Effect of Hepatic Dysfunction due to Liver Metastases on the Pharmacokinetics of Capecitabine and Its Metabolites

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ABSTRACT

Capecitabine (Xeloda) is a rationally designed oral, tumor-selective fluoropyrimidine carbamate aimed at preferential conversion to 5-fluorouracil (5-FU) within the tumor. Because capecitabine is extensively metabolized by the liver, it is important to establish whether liver dysfunction altered the pharmacokinetics of capecitabine and its metabolites. This was investigated in 14 cancer patients with normal liver function and in 13 with mild to moderate disturbance of liver biochemistry due to liver metastases. They received a single oral dose of capecitabine (1255 mg capecitabine/m^2) with serial blood and urine samples collected up to 72 h after administration. Concentrations of capecitabine and its metabolites were determined in plasma by high-performance liquid chromatography or liquid chromatography coupled to mass spectrometry and in urine by ^{19}F-nuclear magnetic resonance spectroscopy. Although plasma concentrations of capecitabine, 5′-deoxy-5-fluorouridine, 5-FU, dihydro-5-FU, and α-fluoro-β-alanine were, in general, higher in patients with liver dysfunction, the opposite was found for 5′-deoxy-5-fluorocytidine. These effects were not clinically significant. Total urinary recovery of capecitabine and its metabolites was 71% of the administered dose in patients with normal hepatic function and 77% in patients with hepatic impairment. The absolute bioavailability of 5′-deoxy-5-fluorouridine was estimated as 42% in patients with normal hepatic function and 62% in patients with impaired hepatic function. In summary, mild to moderate hepatic dysfunction had no clinically significant influence on the pharmacokinetic parameters of capecitabine and its metabolites. Although caution should be exercised when capecitabine is administered to patients with mildly to moderately impaired hepatic function, there is no need for, *a priori*, adjustment of the dose.

INTRODUCTION

The novel fluoropyrimidine carbamate capecitabine (Xeloda) has been designed as a p.o.-administered, tumor-activated, and tumor-selective cytotoxic agent for the treatment of colorectal and breast cancer (1–4). Capecitabine is extensively absorbed intact from the gastrointestinal tract and rapidly passes through the intestinal mucosa. It is designed to generate 5-FU[2] by three step-wise enzyme reactions: (*a*) it is transformed in the liver to 5′-DFCR by hepatic carboxylesterase; (b) 5′-DFCR is transformed to 5′-DFUR by cytidine deaminase, present in high concentrations in many human tumor tissues as well as in healthy liver tissue; and (*c*) 5′-DFUR is converted to 5-FU by the tumor-associated angiogenic factor thymidine phosphorylase (5). This enzyme is expressed predominantly in tumors, thereby reducing the exposure of healthy body tissues to systemic 5-FU (2). Once formed, the breakdown products of 5-FU include FUH_2 and FBAL. Capecitabine and its intermediates themselves are not cytotoxic but become effective only after conversion to 5-FU. The tumor-selective activation of capecitabine allows higher intratumoral 5-FU generation when compared with systemic i.v. 5-FU and is, therefore, pharmacologically different from 5-FU (2).

In Phase I clinical studies, administering capecitabine as a single agent every 12 h either continuously or intermittently (2 weeks treatment, 1 week rest), the MTDs were 1657 mg/m^2/day and 3000 mg/m^2/day, respectively (6, 7). Dose-limiting toxicities were diarrhea, nausea, vomiting, stomatitis, and hand-foot syndrome. The dose level below the MTDs (1331 and 2510 mg/m^2/day, respectively) were well tolerated (6, 7) and could safely be given as home-based treatment in subsequent clinical studies (3, 4). Antitumor activity was seen, particularly when using the intermittent regimen, with responses in heavily pretreated colorectal and breast cancer patients (7, 8). In combination with low-dose oral leucovorin, the MTD was 2000 mg/m^2/day using the intermittent regimen, and dose-limiting toxicities were similar (8). Additional Phase 1 trials exploiting the combination with paclitaxel and docetaxel demonstrated the feasibility of such combinations using doses of each drug that are active as single agents (9, 10).

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[2] The abbreviations used are: 5-FU, 5-fluorouracil; 5′-DFCR, 5′-deoxy-5-fluorocytidine; 5′-DFUR, 5′-deoxy-5-fluorouridine; FUH_2, dihydro-5-FU; FBAL, α-fluoro-β-alanine; FUPA, 5-fluoro-ureido-propionic acid; CI, confidence interval; CV, coefficient of variation; BILI, bilirubin; AP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MTD, maximum tolerated dose; QA, quality assurance; AUC, area under the (plasma concentration *versus* time) curve.

