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ORIGINAL ARTICLE

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Phase I and pharmacokinetic study of 5-fluorouracil administered by 5-day continuous infusion in patients with hepatocellular carcinoma

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Abstract *Purpose:* In this study the maximum tolerated dose of 5-fluorouracil administered by 5-day (120-h) continuous infusion every 4 weeks was investigated and the pharmacokinetics in patients with hepatocellular carcinoma were evaluated. *Methods:* Patients with hepatocellular carcinoma no longer amenable to established forms of treatment were eligible for the study. The starting dose of 5-fluorouracil was 300 mg/m^2 per day and doses were escalated in 50 mg/m^2 per day increments in successive cohorts of three new patients if tolerated. Pharmacokinetic studies were performed at the time of the first course of therapy. *Results:* Enrolled in the study were 20 patients. The maximum tolerated dose was 500 mg/m^2 per day and the dose-limiting toxicity was stomatitis. Other toxicities were mild and well tolerated. Age, gender and associated liver cirrhosis were significant factors influencing 5-fluorouracil clearance. With regard to biochemical parameters, serum alanine aminotransferase and cholesterol levels were correlated with 5-fluorouracil clearance. *Conclusions:* The maximum tolerated dose for 5-day continuous infusion of 5-fluorouracil in hepatocellular carcinoma patients was 500 mg/m^2 per day. The recommended dose for phase II studies using this schedule is 450 mg/m^2 per day. Furthermore, the pharmacokinetic data obtained in this study may be useful in determining chemotherapy dosage adjustments for reduction of toxicity.

Keywords Phase I study · Pharmacokinetics · 5-Fluorouracil · Hepatocellular carcinoma

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in Japan. Recently, screening of high-risk populations for HCC using ultrasonography and serum alpha-fetoprotein levels has increased the number of candidates for effective local treatments such as surgery and percutaneous ethanol injection [18, 24]. However, the overall results of these treatment methods are still unsatisfactory because of the high recurrence rate [14, 17]. Although chemotherapy has been of limited value in the treatment of HCC [15, 16, 28], identification of effective systemic chemotherapy is needed to improve the prognosis of patients with HCC.

5-Fluorouracil (5-FU), first synthesized 40 years ago, is still one of the most widely used agents for digestive cancers including HCC. Recently, in an attempt to increase treatment efficacy, 5-FU has been administered by continuous infusion, often combined with other agents such as cisplatin [8, 11, 25]. However, its optimal dose and schedule have not been fully determined in patients with HCC. Furthermore, although 5-FU is extensively catabolized by the liver, the question as to whether disturbed liver function influences 5-FU pharmacokinetics remains unresolved [6, 22, 29]. As patients with HCC usually have various degrees of liver impairment because of liver replacement by tumor and associated liver disease, an assessment of 5-FU pharmacokinetics in such patients might be informative. We therefore designed the phase I and pharmacokinetic study of continuous infusion of 5-FU to determine the maximum tolerated dose (MTD) and to evaluate the pharmacokinetics of 5-FU in patients with HCC.

Patients and methods

Patients

Only patients with HCC no longer amenable to established forms of treatment were candidates for this study. Eligibility

criteria included: (1) 20–74 years of age; (2) Eastern Cooperative Oncology Group performance status of 0–2 [19]; (3) recovery from the toxic effects of previous therapy; (4) adequate organ function defined as white blood cell count $\geq 3000/mm^3$, platelet count $\geq 50{,}000/mm^3$, hemoglobin ≥ 10 g/dl, normal serum creatinine, serum total bilirubin ≤ 3.0 mg/dl, serum albumin ≥ 2.5 g/dl, and serum transaminases ≤ 200 IU/l (serum aspartate transaminase, AST; serum alanine transaminase, ALT). Patients with hepatic coma and severe ascites were excluded. Written informed consent was obtained from all patients prior to study entry.

