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ORIGINAL ARTICLE

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Pharmacokinetic and pharmacodynamic comparison of fluoropyrimidine derivatives, capecitabine and 5′-deoxy-5-fluorouridine (5′-DFUR)

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Abstract *Purpose*: Capecitabine is a three-step prodrug that was rationally designed to be a more effective and safer alternative to its intermediate metabolite, 5′-deoxy-5-fluorouridine (5′-DFUR). We compared the pharmacokinetics/pharmacodynamics of these drugs in metastatic breast cancer patients. *Methods*: Six patients received oral capecitabine at 1657 mg/m^2 twice daily and 17 received 5′-DFUR at 400 mg three times daily. Both drugs were administered for 21 days followed by a 7-day rest. *Results*: Median daily 5′-DFUR AUC was significantly higher for capecitabine than for 5′-DFUR (81.1 vs 32.6 mmol h/l; $P=0.01$). Following treatment with 5′-DFUR, the median AUC and C_{max} of 5′-DFUR tended to be higher in patients with a partial response (3.83 μg h/ml and 4.88 μg/ml) and stable disease (6.46 μg h/ml and 4.96 μg/ml) than in those with disease progression (2.53 μg h/ml and 1.36 μg/ml). The AUC and C_{max} of 5′-DFUR was significantly related to overall survival. *Conclusions*: These results support the superiority of capecitabine over 5′-DFUR.

Keywords Capecitabine · 5′-DFUR · Pharmacokinetics · Pharmacodynamics · Comparative study · Phase II

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Introduction

The synthesis of 5-fluorouracil (5-FU) in 1957 and its success as a cytotoxic agent has led to the synthesis of a number of fluorinated pyrimidine analogues as anticancer drugs. 5′-Deoxy-5-fluorouridine (5′-DFUR) is an orally administered prodrug of 5-FU which has the potential to be converted into 5-FU through exploitation of the higher concentrations of thymidine phosphorylase (TP) present in many types of tumor tissue compared with adjacent normal tissue [18]. Several clinical studies have demonstrated the efficacy of 5′-DFUR in the treatment of metastatic breast and colorectal cancers and it is commercially available in China, Korea and Japan and used for many years [2, 24]. However, the dose-limiting toxicity of 5′-DFUR remains diarrhea [1, 19] because since TP also exists in normal colorectal tissue, a proportion of the 5′-DFUR dose is activated to 5-FU through presystemic first-pass metabolism.

Capecitabine, a new class of oral fluoropyrimidines, is a prodrug of 5-FU that was rationally designed to overcome this drawback by an ability to pass unmetabolized through the intestinal tract. Capecitabine is converted into 5-FU through a series of three enzymatic steps. Following rapid and almost complete absorption of the intact molecule, capecitabine is first hydrolyzed by carboxylesterase to 5′-deoxy-5-fluorocytidine (5′-DFCR). This occurs predominantly in the liver where carboxylesterase activity is almost exclusively expressed. The second step is the conversion of 5′-DFCR to 5′-DFUR by cytidine deaminase in the liver and/or tumor tissue. Analyses of cytidine deaminase activity have shown that this enzyme is more active in tumor tissue and normal liver cells than in normal tissue adjacent to malignant cells [12, 18]. The third, and final stage of conversion to 5-FU involves TP. The malignant tissue of various, but not all, organs has a higher TP activity than is found in the corresponding normal tissue. These three steps mean that

tumors can be targeted specifically for the selective activation of capecitabine to 5-FU [12].

Capecitabine has been shown to more effectively inhibit tumor growth than 5′-DFUR in human cancer xenografts [10]. In addition, in a phase I study, capecitabine appeared to generate 3.5 times more 5′-DFUR in plasma than is achieved with 5′-DFUR administered at a dose of 400 mg three times a day [5]. However, the pharmacokinetic differences between these two prodrugs have not been investigated, and the superiority of capecitabine to 5′-DFUR in this respect has not been fully evaluated in vivo. The aim of the present work was to characterize the pharmacological properties of capecitabine in comparison to those of 5′-DFUR.