Table 1 Demographic parameters of patients with normal liver function (Group 1) and patients with mild to moderate hepatic dysfunction (Group 2)

Values are given as arithmetic means (± SD) and range.

	Group 1 Patients with normal liver function (n = 17)[a]	Group 2 Patients with liver dysfunction (n = 16)[b]
Demographic data		
Age (years)	59 ± 13.9 (34–84)	62 ± 10.9 (44–84)
Weight (kg)	66.9 ± 16.8 (45–94)	67.4 ± 10.4 (44–84)
Body surface area (m^2)	1.76 ± 0.23 (1.49–2.22)	1.79 ± 0.15 (1.41–2.00)
Sex (males/females)	10/7	12/4
Race (Caucasian)	17	16
Karnofsky status (%)	85.3 ± 11.2 (60–100)	76.7 ± 11.1 (60–90)
Liver function[c]		
Hepatic dysfunction score (points)	0–2	5–9
Total BILI (μmol/liter)	12 ± 5.9 (4–27)	112 ± 153 (16–485)
AST (IU/liter)	39.5 ± 41.9 (6–171)	107 ± 34.1 (46–174)
ALT (IU/liter)	27.1 ± 15.4 (7–58)	112 ± 94.0 (19–341)
AP (IU/liter)	231 ± 150 (76–511)	1816 ± 1096 (370–3233)

[a] Evaluated for pharmacokinetics n = 14.
[b] Evaluated for pharmacokinetics n = 13.
[c] Patients evaluated for pharmacokinetics.

Hepatic dysfunction is relatively common in patients with breast and colorectal cancer because of the high incidence of liver metastases. For example, more than half of the patients with colorectal cancer ultimately develop liver metastases (11). It was, therefore, necessary to study the pharmacokinetics of capecitabine in cancer patients with hepatic dysfunction due to liver metastases. As described above, capecitabine is both extensively activated and broken down in the liver. Any decrease in the metabolic turnover capacity of the liver may result in elevated concentrations of the parent drug and its breakdown products or in unexpectedly low concentrations of the metabolites. This, in turn, may influence the safety and efficacy of a standard dose treatment.

MATERIALS AND METHODS

Chemotherapy. Capecitabine (Xeloda) and its metabolite 5′-DFUR are manufactured by F. Hoffmann-La Roche Ltd (Basel, Switzerland). In the present study, capecitabine was administered as film-coated 150- and 500-mg tablets. Patients received a single oral dose of capecitabine (1255 mg/m^2) taken within 30 min after a standard meal in the morning. To obtain additional information on the possible influence of hepatic dysfunction on the gastrointestinal absorption of capecitabine and its conversion to 5′-DFUR, the metabolite 5′-DFUR (750 mg/m^2) was administered to the same patients as a single 60-min i.v. infusion. The sequence of administration of capecitabine and 5′-DFUR was randomized and separated by 3–7 days.

Patients. Liver dysfunction was defined according to standard liver biochemistry tests. Serum BILI, AP, and either AST or ALT were each scored on a 0–4 scale according to the WHO grading system. These values were then totaled to give a hepatic dysfunction score.

Seventeen patients, either with or without liver metastases, who had normal or near-normal liver biochemistry test values were enrolled in group 1 (hepatic dysfunction score, ≤2). Sixteen patients with liver metastases and mild-to-moderate hepatic dysfunction were enrolled in group 2 (dysfunction score, 5–9). Fourteen patients in group 1 and 13 patients in group 2 were evaluable for pharmacokinetics. All of the patients had histologically or cytologically confirmed advanced and/or metastatic solid cancer (predominantly colorectal, esophageal, and breast carcinoma). Only ambulatory, nonpregnant patients, ages >18 years, having a Karnofsky performance status of ≥60%, and being able to comply with the protocol were included in this study. The following exclusion criteria were applied: (*a*) patients requiring shunting, stenting, or radiotherapy of the liver within 2 weeks before or during the study; (*b*) patients with organ allografts; (*c*) patients with clinically significant cardiovascular, central nervous system, gastrointestinal, hematological, infectious, and/or kidney diseases/disorders; (*d*) patients with central nervous system or bone metastases; (*e*) patients having received cytotoxic chemotherapy or radiation therapy within 4 weeks before study start; (*f*) patients with preexisting liver disease (*e.g.*, cirrhosis); and (*g*) patients with serum creatinine ≥1.5 times the upper normal limit, hemoglobin <9.0 g/dl, total leukocyte count $<4.0 \times 10^9$/liter, and platelet count $<75 \times 10^9$/liter.