Treatment

Patients received continuous infusion of 5-FU for 5 consecutive days (120 h). The starting dose of 5-FU was 300 mg/m^2 per day, and doses were escalated in 50 mg/m^2 per day increments in successive cohorts. At least three patients were treated at each dose level. Three additional patients were entered at the same dose level if dose-limiting toxicity (DLT) was observed in one or two of the first three patients. The MTD was defined as the dose level at which three of three to six patients experienced a DLT. DLT was defined as grade 3 or greater nonhematological toxicity, or grade 4 leukopenia, neutropenia or thrombocytopenia. Treatment was repeated at 4-week intervals until disease progression or the appearance of unacceptable toxicity.

Physical examinations and routine laboratory studies were performed weekly. Tumor response was assessed every 4 weeks. Response and toxicity were evaluated according to the World Health Organization guidelines [26].

Pharmacokinetics

Blood samples for the pharmacokinetic evaluation of 5-FU were collected from patients at the time of their first course of therapy. Heparinized blood samples were obtained before infusion, at 0.5, 2, 6, 24, 48, 72 and 96 h after the initiation of infusion, at the end of infusion (120 h), and at 0.5, 2 and 6 h after the end of infusion. The blood samples were kept on ice, then centrifuged for 15 min at 3000 rpm, and the plasma was separated and stored below –70°C until analysis. Concentrations of 5-FU in plasma were determined by high-performance liquid chromatography [4]. An aliquot of plasma (200 µl) was pipetted into a 15-ml glass centrifuge tube. To the tube were added 50 µl phosphate buffer (0.5 *M*, pH 8.0), 5-chlorouracil as internal standard, and 7 ml ethyl acetate. The tube was shaken vigorously for 30 min. After centrifugation, the supernatant was transferred to a clean glass tube, and concentrated in vacuo. The resulting residue was dissolved in the mobile phase (ethyl acetate/*n*-hexane/formic acid/water 50:50:0.5:0.3). An aliquot of this solution was injected into the high-performance liquid chromatograph. The column used was packed with silica gel (Develosil 60-3, 4.6×100 mm; Nomura Chemicals, Seto, Aichi, Japan). The flow rate of the mobile phase was 0.9 ml/min, and the eluate was monitored at 264 nm. The quantitation limit of 5-FU was 5 ng/ml. The intra- and interday coefficients of variation for 5-FU were $< 10\%$. The 5-FU area under the curve (AUC) was determined by the logarithmic trapezoidal method [27]. 5-FU clearance was calculated by dividing the total dose by the AUC.

The level of correlation between 5-FU dose and AUC or clearance was assessed by simple linear regression analysis. The Mann-Whitney *U*-test was used to identify patient characteristics significantly influencing 5-FU clearance. The relationships between various biochemical parameters and 5-FU clearance were evaluated by nonparametric Spearman's rank analysis. *P*-values less than 0.05 were considered to indicate significance.

This trial was performed after receiving the approval of the investigational review board of our hospital.

Results

Patients

Between June 1991 and February 1994 20 patients with HCC were entered into this study at the National Cancer Center Hospital, Japan. All patients were evaluable for both toxicity and response. The pharmacokinetic study was performed in 19 patients because one patient refused pharmacokinetics. The 20 patients received a total of 28 courses, with a median of 1 course. We planned to continue 5-FU therapy when the tumor response was not progressive disease (i.e. complete response, partial response, and stable disease). However, 14 of 20 the patients unfortunately showed progressive disease 4 weeks after initiation of therapy, and in these patients 5-FU therapy was abandoned. In addition, in two patients treatment was abandoned due to grade 4 stomatitis. The patient characteristics are listed in Table 1. Abnormal liver function was seen in all patients, and liver cirrhosis was histologically and/or clinically diagnosed in 12 patients. Of the 20 patients, 18 had a history of prior treatment such as hepatic resection, transcatheter arterial