Patients and methods

We conducted two phase II studies which were primarily designed to evaluate the efficacy and toxicity of capecitabine and 5′-DFUR, respectively. The results from these two trials were to be compared. In addition, as a secondary endpoint the pharmacokinetics of the two drugs were analyzed using samples obtained from patients in both studies who gave their permission for blood samples to be taken; not all patients agreed to this procedure. The capecitabine study was a multi-institutional phase II study and the blood sampling data used in this study were obtained from the National Cancer Center Hospital East. The phase II study of 5′-DFUR was a single institution study. We report here only the results of the pharmacokinetic investigations of capecitabine and 5′-DFUR in the two studies. The clinical results will be reported elsewhere and will include all participating patients and not, as here, just those who gave permission for pharmacokinetic sampling.

The eligibility criteria and clinical assessments in both studies were identical, and the studies were approved by the Institutional Review Board of the National Cancer Center, Japan. All patients had histologically confirmed metastatic breast cancer, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, a life expectancy of at least 12 weeks, and had failed previous treatment with docetaxel. Additional eligibility criteria were: adequate hematopoietic function including white blood cell (WBC) count $>3000/\mu l$ and $<12{,}000/\mu l$, absolute neutrophil count $>1500/\mu l$, platelet count $>100{,}000/\mu l$, and hemoglobin level >9.0 g/dl; adequate hepatic function including total bilirubin level less than 1.5 times the upper limit of normal (ULN), and aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase <2.5 times ULN; and adequate renal function including serum creatinine <1.5 times ULN. All patients gave written informed consent before treatment.

Patients treated in the capecitabine study received oral capecitabine 1657 mg/m^2 twice daily for 21 days. For patients in the 5′-DFUR study, 400 mg 5′-DFUR was administered orally three times daily for 21 days. In order to investigate pharmacokinetics, 5′-DFUR was administered once daily at 400 mg on day 1 of the first cycle, and on days 1 and 14 of the first cycle, 400 mg 5′-DFUR was administered in the morning before food, with breakfast eaten 2 h later after the first dose. Patients in both studies had a 7-day rest period between cycles. These 28-day cycles were repeated. The doses and schedules for capecitabine and 5′-DFUR were as approved for use in Japan.

Medical histories were taken, and physical examinations and routine laboratory studies were performed before treatment. Physical examinations and laboratory evaluations were repeated every 2 weeks during treatment. Toxicity was reported according to the National Cancer Institute of Canada Common Toxicity Criteria, version 1.0. Responses were assessed in each cycle using the standard World Health Organization (WHO) response criteria [17] and treatment was continued until disease progression or unacceptable toxicity. However, analysis of response is only reported here for the 17 patients in the 5′-DFUR group. This is because the number of patients in the capecitabine group who gave their consent to participate in the pharmacological aspect of the study, and are therefore discussed in this paper, was not large enough to make any comment on response rates.

Pharmacokinetic analysis

To study the pharmacokinetics of both capecitabine and 5′-DFUR, blood samples were obtained from an indwelling venous catheter placed in the arm. The sampling schedule was the same for both groups: samples were taken before dosing, and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8 and 11 ± 1 h after dosing on day 1 of the first cycle. Blood sampling was repeated for both drugs on day 14 of the first cycle: before dosing, and at 0.25, 0.5, 1, 2, 3, 4, 5 and 6 h after the first administration. The blood samples were immediately placed in heparinized tubes, the plasma was separated by centrifugation and then frozen at -70°C until analysis.

Concentrations of capecitabine and its metabolites 5′-DFCR, 5′-DFUR, 5-FU, and α-fluoro-β-alanine (FBAL) were measured by means of a validated liquid chromatography mass spectrometry method as previously described [20, 21].