Their demographic characteristics, including liver biochemistry tests, are shown in Table 1. Individual values of the liver function tests and corresponding scores in the 13 patients who were included in the hepatic dysfunction group are presented in Table 2. None of the patients in the hepatic dysfunction group had a very high score; their individual hepatic dysfunction scores were between 5 and 9 on a scale that could range from 5 to 12. Because there was no patient with a score of 10–12, we consider that no patient had severe hepatic dysfunction, but rather all had mild-to-moderate hepatic dysfunction.

After completion of the pharmacokinetic studies, patients with normal or near-normal liver biochemistry (group 1) could continue capecitabine at a dose of 2510 mg/m^2/day given intermittently (2 weeks treatment, 1 week rest).

Table 2 Individual values of the liver function tests and corresponding score in the 13 patients included in the hepatic dysfunction group

Patient no.	BILI (μmol/liter)	AP (units/liter)	ALT (units/liter)	AST (units/liter)	Albumin g/liter	Prothrombin time (s)	Score
221	29	1449	37	135	40	16	6
222	487	1269	140	63	40	33	8
223	33	2271	38	50	38	16	5
224	22	1680	111	99	43	14	5
225	11	1995	123	97	34	16	5
227	45	3360	52	78	40	16	6
321	19	658	53	153	39	16	5
322	28	688	189	84	30	17	5
421	349	963	53	90	29	14	9
422	270	307	27	167	6	14	8
1121	36	761	52	101	32	13	6
1226	19	2106	116	90	41	13	5
1228	120	3433	206	157	37	16	9

Study Design. This was an open-label, multicenter, pharmacokinetic study in 33 patients with advanced cancer. The study was conducted in accordance with the principles of the Declaration of Helsinki III (as amended in Tokyo, Venice, and Hong Kong). Before starting the study, the trial protocol was approved by the local Ethical Review Boards, and written informed consent was obtained from each patient. Screening before the start of the study included a physical examination, medical history, vital signs, laboratory safety tests (hematology, serum biochemistry, and urinalysis), and an evaluation of Karnofsky performance status; and the hepatic dysfunction score was calculated. During treatment, vital signs, laboratory safety parameters, and adverse events were assessed. All of the patients had to meet the carefully selected inclusion/exclusion criteria taking into account the stage of the disease, current medical status, and life expectancy.

Blood Sampling. For pharmacokinetic evaluation, 5-ml blood samples were taken at 0 (*i.e.*, predose), 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, and 72 h after drug administration on study day 1, using Vacutainers containing EDTA as anticoagulant. Blood samples were centrifuged, and the supernatant plasma was removed and stored in plastic tubes at −20°C until analysis.

Urine Sampling. For the determination of the urinary excretion of capecitabine and its metabolites, urine samples were collected before treatment (predose) and between 0–12 and 12–24 h after drug intake on study day 1.

Drug Assay. Capecitabine and its five metabolites were extracted from plasma samples after the addition of internal standards (Ro 09-1977, tegafur, [$^{15}N_2$]-5-FU, [2-^{13}C, $^{15}N_2$]-5-FUH_2, and β-Ala-Ala) and quantified as described previously (12). Capecitabine, 5′-DFCR, and 5′-DFUR were determined by high-performance liquid chromatography with subsequent UV detection; and 5-FU, FUH_2, and FBAL were assayed by liquid chromatography coupled to mass spectrometry.

For capecitabine, 5′-DFCR, 5′-DFUR, and 5-FUH_2 the limit of quantification was 0.05 μg/ml using a 0.5-ml plasma specimen; the interassay precision from standard curve and QA samples (overall CV%) was 1.9, 2.9, 2.8, and 3.2% in the calibration range 0.05–20 μg/ml, respectively. For 5-FU, the limit of quantification was 3 ng/ml using a 0.5-ml plasma specimen, and the interassay precision from standard curve and QA samples (overall CV%) was 3.8% in the calibration range 3–1500 ng/ml; for FBAL, the limit of quantification was 0.02 μg/ml (0.5-ml plasma), and the interassay precision reached 6.4% in the calibration range 0.02–10 μg/ml.

Urine samples were concentrated and analyzed for capecitabine, 5′-DFCR, 5′-DFUR, 5-FU, FUH_2, FUPA, and FBAL by ^{19}F-nuclear magnetic resonance spectroscopy using *p*-fluoro-D-phenylalanine as internal standard (13). Interassay precision from QA samples (%CV) was 2.69% for capecitabine, 2.26% for 5′-DFUR, 3.99% for 5-FU, and 2.23% for FBAL. The lower limit of quantification for capecitabine, 5′-DFCR, 5′-DFUR, 5-FU, FUH_2, and FBAL was 0.02 μmol/ml using 5 ml of urine. Under the same conditions, the lower limit of quantification for FUPA was 0.05 μmol/ml.

