UFT achieves a comparable area under the curve (AUC) to 5-FU administered by protracted i.v. infusions.[20]

UFT was reported to prevent hepatocarcinogenesis[21] and to inhibit the progress of micrometastasis.[22] Patients with HCC complicated by chronic liver disease (CLD) reportedly suffered, however, from adverse reactions such as gastrointestinal symptoms and hepatic encephalopathy due to UFT.[23,24] A standard schedule has not yet been established for HCC patients with CLD. We designed the schedule of UFT administration with 2 days rest each week to promote good tolerance for patients with HCC. The aim of this study was to establish the optimal administration schedule for UFT through a crossover trial, in which the serum concentrations of 5-FU, ftorafur and uracil were serially determined in order to evaluate the pharmacokinetics and tolerability.

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Patients and methods

Patients

Ten HCC patients with CLD related to hepatitis C virus were enrolled in this study between September 1995 and October 1996. All the patients were histologically confirmed as having HCC and their informed consent was obtained. They had previously undergone successful therapy for HCC by hepatic resection ($n=8$) or microwave coagulation ($n=2$). The eligible patients had the following conditions: no history of treatment for HCC within 6 weeks; age of 18–75 years; performance status of ≤ 2 according to the Eastern Cooperative Oncology Group criteria; requisite laboratory criteria as defined by total bilirubin of <2.0 mg/dl, serum albumin of >3.0 g/dl, a leukocyte count of $\leq 3500/\mu l$ and platelet count of $\geq 70000/\mu l$, and a

Table 1. Background factors of the patients

Case	Age (years)	Gender	Total bilirubin (mg/dl)	Albumin (mg/dl)	Initial therapy
1	46	male	0.7	3.9	hepatectomy
2	70	male	0.5	3.5	hepatectomy
3	61	male	0.3	4.2	hepatectomy
4	57	female	0.7	4.1	MCT
5	63	male	1.2	3.4	hepatectomy
6	64	male	1.4	3.4	hepatectomy
7	63	male	0.6	3.8	hepatectomy
8	63	male	0.5	4.1	MCT
9	61	male	1.7	3.7	hepatectomy
10	61	male	1.5	4.2	hepatectomy
	62 (46–70)	male: 9 female: 1	0.7 (0.3–1.7)	3.8 (3.4–4.2)	hepatectomy: 8 MCT: 2

MCT, microwave coagulation therapy.
Data are shown as median (range).