In the 5′-DFUR phase II study, plasma samples spiked with [^{13}C,^{15}N$_2$]-5′-DFUR and [^{15}N$_2$]-5-FU as internal standards, respectively, for 5′-DFUR and 5-FU were precipitated with acetonitrile. After centrifugation, the supernatant was dried under a nitrogen stream. The residue was dissolved in 0.2 ml water. 5′-DFUR was analyzed on a reversed-phase column (Inertsil ODS-3, 250×4.6 mm i.d.; GL Science) with turbo ion spray MS/MS detection (negative, selected reaction monitoring ions were m/z 245/129 and 248/132 for 5′-DFUR and [^{13}C,^{15}N$_2$]-5′-DFUR, respectively). 5-FU was also analyzed on a reversed-phase column (Inertsil ODS-3, 250×4.6 mm i.d.; GL Science) with turbo ion spray MS/MS detection (negative, selected reaction monitoring

ions were m/z 129/42 and 131/43 for 5-FU and [$^{15}N_2$]-5-FU, respectively). The mobile phase consisted of methanol and 5 mmol/l ammonium acetate solution in the volumetric ratio of 4:6 for 5′-DFUR and 1:9 for 5-FU. For both analytes, the flow rate was 1 ml/min at room temperature. Calibration ranges using 0.2 ml plasma were 20–10,000 ng/ml for 5′-DFUR and 2–10,000 ng/ml for 5-FU, with the respective limits of quantification of 20 ng/ml and 2 ng/ml. The interassay variabilities (overall CV%) of quality control samples for 5′-DFUR and 5-FU were 3.2% and 1.9%, respectively.

The pharmacokinetic parameters of capecitabine, 5′-DFUR and their metabolites were estimated according to a standard noncompartmental method. Maximum observed plasma concentration (C_{max}) and time to occurrence of C_{max} (t_{max}) were taken from the observed data. The terminal phase elimination half-life ($t_{1/2}$) was estimated as ln(2)/k, where the apparent rate constant of elimination (k) was estimated by linear regression on the logarithm of the plasma concentration versus time. The area under the plasma-concentration time curve (AUC) for time 0 to infinity ($AUC_{0–inf}$) was estimated by summing AUC from zero to time t ($AUC_{0–t}$) and C_{tlast}/k where C_{tlast} is the concentration at the last measured point. $AUC_{0–t}$ was estimated using the log trapezoidal method.

Statistical analysis

Differences in pharmacokinetic parameters between day 1 and day 14 for each drug and between capecitabine and 5′-DFUR were tested. The Mann-Whitney *U*-test was used to compare two independent, continuous distributions, whereas the Wilcoxon signed-ranks test was used to determine whether two distributions of continuous, paired data collected at two different time points were significantly different. Statistical significance was at the $P < 0.05$ level.

The pharmacodynamics of 5′-DFUR were evaluated by linear regression analysis. The pharmacodynamic endpoints tested were complete blood cell counts, biochemistry, and all side effects recorded in the first cycle.

The Cox proportional hazards model was used for the analysis of time-to-event data. As the first step in the analysis, univariate Cox regression was performed on each dependent variable with each of four independent variables (AUC and C_{max} of 5′-DFUR and 5-FU). In the second step, multivariate Cox regression was performed to confirm the impact of pharmacokinetic parameters which were significant at $P \leq 0.05$ in the univariate analysis.

All statistical calculations were performed using NCSS 2001 (Kaysville, Utah).

Results

Entered into the phase II studies of capecitabine and 5′-DFUR were 60 and 26 female patients with breast cancer, respectively. Of these patients, 6 and 17 in the capecitabine and 5′-DFUR groups, respectively, underwent blood sampling for pharmacokinetic study, the analysis of which is reported here. The baseline and clinical characteristics of the patients were comparable between the two groups, although the patients in the 5′-DFUR group had a slightly worse performance status (Table 1). The pharmacokinetic parameters for capecitabine and its metabolites are listed in Table 2. One patient in this capecitabine group could not be assessed for pharmacokinetics on day 14 because her treatment was stopped due to grade 3 abnormal liver enzyme levels. Peak plasma concentrations of capecitabine, 5′-DFCR, 5′-DFUR and 5-FU were observed within 1 h of oral administration in most patients, and half-lives were short, except for that of FBAL. High interpatient variability was observed for the C_{max} and AUC of capecitabine. The pharmacokinetic parameters of 5′-DFUR following oral administration are listed in Table 3. 5′-DFUR is rapidly absorbed via this route and t_{max} was about 1 h.