Pharmacokinetic Parameters. The pharmacokinetic parameters of capecitabine and its metabolites (5′-DFCR, 5′-DFUR, 5-FU, FUH_2, and FBAL) were determined from the concentration-time data on days 1 and 8 and estimated using noncompartmental methods (14).

Maximum plasma concentration (C_{max}) and time of its occurrence (t_{max}) were determined from the observed highest concentration and the time of its occurrence, respectively. Apparent elimination half-life ($t_{1/2}$) was estimated from 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 data. The area under the plasma concentration time curve from time 0 to infinity ($AUC_{0-\infty}$) was estimated from the sum of AUC_{0-t} and $C_{t\ last}/k$. AUC_{0-t} is the area under the curve from time 0 to the last sampling time (t_{last}) at which the concentration could be measured ($C_{t\ last}$). AUC_{0-t} was estimated using the linear trapezoidal rule.

Total and individual urinary recovery (% of dose excreted) of capecitabine, 5′-DFCR, 5′-DFUR, 5-FU, FUH_2, FUPA, and FBAL was estimated from their concentrations in urine.

Descriptive Statistics. Descriptive statistics were used to summarize the pharmacokinetic parameters. Geometric mean and geometric CV are reported for C_{max} and $AUC_{0-\infty}$, arithmetic mean and arithmetic CV are reported for $t_{1/2}$ and urinary recovery (% of dose), and median, minimum, and maximum values are reported for t_{max}.

Comparative Statistics. The primary parameter for testing of the effect of hepatic dysfunction on the pharmacokinetics of capecitabine and its metabolites was the dose-adjusted $AUC_{0-\infty}$ of the analyte 5′-DFUR. A one-way ANOVA (PROC MIXED, SAS 6.11) with the factor group was performed for the