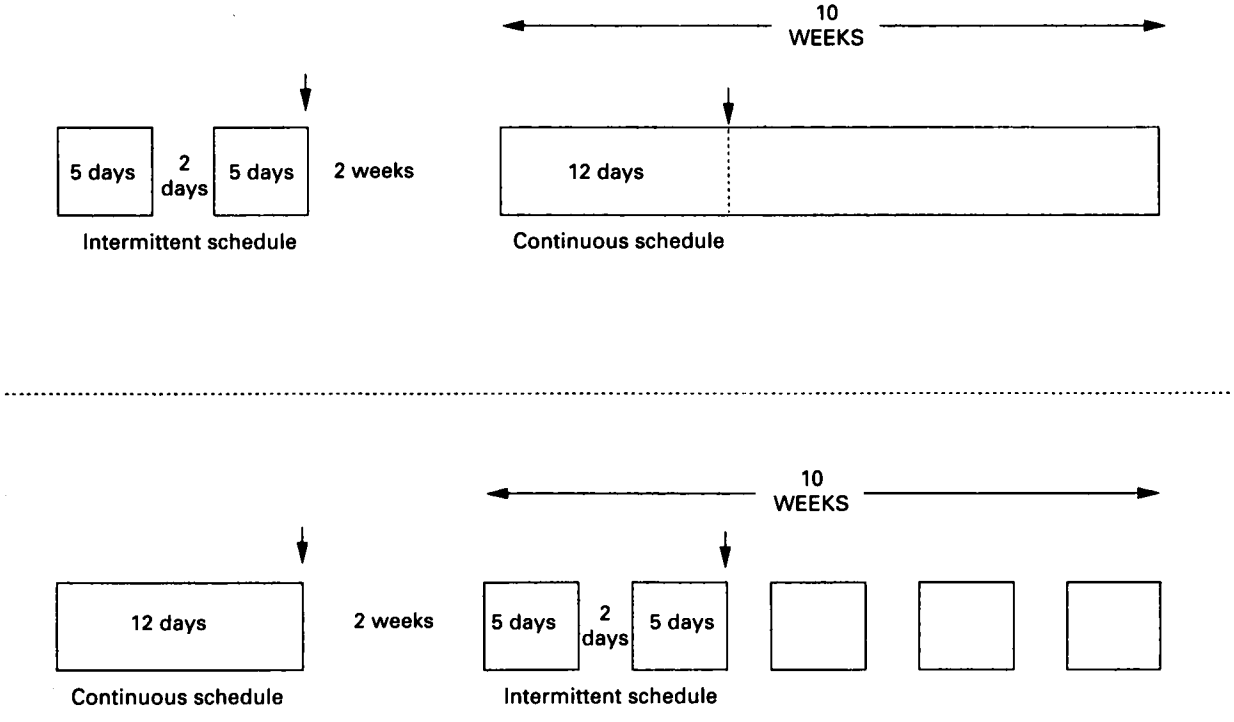

Figure 1. A schematic presentation of the schedule of this study. IS: intermittent schedule; CS: continuous schedule; □: oral administration of UFT; ↓: blood sampling.

serum creatinine level of $\leqslant 1.5$ mg/dl. During the study period, no patient received any other anticancer therapy, immune therapy or radiation. The patient profiles are shown in Table 1.

Study protocol

The schedules of oral administration of UFT are schematically shown in Figure 1. UFT was supplied by Taiho Pharmaceutical (Tokyo, Japan) in the form of 100 mg capsules (referring to 100 mg of ftorafur). Aota *et al.* reported that the concentrations of 5-FU in HCC tissue were significantly higher in patients who received oral UFT at 400 mg/day than in those who received 300 mg/day.[25] The doses of UFT used in this study were therefore determined by the following equation: dose of UFT = (400 mg/1.54) × patient's body surface area, where 1.54 is the standard body surface area of Japanese. Accordingly, the dose of UFT was set as 260 (400/1.54 = 260) mg/m^2/day and the patients were to receive 130 mg/m^2 twice a day. The calculated UFT dose was rounded off to the nearest 100 mg.[16] The patients were randomized to the following regimens: (i) intermittent schedule (IS), oral administration of UFT (260 mg/m^2/day) with 2 days rest per week, or (ii) continuous schedule (CS), consecutive administration of the same dose of UFT. On day 12, the serum concentrations of 5-FU, ftorafur and uracil were measured. After 2 weeks rest, each patient was to be transferred to the other schedule for 10 weeks, and the concentrations of 5-FU, ftorafur and uracil were determined on day 12. The 2 day rest period was set on the basis of Hobara's report that the serum concentrations of ftorafur administered to cirrhotic patients were reduced to 1/16 with 2 days of rest.[26] It was also influenced by Sadahiro's study which showed that setting a 2 day rest period in the administration of UFT decreased adverse reactions in Yoshida sarcoma bearing rats.[27] The concentrations of 5-FU, ftorafur and uracil were measured by high-pressure liquid chromatography or GLC-mass spectrometry.[28] On day 12, blood samples were collected 30 min before the administration of UFT, and 1, 2, 3 and 6 h after administration in order to measure the area under the curve ($AUC_{0-6\ h}$). The patients were kept under careful observation during the study for their general condition and drug tolerance.

Statistical analysis

Data were expressed as the median (range). The Wilcoxon signed-rank test, Mann-Whitney *U*-test and Fisher's exact probability test were used as appropriate. A statistically significant difference was confirmed at $p < 0.05$.

Results

No patients showed recurrence of HCC during the study period. Crossover determinations were performed in eight patients. Two patients were unable to undergo the crossover trial because case 9 was complicated by hemorrhagic gastritis 5 days after the CS period and case 10 had not had the blood drawn on day 12 in CS. Consequently, nine CS and IS cases were included among the enrolled patients.