Table 1 Patient characteristics

Age (years)	
Median	59
Range	30–71
Male/female	16/4
Hepatitis B virus surface antigen	2
Hepatitis C virus antibody	12
Alcohol abuse[a]	10
Cirrhosis	12
Ascites	8
Portal vein tumor thrombus	7
Child's classification	
A	5
B	12
C	3
Tumor size (%)	
< 25	6
≥ 25 to < 50	7
≥ 50	7
Extrahepatic metastasis	8
Prior treatment	
Operation	1
Percutaneous ethanol injection	1
Transcatheter arterial embolization/infusion	4
Chemotherapy	12
Bilirubin (mg/dl)	
Median	1.3
First to third quartile	1.1–2.4
Albumin (g/dl)	
Median	3.3
First to third quartile	2.8–3.5
Aspartate transaminase (IU/l)	
Median	82
First to third quartile	63–129
Alanine transaminase (IU/l)	
Median	52
First to third quartile	29–77

[a]Ethanol intake ≥ 80 g/day for ≥ 5 years

Table 2 Toxicity during the first course (WHO toxicity grades)

	5-FU dose (mg/m^2/day)																			
	Grade																			
	300 (n = 3)				350 (n = 3)				400 (n = 3)				450 (n = 6)				500 (n = 5)			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Hematological																				
Leukopenia	1	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	1	0	0	0
Neutropenia	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	1	0	0	0
Anemia	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0
Thrombopenia	1	0	0	0	1	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0
Nonhematological																				
Nausea and vomiting	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0
Diarrhea	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Loss of appetite	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Stomatitis	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	2	2
Skin rash	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Fever	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0

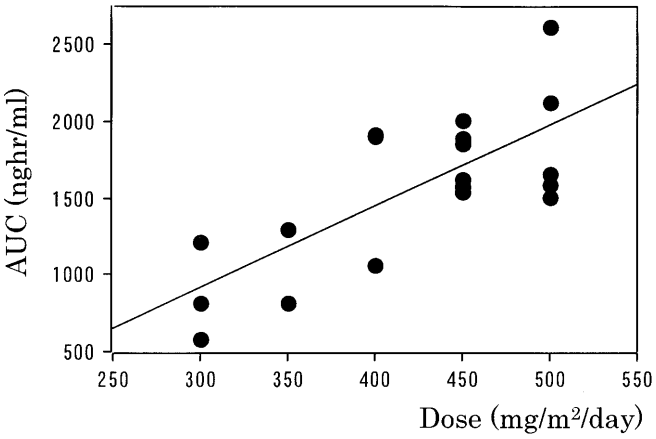

Fig. 1 There was a significant linear relationship between the 5-FU dose and the AUC ($r = 0.74$, $P < 0.01$)

embolization, and chemotherapy, while the remaining 2 had not received any treatment before chemotherapy.

Toxicity

Toxicities are summarized in Table 2. There was no grade 3 or greater toxicity seen in patients at level 3 or lower. However, grade 3 or 4 stomatitis was observed in one of six patients at level 4 (450 mg/m^2 per day), and in four of five patients at level 5 (500 mg/m^2 per day). The MTD was, therefore, judged to be 500 mg/m^2 per day with stomatitis as the DLT. However, it may be more appropriate to conclude that the MTD had been exceeded at 500 mg/m^2 per day, since four of five patients had DLT at this dose. Therefore, the recommended dose for phase II studies using this schedule is considered to be 450 mg/m^2 per day. Other nonhematological toxicities including diarrhea were mild and well tolerated. None of the patients experienced grade 3 or greater hematological toxicity in this study.

Responses and survival

None of the 20 patients achieved an objective tumor response. Six patients showed no change and the remaining 14 showed progressive disease. The median time to progression was 4 weeks (range 4 to 12 weeks). All patients had died by the time of analysis. The median survival time and 1-year survival rate was 12 weeks and 10%, respectively.