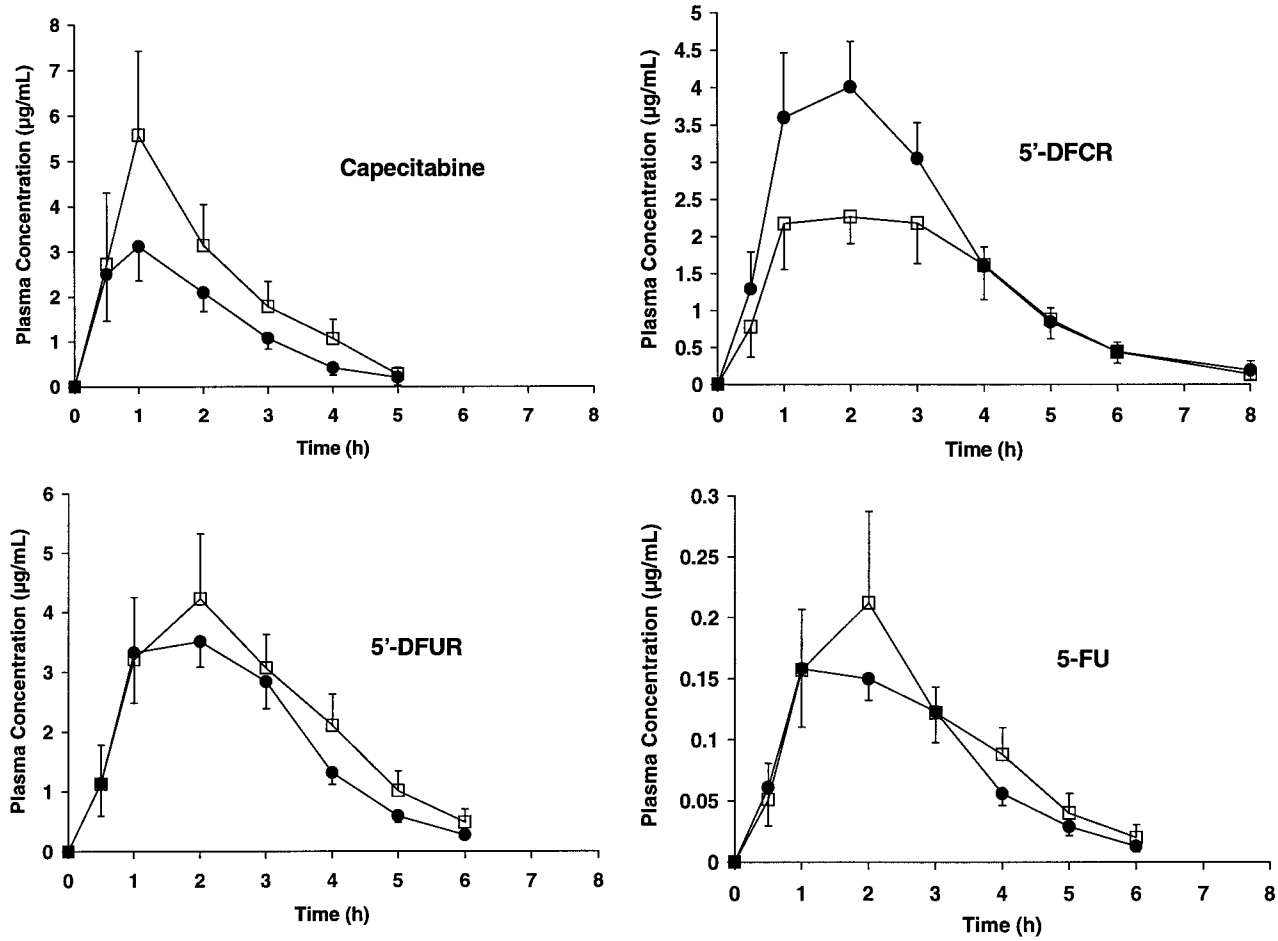

Fig. 1 Plasma concentration of capecitabine, 5′-DFCR, 5′-DFUR, and 5-FU (arithmetic mean values with SE) *versus* time data after oral administration of capecitabine (dose-level of 1255 mg/m^2) in 14 cancer patients with normal liver function (●) and in 13 cancer patients with hepatic dysfunction (□).

log-transformed variables. Because it is generally accepted that pharmacokinetic parameters follow a distribution that is closer to a log-normal distribution than to a normal distribution, statistical tests were performed after log transformation of the pharmacokinetic parameters. Two-sided 95% CIs for the ratio of the parameters in patients with hepatic impairment relative to the parameters in patients without impairment were calculated.

The 95% CIs have been calculated in the same way for the secondary kinetic parameter $AUC_{0-\infty}$ and C_{max} of the capecitabine and the metabolites 5′-DFCR, 5-FU, and FBAL, and for C_{max} of 5′-DFUR. The results for all of the secondary parameters have been interpreted in an exploratory sense only. Comparisons were made at the significance level $\alpha = 0.05$.

RESULTS

At baseline, the patients with normal liver function and those with hepatic dysfunction were similar in relation to all of the demographic characteristics except gender. By definition, they also differed with respect to liver biochemistry tests.

Pharmacokinetics. The pharmacokinetic profiles (arithmetic mean plasma concentrations *versus* time) after single oral administration of 1255 mg/m^2 capecitabine in the two treatment groups are presented for capecitabine, 5′-DFCR, the primary metabolite 5′-DFUR, and the cytotoxic 5-FU in Fig. 1, respectively. These profiles show that higher plasma concentrations were measured in the patients with liver dysfunction for capecitabine, 5′-DFUR, and 5-FU, whereas the opposite was found for 5′-DFCR, the first metabolic product of capecitabine. Descriptive statistics on the pharmacokinetic parameters (including urinary excretion) of capecitabine and its metabolites (5′-DFCR, 5′-DFUR, 5-FU, FUH_2, and FBAL) in the two treatment groups are presented in Table 3. Comparative statistics on the log-transformed kinetic parameters C_{max} and $AUC_{0-\infty}$ for capecitabine and its metabolites are shown in Table 4.

After oral administration, peak concentrations of capecitabine were rapidly achieved in both patients with normal liver function and patients with mild-to-moderate liver dysfunction, and similar elimination half-lives were determined in the two patient groups. By contrast, the C_{max} values, $AUC_{0-\infty}$ values, and urinary (drug) recovery were increased by 49, 48, and 83%, respectively, in patients with hepatic dysfunction when compared with patients with normal liver function (Table 3).

Table 3 Descriptive statistics of pharmacokinetic parameters of capecitabine and its metabolites following single oral administration of 1255 mg/m^2 of capecitabine

Geometric means (CV) are reported for C_{max} and $AUC_{0-\infty}$; median values (min–max) are reported for t_{max}; arithmetic means (CV) are reported for $t_{1/2}$ and urinary recovery (% of capecitabine dose).