Figures 2, 3 and 4 show comparisons of the levels of the AUC, maximum concentration (C_{max}) and trough of 5-FU, ftorafur and uracil in the CS and IS groups for the eight patients who successfully underwent the crossover study. The AUC and C_{max} of 5-FU, and the AUC of ftorafur were significantly lower in the IS group than in the CS group.

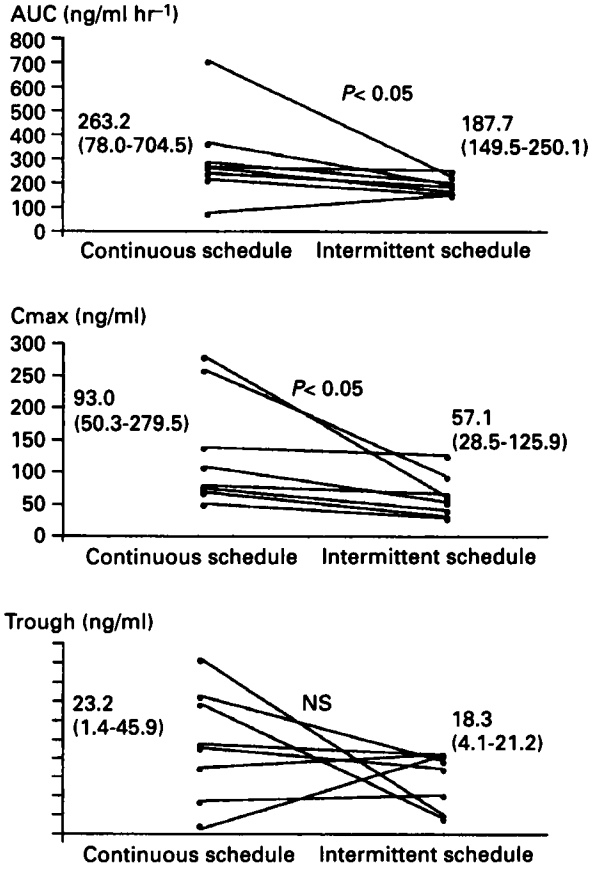

Figure 2. Comparisons of the levels of the AUC, C_{max} and trough of 5-FU. The AUC and C_{max} were significantly lower in the IS compared to those in the CS. NS: not significant.

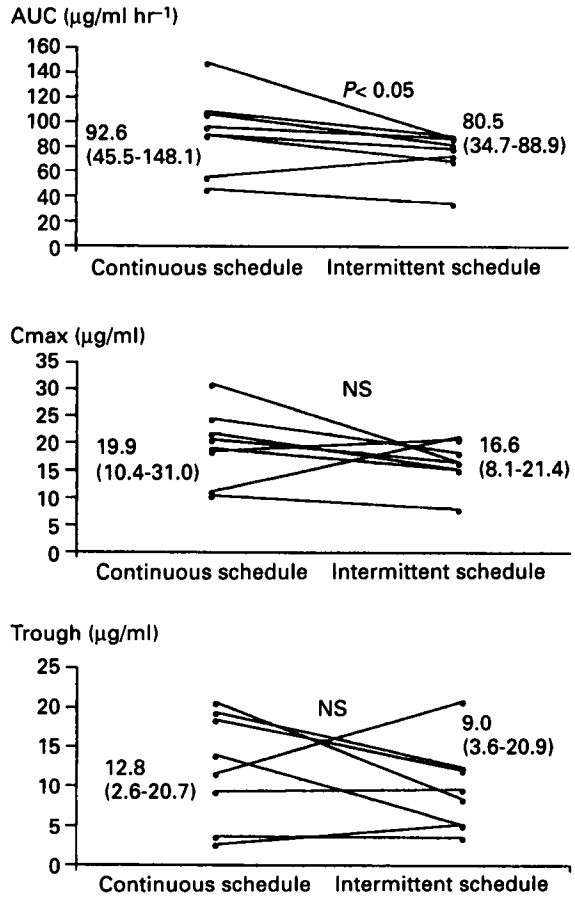

Figure 3. Comparisons of the levels of the AUC, C_{max} and trough of ftorafur. The AUC was significantly lower in the IS compared to that in the CS. NS: not significant.