Pharmacokinetics

There was a significant linear relationship between the 5-FU dose and AUC ($r = 0.74$, $P < 0.01$; Fig. 1). Conversely, at the doses evaluated, 5-FU clearance was not diminished with increasing doses ($r = 0.04$, $P = 0.85$). Table 3 shows the correlations between patient characteristics and 5-FU clearance. Among seven variables investigated, age, gender and cirrhosis were identified as significant factors influencing 5-FU clearance; older patients (≥60 years), females, and cirrhosis patients showed reduced 5-FU clearance. The results from nonparametric Spearman's rank analysis of various biochemical parameters versus 5-FU clearance are shown in Table 4. Nine variables which were likely to be related to 5-FU clearance were selected. Serum ALT levels ($P = 0.03$) and cholesterol levels ($P = 0.01$) were correlated with 5-FU clearance.

Discussion

Although 5-FU is one of the most commonly used agents in chemotherapy for HCC, its optimal dose schedule has not been fully evaluated. We therefore conducted a phase I study of 5-FU in patients with HCC. We decided to use 5-FU by intravenous continuous infusion, since

Table 3 Relationship between patient characteristics and 5-FU clearance (*NS* not significant)

Variable		No. of patients	5-FU clearance (ml/min/m^2)			*P*-value[a]
			Mean ± SD	Median	Range	
Age (years)	< 60	11	2564 ± 660	2430	1716–3463	0.02
	≥60	8	1868 ± 328	1860	1518–2460	
Gender	Male	15	2407 ± 650	2278	1518–3463	0.05
	Female	4	1761 ± 176	1784	1564–1974	
Cirrhosis	+	11	2005 ± 550	1746	1518–3417	0.03
	–	8	2637 ± 591	2278	1837–3463	
Ascites	+	7	2289 ± 801	2278	1564–3417	NS
	–	12	2261 ± 561	2050	1518–3463	
Child's classification	A	5	2419 ± 532	2228	1716–3463	NS
	B, C	14	2218 ± 684	2164	1518–3417	
Tumor size (%)	< 50	7	2274 ± 696	2278	1518–3463	NS
	≥50	12	2269 ± 640	2250	1518–3417	
Prior chemotherapy	+	11	2455 ± 749	2240	1518–3463	NS
	–	8	2018 ± 364	1974	1518–3417	

[a]Mann-Whitney *U*-test

Table 4 Correlations between biochemical parameters and 5-FU clearance

Parameter	Correlation coefficient (*r*)	*P*-value
Bilirubin	–0.06	0.77
Albumin	0.08	0.72
Aspartate transaminase	–0.4	0.08
Alanine transaminase	–0.5	0.03
Alkaline phosphatase	–0.31	0.18
Lactate dehydrogenase	–0.02	0.92
Cholinesterase	–0.24	0.29
Cholesterol	0.66	0.01
Creatinine	0.2	0.38

continuous infusion of 5-FU is known to induce a response superior to that induced by bolus injection in several malignancies [12].

The MTD of 5-FU administered by 5-day continuous infusion was determined to be 500 mg/m^2 per day with stomatitis as the DLT. However, other nonhematological toxicities including diarrhea were mild, and there was no grade 3 or greater hematological toxicity observed. Since continuous infusion of 5-FU is known to shift the usual limiting toxicity from myelosuppression to stomatitis [11, 12], the toxicities observed were expected. However, the MTD determined was unexpectedly low: the MTD of 500 mg/m^2 per day was approximately 50% that of 5-FU in patients with normal organ function [1, 2, 11, 13]. Since all patients had chronic liver disease, reduced intrinsic hepatic clearance and/or reduced liver blood flow are the most likely explanations for this discrepancy in MTD. However, despite numerous pharmacokinetic studies of 5-FU, the question as to what factors influence 5-FU pharmacokinetics and pharmacodynamics remains unresolved [6, 22, 29]. Therefore, the pharmacokinetic study of 5-FU was performed.