Parameter	Capecitabine	5′-DFCR	5′-DFUR	5-FU	FUH_2	FBAL
Cancer patients with normal hepatic function (n = 14)						
C_{max} (μg/ml)	3.96 (71%)	5.02 (53%)	4.64 (54%)	0.218 (61%)	1.06 (26%)	6.23 (41%)
t_{max} (h)	2.00 (0.47–3.0)	2.00 (0.57–4.0)	2.00 (1.0–5.0)	2.00 (1.0–3.0)	3.00 (1.0–6.6)	3.55 (2.0–6.6)
$AUC_{0-\infty}$ (μg · h/ml)	7.25 (48%)	14.1 (30%)	11.7 (25%)	0.526 (29%)	4.04 (32%)	51.1 (43%)
$t_{1/2}$ (h)	0.73 (81%)	0.95 (40%)	0.94 (46%)	0.98 (46%)	1.26 (36%)	11.5 (43%)
Urinary recovery (% of dose)	1.89 (37%)	6.45 (46%)	6.80 (44%)	0.325 (93%)	0.081 (158%)	51.8 (25%)
Cancer patients with hepatic dysfunction (n = 13)						
C_{max} (μg/ml)	5.91 (94%)	3.56 (71%)	6.19 (47%)	0.280 (65%)	1.16 (29%)	6.74 (29%)
t_{max} (h)	2.00 (1.0–4.0)	2.00 (1.0–4.0)	2.00 (1.0–4.0)	2.00 (1.0–4.0)	3.02 (1.0–5.0)	3.02 (2.0–8.0)
$AUC_{0-\infty}$ (μg · h/ml)	10.7 (65%)	9.15 (49%)	14.0 (31%)	0.606 (43%)	4.15 (40%)	63.2 (53%)
$t_{1/2}$ (h)	0.57 (33%)	0.99 (42%)	0.87 (37%)	0.86 (35%)	1.34 (26%)	6.49 (29%)
Urinary recovery (% of dose)	3.45 (48%)	5.38 (42%)	6.14 (46%)	0.468 (25%)	0.263 (93%)	56.7 (27%)

Table 4 Statistical analysis of the effect of hepatic dysfunction on the primary and secondary kinetic parameters of capecitabine and its metabolites after a single oral administration of 1255 mg/m^2 capecitabine using the log transformation

Parameter and analytes	Backtransformed least squares means		Change (%)		Test for group difference, P
	Normal hepatic function	Hepatic dysfunction	Estimate	95% CI	
$AUC_{0-\infty}$					
Capecitabine	7.25	10.7	48.2	−3.95–128.6	0.073
5′-DFCR	14.1	9.16	−35.2	−52.6–−11.3	0.009
5′-DFUR	11.7	14.0	19.5	−4.08–48.9	0.108
5-FU	0.53	0.61	15.1	−12.95–52.2	0.310
FBAL	51.1	63.2	23.6	−22.9–98.2	0.353
C_{max}					
Capecitabine	3.95	5.91	49.5	−15.6–164.7	0.160
5′-DFCR	5.02	3.53	−29.8	−52.6–4.07	0.076
5′-DFUR	4.64	6.19	33.4	−8.95–95.4	0.133
5-FU	0.22	0.28	28.3	−18.8–102.9	0.272
FBAL	6.22	6.74	8.28	−17.8–42.6	0.557

Changes in the opposite direction were observed for 5′-DFCR, the first metabolite of capecitabine. In patients with liver dysfunction, the C_{max} and $AUC_{0-\infty}$ values and urinary recovery were decreased by 29, 35, and 17%, respectively, in comparison with patients having normal liver function. No changes were observed for t_{max} and the elimination half-life of 5′-DFCR.

C_{max} and AUC-$_{0-\infty}$ values of the primary metabolite 5′-DFUR were increased in the patients with liver dysfunction by 33 and 20%, respectively. Urinary recovery, t_{max}, and elimination half-life were practically the same in both of the patient groups.

For 5-FU, no changes in t_{max} and elimination half-life were observed between the two patient groups, but C_{max}, $AUC_{0-\infty}$, and urinary recovery were increased by 28, 15, and 44%, respectively, in the patients with liver impairment.

The breakdown products of 5-FU were also studied. Pharmacokinetic parameters of FUH_2 were not influenced by hepatic dysfunction, with the exception of increased urinary excretion in the patients with liver impairment (0.08 *versus* 0.26% of the dose). t_{max}, C_{max}, and urinary excretion of FBAL were similar in both of the patient groups, whereas $AUC_{0-\infty}$ was higher and elimination half-life was shorter in the patients with hepatic dysfunction.

Overall, urinary elimination of capecitabine and its metabolites was compared in patients with normal and abnormal liver biochemistry. Within 24 h after capecitabine intake, 70.7% (range, 36.9- 89.1%) of the dose was recovered from urine in patients with normal liver function, and 77.2% (range, 50.7–124%) was recovered in patients with liver dysfunction. The majority of the dose was recovered as FBAL (51.8% in group 1 and 56.7% in group 2). All of the other compounds made only a minor contribution.