The influence of repeated doses on the pharmacokinetics of 5′-DFUR and its metabolite 5-FU was investigated. In contrast to their short half-lives, the AUCs of 5′-DFUR and 5-FU were significantly higher on day 14 than on day 1 ($P = 0.01$ and $P < 0.001$, respectively).

Daily systemic exposure to 5′-DFUR and 5-FU in each treatment group was calculated by multiplying the $AUC_{0–t}$ of 5′-DFUR or 5-FU on day 14 by the number of daily 5′-DFUR or capecitabine doses (Table 4). There was no difference in the daily systemic exposure to 5-FU between patients treated with capecitabine and 5′-DFUR. However, the daily exposure to 5′-DFUR was significantly higher in patients treated with capecitabine than in those treated with 5′-DFUR ($P = 0.01$) (Table 4).

Because the doses of capecitabine and 5′-DFUR were different, the AUC of 5′-DFUR after administration of capecitabine and 5′-DFUR were compared after adjustments for the dose administered (Table 4). The

Table 1 Patient characteristics

Characteristic	Capecitabine	5′-DFUR
Total no. of patients	6	17
Age (years)		
Median	53	58
Range	42–61	43–71
Performance status		
0	4	6
1	1	7
2	1	4
No. of prior chemotherapy courses		
1	2	1
2	3	11
3	1	4
4	0	1
Dose	828 mg/m^2 (3.34 mol) twice daily	400 mg/body (1.62 mol) three times daily

Table 2 Pharmacokinetic parameters for capecitabine presented as median values (range)

Parameter	Capecitabine	5′-DFCR	5′-DFUR	5′-FU	FBAL
Day 1 ($n=6$)					
C_{max} (μg/ml)	4.82 (0.90–9.15)	5.13 (0.61–9.65)	5.77 (2.35–10.1)	0.16 (0.06–0.58)	3.47 (2.38–4.07)
t_{max} (h)	0.51 (0.25–3.97)	0.51 (0.25–3.97)	0.51 (0.50–3.97)	0.51 (0.25–3.97)	2.07 (0.97–5.90)
AUC (μg h/ml)	3.61 (2.68–4.45)	7.40 (2.28–14.9)	8.24 (6.72–11.8)	0.29 (0.22–0.40)	14.7 (12.9–21.6)
$t_{1/2}$ (h)	0.40 (0.26–0.90)	0.74 (0.61–1.29)	0.66 (0.52–1.33)	0.68 (0.48–1.23)	2.42 (2.17–3.05)
Day 14 ($n=5$)					
C_{max} (μg/ml)	2.81 (2.10–8.83)	3.88 (1.94–10.0)	5.29 (2.55–11.7)	0.28 (0.13–1.59)	4.18 (3.40–4.39)
t_{max} (h)	0.53 (0.25–2.00)	2.00 (0.25–3.00)	2.00 (0.25–3.00)	2.00 (0.25–3.00)	3.00 (0.98–4.00)
AUC (μg h/ml)	3.68 (2.89–4.27)	6.80 (3.49–16.3)	10.0 (4.77–14.3)	0.49 (0.24–0.82)	17.7 (15.2–23.0)
$t_{1/2}$ (h)	0.29 (0.23–0.34)	0.63 (0.54–0.86)	0.59 (0.50–0.80)	0.50 (0.47–0.86)	2.81 (2.20–3.28)

5′-DFUR AUC produced by 1 mole of capecitabine tended to be higher than that produced by 5′-DFUR, although this did not reach statistical significance ($P=0.22$).

The relationships between systemic exposure and safety outcomes of orally administered 5′-DFUR were analyzed. AUC and C_{max} of 5′-DFUR and 5-FU were not related to changes in laboratory data or safety outcomes except for a negative correlation between pretreatment WBC count and 5′-DFUR C_{max} ($P=0.04$).