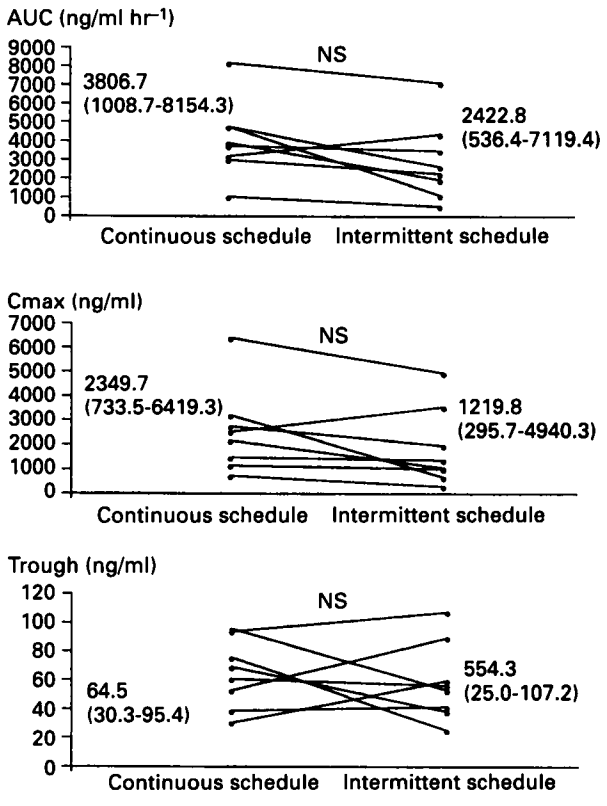

Figure 4. Comparisons of the levels of the AUC, C_{max} and trough of uracil. NS: not significant.

Adverse reactions

The enrolled patients were divided into toxic (patients with adverse reaction) and non-toxic (patients without adverse reaction) groups. As shown in Table 2, the toxic group had a higher AUC of 5-FU as compared with the non-toxic group. CS patients were observed more frequently in the toxic group than in the non-toxic group. However, no statistical differences between the two groups were found. One patient in the IS group had tolerable diarrhea, while three of the patients in the CS group had intolerable nausea and one had hemorrhagic gastritis.

Discussion

This study demonstrated that the present pharmacokinetic profiles of the IS patients were similar to those of the patients without CLD;[16] Meropol *et al.* reported that in patients with several advanced cancers without CLD treated with oral UFT (350 mg/m^2/day), the AUC of 5-FU was 182 ng/ml/h (AUC in the present study was 189.2 ng/ml/h). The IS patients tolerated this trial, while the CS group was associated with intolerable adverse reaction. Intermittent administration of UFT may therefore be an adequate treatment for patients with CLD. Une *et al.* reported that oral administration of UFT (200 mg b.i.d.) 5 days a week was tolerable for patients with HCC treated by hepatectomy.[29] They also reported that sufficient concentrations of 5-FU in the tumor tissues were obtained in the pilot study.

In case 9, who developed hemorrhagic gastritis, the level of C_{max} of 5-FU was 193.1 ng/ml. This value was almost two times the median concentration for CS patients. Thus, monitoring of the levels of 5-FU may be of help in avoiding adverse reactions. Moreover, the patient had a past history of gastric ulcer, which may affect the emergence of the complication. A prophylactic gastric medication may be necessary in such a case.

Table 2. Comparisons of the factors between the toxic and non-toxic groups

Factor	Toxic group	Non-toxic group	*p*
AUC of 5-FU (ng/ml/h) [median (range)]	262.9 (213.2–298.8)	198.4 (78.0–704.5)	NS[a]
Type of schedule [number (%)]			
intermittent	1 (20)	8 (61)	NS[b]
continuous	4 (80)	5 (39)	

Toxic group: patients with adverse reaction.
Non-toxic group: patients without adverse reaction.
[a]Mann–Whitney *U*-test.
[b]Fisher's exact probability.