To obtain additional information on the possible influence of hepatic dysfunction on the gastrointestinal absorption of capecitabine and its conversion to 5′-DFUR, 5′-DFUR was administered to the same patients also as a single i.v. infusion (750 mg/m^2 over 60 min). The $AUC_{0-\infty}$ values of 5′-DFUR after i.v. infusion were similar in both of the patient groups (26.0 μg·h/ml in group 1 and 22.0 μg·h/ml in group 2) with low coefficients of variation (24 and 33%, respectively). The least squares means and 95% CIs do not indicate a statistically significant difference. Comparison of the $AUC_{0-\infty}$ values of

5′-DFUR after oral administration of capecitabine with those after i.v. infusion of 5′-DFUR indicated a mean absolute bioavailability of 5′-DFUR of 42% in patients with normal hepatic function and of 62% in patients with hepatic dysfunction. Coefficients of variation of 30 and 33%, respectively, indicated relatively low variability in both of the patient groups.

The relationship between hepatic dysfunction score and the AUC of capecitabine and 5′-DFUR was investigated as well as the relationships between liver enzyme activities or BILI concentration and the $AUC_{0-\infty}$ of capecitabine, 5′-DFCR, and 5-FU. However, none of the investigated correlations seemed to be strong, and no meaningful interpretation could be deduced from these results.

Statistical Results. The effect of hepatic dysfunction on the primary pharmacokinetic parameter $AUC_{0-\infty}$ of 5′-DFUR after the treatment with capecitabine using the log transformation is shown Table 4.

The $AUC_{0-\infty}$ of 5′-DFUR in the patient group with hepatic dysfunction was increased by 19% relative to the group with normal liver function (95% CI, −4–49). The null hypothesis that there are no differences between the two groups could not be rejected (*P*, 0.108). The analysis of the untransformed primary parameter $AUC_{0-\infty}$ of 5′-DFUR after administration with capecitabine gave similar results. The AUC in group 1 was estimated to be increased by 21% relative to the group without hepatic impairment (95% CI, −4–46). The null hypothesis that there were no differences between the two groups could not be rejected (*P*, 0.095).

The results for the secondary pharmacokinetic parameters after oral administration of capecitabine are provided in Table 4. These results have been interpreted in an exploratory sense only. After treatment with capecitabine, the $AUC_{0-\infty}$ of 5′-DFCR is estimated to be 35% lower in the group with hepatic dysfunction compared with the group with normal liver function (95% CI, −53–11; *P*, 0.009).

Safety. No clinically relevant differences were seen in the adverse events between the two patient groups with and without hepatic dysfunction. In group 1 (normal hepatic function), 11 (65%) patients reported 6 mild, 19 moderate, and 5 severe adverse events. Three of these adverse events were possibly, and 2 were probably, related to trial medication. In group 2 (hepatic dysfunction), 6 (43%) patients experienced 9 mild, 3 moderate, and 2 severe events. Five of these events were probably related to trial medication. No life-threatening adverse reactions were observed. In both of the treatment groups, the most frequently reported adverse events were vomiting, followed by nausea, abdominal pain, and fatigue. No patient was withdrawn from the study because of laboratory abnormalities.

Because of the small number of patients in each group and because only a single dose of capecitabine was administered, the safety of capecitabine in patients with normal or abnormal liver biochemistry could only be tentatively assessed in this study.

DISCUSSION

The primary objective of this study was to investigate the influence of hepatic dysfunction due to liver metastases on the pharmacokinetics of capecitabine and its metabolites in patients with cancer. Hepatic dysfunction is relatively common in patients with breast and colorectal cancer because of the high incidence of liver metastases, with more than one-half of patients with colorectal cancer ultimately developing liver metastases (11). Hepatic malignancies in humans can be associated with decreased drug-metabolizing ability, and the impairment of drug metabolism may increase with the degree of histological evidence of malignancy (15). In clearly malignant cases, cytochrome P-450 levels seem to be markedly reduced, and specific qualitative changes in the drug metabolism pattern may occur (16). The pharmacokinetics of the anthracyclines (17, 18) and of docetaxel (19) are altered in patients with liver dysfunction. Depending on the enzyme affected, the impairment of capecitabine metabolism may have resulted either in elevated concentrations of the parent drug and breakdown products or in unexpectedly low concentrations of the metabolites. As a consequence, patients with liver dysfunction may experience an increase in toxicity or a decrease in the efficacy of capecitabine. Therefore, the assessment of capecitabine pharmacokinetics in patients with liver dysfunction has important clinical implications.