Of 17 patients treated with 5′-DFUR, three achieved a partial response (PR), five achieved stable disease (SD), and eight developed progressive disease (PD). In one patient, a target lesion in the liver was revealed to be hepatocellular carcinoma after the start of 5′-DFUR treatment, and she was excluded from the analysis of response and survival. Median 5′-DFUR C_{max} and AUC on day 14 in PR and SD patients were higher than in PD patients. Median day-14 5′-DFUR AUC in PR and SD patients were 3.83 μg h/ml and 6.46 μg h/ml, respectively, and 2.53 μg h/ml in PD patients: PD versus PR patients, $P=0.08$; PD versus SD patients, $P=0.02$. Median C_{max} of 5′-DFUR on day 14 was 4.88 μg/ml and 4.96 μg/ml for PR and SD patients, respectively, compared with 1.36 μg/ml for PD patients: PD versus PR patients, $P=0.08$; PD versus SD patients, $P=0.02$

Table 3 Pharmacokinetic parameters of 5′-DFUR presented as median values (range)

Parameter	5′-DFUR			5-FU		
	Day 1	Day 14	*P* value[a]	Day 1	Day 14	*P* value[a]
C_{max} (μg/ml)	3.30 (0.20–6.99)	2.25 (0.92–9.29)	0.82	0.16 (0.02–0.36)	0.14 (0.06–0.96)	0.51
t_{max} (h)	0.98 (0.50–3.08)	1.00 (0.50–3.00)		0.52 (0.25–3.08)	0.98 (0.30–3.00)	
AUC (μg h/ml)	2.48 (1.37–6.07)	2.80 (1.60–7.11)	0.01	0.14 (0.07–0.29)	0.20 (0.08–0.65)	< 0.001
$t_{1/2}$ (h)	0.31 (0.17–4.34)	0.47 (0.23–5.26)	0.06	0.37 (0.21–5.68)	0.45 (0.21–1.80)	0.16

[a]Day 1 vs day 14 evaluated by the Wilcoxon signed ranks test

Table 4 Comparison of 5′-DFUR and 5-FU exposure in the treatment of capecitabine and 5′-DFUR. The results are presented as medians (range)

	Daily exposure (mmol h/l)				AUC per mole (h/ml)		
	Capecitabine	5′-DFUR	Ratio	*P* value[a]	Capecitabine	5′-DFUR	*P* value[a]
Dose (mmol/day)	6.68	4.87	1.37	–			
5′-DFUR	81.1 (37.9–115.6)	32.6 (17.1–83.4)		0.01	12.2 (5.80–17.4)	6.82 (4.00–17.2)	0.22
5-FU	3.95 (1.94–6.66)	4.23 (1.77–14.8)		0.40	1.13 (0.56–1.89)	0.95 (0.38–3.06)	0.76

[a]Capecitabine vs 5′-DFUR evaluated by the Mann-Whitney *U*-test

(Fig. 1). When the data from the patients who had PR and SD were combined and compared with those from patients with PD, the C_{max} (4.92 μg/ml) and AUC (4.36 μg h/ml) of PR and SD patients were higher than those of PD patients ($P = 0.007$ for both).

To assess the relationship between systemic exposure and antitumor activity, univariate analysis was performed for time to progression and overall survival using C_{max} and AUC (Table 5). The higher AUC and C_{max} of 5′-DFUR on day 14 tended to correlate with a delay to progression ($P = 0.08$ and $P = 0.07$, respectively). For overall survival, the AUC and C_{max} of 5′-DFUR were statistically significant in the univariate analysis ($P = 0.03$ and $P = 0.05$, respectively). Multivariate Cox regression analysis was performed on each significant variable, with age as marginally significant ($P = 0.10$) in the univariate analysis. The AUC and C_{max} of 5′-DFUR remained significant in the multivariate model ($P = 0.04$ for day-14 AUC, and $P = 0.03$ for day-14 C_{max}, respectively). The AUC and C_{max} of 5-FU were not correlated with either time to progression or overall survival.