Ikeda *et al.* reported that oral administration of UFT (200 mg/body/day) as adjuvant chemotherapy did not enhance the survival time of patients with HCC who underwent transcatheter arterial embolization.[24] The Tokyo Liver Cancer Study Group conducted an unsatisfactory phase II study of oral UFT (400 mg/m^2/day) in patients with HCC and showed a high incidence of adverse gastrointestinal reactions.[23] In the present trial, the hepatic function was relatively well preserved (the median levels of serum bilirubin and albumin were 0.7 and 3.8 mg/dl, respectively) in patients who tolerated surgical treatment by hepatic resection and microwave coagulation. Patients without severe CLD may therefore be good candidates for oral administration of UFT.

As shown by the comparisons of the C_{max} and trough levels of 5-FU and ftorafur, the concentrations of ftorafur were more constant over the dosing interval than the concentrations of 5-FU. These data may indicate the suitability of ftorafur as a prodrug for 5-FU.

Conclusion

Oral administration of UFT (260 mg/m^2/day) 5 days a week seemed to be a suitable method for patients with CLD. Further investigation is thought to be necessary to elucidate whether this schedule can be tolerated over long periods and can reduce the recurrence of HCC, achieving a good prognosis for HCC.

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References

1. Shiina S, Tagawa K, Unuma T, Terano A. Percutaneous ethanol injection therapy for treatment of hepatocellular carcinoma. *Am J Rheumatol* 1990; **154**: 947-51.
2. Livarghi T, Festi D, Monti F, Salmi A, Vettori C. US-guided percutaneous ethanol injection of small hepatic and abdominal tumors. *Radiology* 1986; **161**: 309-12.
3. Yamada R, Sato M, Kawabata M, Nakatsuka H, Nakamura K, Takashima S. Hepatic artery embolization in 120 patients with unresectable hepatoma. *Radiology* 1983; **148**: 397-401.
4. Yamashita F, Tanaka M, Satomura S, Tanikawa K. Monitoring of lectin-reactive α-fetoproteins in patients with hepatocellular carcinoma treated using transcatheter arterial embolization. *Eur J Gastroenterol Hepatol* 1995; **7**: 627-33.
5. Seki T, Wakabayashi M, Nakarawa T, *et al.* Ultrasonically guided percutaneous microwave coagulation therapy for small hepatocellular carcinoma. *Cancer* 1994; **74**: 817-25.
6. Tang ZY, Liu KD, Bao YM, *et al.* Radioimmunotherapy in the multimodality treatment of hepatocellular carcinoma with reference to second-look resection. *Cancer* 1990; **65**: 211-5.
7. Ando E, Yamashita F, Tanaka M, Tanikawa K. A novel chemotherapy for advanced hepatocellular carcinoma with tumor thrombosis of the main trunk of the portal vein. *Cancer* 1997; **79**: 1890-6.
8. Iwamiya T, Sawada S, Ohta Y. Repeated arterial infusion chemotherapy for inoperable hepatocellular carcinoma using an implantable drug delivery system. *Cancer Chemother Pharmacol* 1994; **33** (suppl): S134-8.
9. Okuda K, Ohtsuki T, Obata H, *et al.* Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. *Cancer* 1985; **56**: 918-28.
10. Kojiro M, Nakashima T. Pathology of hepatocellular carcinoma. In: Okuda K, Ishak KG, eds. *Neoplasms of the liver*. Tokyo: Springer 1987: 87-104.
11. Nakashima T, Okuda K, Kojiro M, *et al.* Pathology of hepatocellular carcinoma in Japan. 232 consecutive cases autopsied in ten years. *Cancer* 1983; **51**: 863-77.
12. Goldie JH, Coldman AJ. Quantitative model for multiple levels of drug resistance in clinical tumors. *Cancer Treat Rep* 1983; **67**: 923-31.