5-FU clearance was not changed with increasing 5-FU doses in the range 300 to 500 mg/m^2, suggesting linear pharmacokinetics of 5-FU. These results are not consistent with the results of some earlier studies, in which 5-FU clearance has been found to be saturable (nonlinear) with increasing 5-FU doses when the drug is administered by intravenous bolus infusion [3, 5, 21]. However, our findings agree with the results of certain other studies. Erlichman et al. [7] have reported that steady-state concentrations of 5-FU increase linearly with dose following continuous administration of 5-FU. Fleming et al. [9] have also reported that 5-FU clearance following continuous infusion does not depend upon the 5-FU dose. Therefore, these results suggest that when 5-FU is administered by continuous infusion, 5-FU clearance is not likely to be influenced by the 5-FU dose within the therapeutic range.

With regard to the relationship between various patient characteristics and 5-FU clearance, age, gender and cirrhosis were found to be significant factors influencing 5-FU clearance. Similar results have been reported concerning the effects of age and gender on the pharmacokinetics of 5-FU. Port et al. [21] have demonstrated that clearance is higher in males than in females by an average of 0.22 l/min, and clearance decreases by 0.072 l/min with every 10-year increase in age. Furthermore, the clinical significance of the pharmacokinetic relationship has been extended by Stein et al. [23], who have shown age and gender to be independent predictors of 5-FU toxicity. They assumed that gender- and age-specific differences in the activity of dihydropyrimidine dehydrogenase (DPD), by which the majority of 5-FU is catabolized, would explain the gender- and age-dependency of 5-FU clearance.

Since the greatest activity of DPD is found in the liver, it is a concern that liver dysfunction may alter the disposition of 5-FU. However, the findings concerning the effects of liver dysfunction on 5-FU pharmacokinetics are controversial. Although the clearance of 5-FU has been shown in several studies to be altered in the presence of liver dysfunction [10], these findings have not been

confirmed in other studies in patients with disturbed liver function [9]. In practice, mild liver dysfunction is not usually considered an indication for 5-FU dose reduction, but some authors have recommended caution in the administration of 5-FU to patients with severe liver dysfunction [22]. Therefore, we performed a pharmacokinetic study of 5-FU in patients with cirrhosis. Patients with cirrhosis had significantly lower 5-FU clearance than those without cirrhosis ($P = 0.03$). In patients with cirrhosis, reduced hepatic clearance of a variety of drugs has been reported [20, 22]. The mechanism of reduced drug clearance in patients with cirrhosis may be due to (1) reduced liver blood flow, (2) impaired ability of the liver to remove the drug from the blood, or (3) the combined effect of these two factors. Although there are no systematic studies of the toxicity of 5-FU in patients with cirrhosis, our findings suggest that caution in selecting 5-FU doses should be exercised when 5-FU is administered to patients with cirrhosis.

Following these results, the level of correlation between biochemical parameters and 5-FU clearance was assessed. Serum ALT and cholesterol levels were found to be correlated with 5-FU clearance. It is known that the increased activity of ALT, a microsomal enzyme of the liver, indicates damage to hepatocytes, and synthesis of serum cholesterol is affected by hepatic reserve. However, it is curious that 5-FU pharmacokinetics were correlated more strongly with serum ALT and cholesterol levels than with bilirubin or albumin levels, since serum albumin and bilirubin levels are known to reflect hepatic reserve more directly. Patient selection bias (serum total bilirubin level ≤ 3.0 mg/dl, serum albumin level ≥ 2.5 g/dl) is one possible explanation for these findings. Further clinical investigation of the relationship between 5-FU pharmacokinetics and liver function tests is desirable to determine 5-FU dosage adjustments to reduce toxicity.

No patients achieved an objective tumor response. Although 12 of the 20 patients had a history of prior chemotherapy, the anticancer activity of 5-FU as a single agent for HCC might be limited. Since the activity of 5-FU has been reported to be potentiated by certain other agents [8, 25], combinations of 5-FU with other agents might be investigated in future trials.

In conclusion, the MTD of 5-FU as a 5-day continuous infusion in HCC patients was estimated to be 500 mg/m^2 per day with stomatitis as the DLT. The recommended dose for phase II studies using this schedule is 450 mg/m^2 per day. Pharmacokinetic data suggest that caution is necessary when 5-FU is administered to patients with cirrhosis, or to elderly or female patients.

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