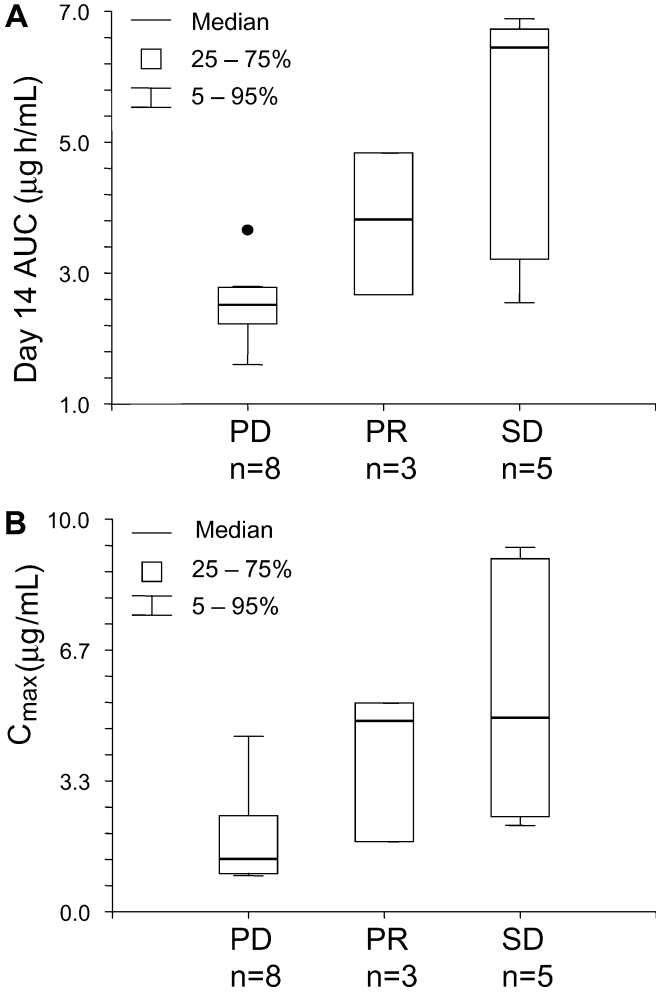

Fig. 1 C_{max} and AUC of 5′-DFUR, categorized according to treatment response to 5′-DFUR. The *black dot* over the PD AUC is an outlier (*PR* partial response, *PD* progressive disease, *SD* stable disease)

Discussion

In this study, the pharmacokinetics of capecitabine and 5′-DFUR were found to be similar to those found in previous studies [13, 20, 26]. The influence of repeated doses on the pharmacokinetics of 5′-DFUR showed an accumulation of 5′-DFUR and 5-FU, although their half-lives were short and their plasma concentrations declined to below the limit of analytical quantification within 11 h of the previous dose. In previous pharmacokinetic studies of 5′-DFUR [27] and capecitabine [5, 14], 5′-DFUR did not accumulate in plasma, but 5-FU AUC showed an increase on day 5 and day 14 compared with day 1. A NONMEN population analysis of 5-FU clearance identified that increased length of infusion time significantly reduces 5-FU clearance [7]. In addition, inhibition of dihydropyrimidine dehydrogenase activity was observed after 5-FU administration in both colorectal cancer patients and an animal model [15]. These results may support our findings that the AUC of 5-FU is increased by repeated administration. However, the mechanisms for the accumulation of 5′-DFUR remain unclear.

The 5′-DFUR AUC produced from 1 mole of capecitabine tended to be higher than that produced from 1 mole of 5′-DFUR, although the difference did not reach statistical significance due to the small sample size. The number of patients who had pharmacokinetic investigation in the capecitabine study was approximately one-third the number in the 5′-DFUR study. The phase II study of capecitabine was a multi-institutional study and pharmacokinetic data for this analysis were obtained only at the National Cancer Center Hospital East, while the phase II study of 5′-DFUR was a single-institution study conducted at the same hospital. This is the reason for the small size of the capecitabine study. Capecitabine can pass through the intestinal mucosa, in contrast to 5′-DFUR, which is partly activated to 5-FU by TP as it passes through the intestinal mucosal membrane. Our results appear to support the concept of pharmacological superiority of capecitabine over 5′-DFUR with regard to both the efficacy and safety.