13. Daniels M, Diaz-Rubio E, Guillem V, *et al.* Phase II trial of UFT activity in pretreated breast cancer patients. *Jpn J Clin Oncol* 1993; **23**: 363–5.
14. Gonzalez-Baron M, Ordonez FA, Colmenarijo A, *et al.* Phase I study of UFT plus leucovorin in advanced colorectal cancer: a double modulation proposal. *Anticancer Res* 1993; **13**: 759–62.
15. Muggia FM, Jeffers S, Leichman CG, *et al.* Potential for uracil + ftorafur (UFT) to mimic protracted infusions of 5-fluorouracil (FU). *Proc Am Soc Clin Oncol* 1992; **11**: 135 (abstr 362).
16. Meropol NJ, Rustum YM, Petrelli NJ, *et al.* A phase I and pharmacokinetic study of oral uracil, ftorafur, and leucovorin in patients with advanced cancer. *Cancer Chemother Pharmacol* 1996; **37**: 581–6.
17. Fujii S, Kitano S, Ikenaka K, Shirasaka 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.
18. Kimura S, Suga S, Shimaji T, *et al.* Clinical basis of chemotherapy for gastric cancer with uracil and 1-(2-tetrahydrofuryl)-5-flourouracil. *Gastroenterol Jpn* 1980; **15**: 116–24.
19. Mani S. An ongoing phase II study. UFT plus leucovorin in advanced hepatobiliary tumors and pancreatic adenocarcinomas. *Oncology* 1997; **11**: 124–7 (suppl 10).
20. Pazdur R, Convington WP, Brown NS, Lassere Y, Canton ED, Ho DH. Comparative steady state pharmacokinetics of oral UFT versus protracted intravenous 5-fluorouracil (FU). *Proc Am Soc Clin Oncol* 1996; **15**: 474 (abstr 1498).
21. Sakamoto S, Hirai H, Taga H, *et al.* Inhibition by 1-(2-tetrahydrofuryl)-5-fluorouracil in combination with uracil and hepatocarcinogenesis induced by 3'-methyl-4-dimethylaminoazobenzene in rats. *Anticancer Res* 1991; **11**: 561–6.
22. Kurebayashi J, Nukatsuka M, Fujioka A, *et al.* Postsurgical oral administration of uracil and tegafur inhibits progression of micrometastasis of human breast cancer cells in nude mice. *Clin Cancer Res* 1997; **3**: 653–9.
23. Tokyo Liver Cancer Chemotherapy Study Group. Phase II study of co-administration of uracil and tegafur (UFT) in hepatocellular carcinoma. *Jpn J Clin Oncol* 1985; **15**: 559–62.
24. Ikeda K, Saitoh S, Koida I, *et al.* A prospective randomized evaluation of a compound of tegafur and uracil as an adjuvant chemotherapy for hepatocellular carcinoma treated with transcatheter arterial chemoembolization. *Am J Clin Oncol* 1995; **18**: 204–10.
25. Aota M, Nakayama S, Yokomine H, Jinno K, Daitoh N. Serum and tissue concentrations of UFT in patients with lung cancer. *Jpn J Cancer Chemother* 1986; **13**: 3046–55.
26. Hobara N, Watanabe A, Nagashima H. Pharmacokinetic study on the impaired metabolisms of drugs in patients with liver injury. *Saishin Igaku* 1981; **36**: 364–70 (in Japanese).
27. Sadahiro S, Mukai M, Tokunaga N, Tajima T, Mitomi T. Preliminary study on the new optimal dosage schedule for oral UFT. *Proc Am Soc Clin Oncol* 1997; **16**: 207a (abstr 726).
28. Marunaka T, Umeno Y, Yoshida K, Nagamachi M, Minami Y, Fujii S. High-Pressure liquid chromatographic determination of ftorafur [1-(tetrahydro-2-furanyl)-5-fluorouracil] and GLC-mass spectrometric determination of 5-fluorouracil and uracil in biological materials after oral administration of uracil plus ftorafur. *J Pharm Sci* 1980; **69**: 209–13.
29. Une Y, Kamiyama T, Nishibe M, *et al.* A pharmacological pilot study: application of an intermittent schedule of oral uracil and ftorafur (UFT) for hepatocellular carcinoma patients. *Anti-Cancer Drugs* 1996; **7**: 881–4.

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