With respect to the clinical dosage, the daily AUC of 5′-DFUR was significantly higher in the capecitabine group than in the 5′-DFUR group. In a preclinical study, greater doses of capecitabine than 5′-DFUR could be given to mice effectively and safely because it was less toxic, although the antitumor activity of the two drugs appeared similar at the same dose [18]. In addition, in a colon cancer xenograft model, the maximum tolerated dose (MTD) of capecitabine was twice that of 5′-DFUR (10.5 and 5.25 mmol/kg per week, respectively). At the MTD, capecitabine inhibited 7 of 24 human cancer xenograft models, whereas at the MTD 5′-DFUR inhibited tumor growth by >90% in only 1 of

Table 5 Cox regression analysis (univariate)

	Day	Time to progression			Overall survival		
		Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
AUC							
5′-DFUR	1	0.584	0.32–1.057	0.08	0.347	0.14–0.83	0.02
	14	0.664	0.42–1.05	0.08	0.458	0.22–0.94	0.03
5-FU	1	0.263	0.0001–737	0.74	0.302	0.0000–4314	0.80
	14	0.194	0.01–3.55	0.27	0.158	0.004–6.08	0.32
C_{max}							
5′-DFUR	1	0.710	0.46–1.09	0.12	0.544	0.33–0.89	0.02
	14	0.768	0.58–1.02	0.07	0.697	0.48–1.00	0.05
5-FU	1	0.161	0.0005–48	0.53	0.022	0.0000–38	0.31
	14	0.239	0.03–1.79	0.16	0.202	0.02–2.64	0.22

24 models [10]. Comparing the approved doses of capecitabine and 5′-DFUR expressed as moles, capecitabine is 1.37 times higher than 5′-DFUR. These results suggest that capecitabine, which appears to be less toxic than 5′-DFUR, can be given at a higher dose, and therefore it may be more effective than 5′-DFR in the clinical setting.

Toxicities in the 5′-DFUR study were mild and similar among patients. There was no relationship between the pharmacokinetics and toxicities except for the negative relationship between C_{max} and pretreatment WBC count. Since the concentrations of metabolites in plasma may not necessarily reflect those in organs and tissues [11, 22, 23], this might explain why no clear relationship was observed between the pharmacokinetics of 5′-DFUR and toxicities in this study. Similarly, only weak relationships have been shown for capecitabine [8, 25]. The negative relationship between C_{max} and pretreatment WBC count may be attributed to multiple hypothesis testing. However, as WBC produce cytokines such as tumor necrosis factor and interleukin-1α, which induce the expression of thymidine phosphorylase [6, 28], the WBC counts might indirectly reflect the thymidine phosphorylase activity.

In a phase II study of capecitabine, patients whose best response was SD had a median survival time similar to that of responders, whereas patients with early PD had a much shorter survival time [4]. Howell et al. [9] have shown that disease stabilization is a meaningful clinical outcome. This has relevance to our study where our data showed the AUC and C_{max} of 5′-DFUR were higher in patients with PR and SD than in those with PD.

The AUC and C_{max} of 5′-DFUR were significantly associated with survival. A previous population pharmacokinetic analysis of capecitabine has revealed an association between C_{max} of 5′-DFUR and survival, but not for AUC [3, 8]. In that study, the lack of association between efficacy and AUC of 5′-DFUR was attributed to the narrow ranges of observed AUC. However, in another study in head and neck cancer, the AUC of 5-FU was significantly related to both tumor response and survival in patients who had received a 5-day continuous venous infusion of 5-FU [16]. The results of this study suggested an association between efficacy and AUC of 5′-DFUR, although they should be interpreted with caution because the results were derived from small numbers of patients, and the confidence intervals of each response group overlap.

In conclusion, we showed that oral capecitabine increased exposure to 5′-DFUR in comparison to oral administration of 5′-DFUR at the approved dosage. Furthermore, AUC and C_{max} of 5′-DFUR were positively related to the response and survival of breast cancer patients treated with 5′-DFUR. Taken together, our results suggest that capecitabine may be superior to 5′-DFUR, as judged by pharmacokinetics and pharmacodynamics at the approved dosage.

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