Although many patients receiving cytotoxic chemotherapy have abnormal liver biochemistry test values, there is no accepted scheme to define liver dysfunction in patients with cancer. The Child-Pugh classification, based on serum albumin, BILI, prothrombin time, the degree of ascites and encephalopathy, is widely used in patients with cirrhosis (20). It is, however, unsuited to patients with liver metastases and has not been shown to be reflective of the altered metabolism of cytotoxic drugs. Alternate dynamic measures of liver function such as indocyanine green clearance (21) and monoethylglycinexylidide clearance (22) have been proposed. All of them require additional procedures, and their relevance to the metabolism of cytotoxic drugs is unclear. Hence, the current study required a new means of defining liver dysfunction. Conventional liver biochemistry tests: (*a*) are used to determine eligibility for clinical trials; (*b*) are widely available in clinical practice; and (*c*) correlate with the altered pharmacokinetics of doxorubicin (18), epirubicin (23), and docetaxel (19). Therefore, we devised a new scoring system to define liver dysfunction as described in the "Materials and Methods" section.

All of the patients in the hepatic dysfunction group had elevated values of their liver function tests because of liver metastases. As defined in the protocol, patients with preexisting liver disease, such as cirrhosis, were not included in this study. In addition, patients with bone metastases or other bone diseases were not eligible because AP could have been greatly increased in these patients, and this AP result would have distorted the scoring of the patients. For these reasons, the group of patients with liver dysfunction was homogeneous (all of the patients had liver metastases, and none of the patients had cirrhosis or viral hepatitis).

The current study shows that the absorption and metabolism of capecitabine was not affected to a clinically significant extent in cancer patients with mild-to-moderate hepatic dysfunction. Although $AUC_{0-\infty}$ and C_{max} values of capecitabine and its metabolites 5′-DFUR and 5-FU were higher in the patients with liver impairment, these differences were not statistically significant ($P > 0.07$). No major changes concerning the concentrations of FUH_2 and FBAL were observed between the two

groups. Only the $AUC_{0-\infty}$ of the first capecitabine metabolite 5′-DFCR showed a statistically significant ($P = 0.01$) decrease in patients with hepatic dysfunction. One may speculate that reduced liver function may specifically affect the carboxylesterase that converts capecitabine to 5′-DFCR. However, this effect was not strong and is unlikely to have clinical consequences. In addition, total urinary recovery (capecitabine plus metabolites) was almost identical in both of the patient groups.

The pharmacokinetic parameters of capecitabine and its metabolites determined in the present study are in agreement with previously published data on cancer patients with normal liver function (7, 8, 12, 13, 24). Clinical studies have shown that the efficacy and safety of 5-FU correlate better with AUC than with C_{max} (25). Therefore the small increase of the $AUC_{0-\infty}$ of 5-FU by 15% is acceptable in terms of safety and will have no significant effect on efficacy.

We conclude that in patients with mild-to-moderately impaired hepatic function, caution should be exercised when capecitabine is administered, but the results of this study indicate that there is no need for, *a priori*, adjustment of the dose. There is no evidence that mild-to-moderate hepatic dysfunction due to liver metastases may significantly alter the therapeutic activity of capecitabine.

REFERENCES

1. Kemeney, N. Current approaches to metastatic colorectal cancer. Semin. Oncol., *21* (Suppl. 7)*:* 67–75, 1994.

2. Schueller, J., Cassidy, J., Reigner, B., Durston, S., Roos, B., Ishitsuka, H., Utoh, M., and Dumont, E. Tumor selectivity of XELODA™ in colorectal cancer patients. Proc. Am. Soc. Clin. Oncol., *16:* 227, 1997.

3. Findlay, M., Van Cutsem, E., Kocha, W., Allman, D., Laffranchi, B., Griffin, T. Osterwalder, B., Dalley, D., Pazdur, R., and Verweij, J. A randomized Phase II study of Xeloda (capecitabine) in patients with advanced colorectal cancer. Proc. Am. Soc. Clin. Oncol., *16:* 227, 1997.

4. Blum, J. L., Buzdur, A. U., LoRusso, P. M., Kuter, I., Vogel, C., Burger, H. U., Brown, C., and Griffin, T. A multicenter Phase II trial of Xeloda™ (capecitabine) in Paclitaxel-refractory metastatic breast cancer. Proc. Am. Soc. Clin. Oncol., *17:* 476, 1998.

5. Takebayashi, Y., Akiyama, S., Akiba, S., Yamada, K., Miuadera, K., Sumizawa, T., Yamada, Y., Murata, F., and Aikou, T. Clinicopathologic and prognostic significance of an angiogenic factor, thymidine phosphorylase, in human colorectal carcinoma. J. Natl. Cancer Inst., *88:* 1110–1117, 1996.

6. Budman, D. R., Meropol, N. J., Reigner, B., Creaven, P. J., Lichtman, S. M., Berghorn, E., Behr, J., Gordon, R. J., Osterwalder, B., and Griffin, T. Preliminary studies of a novel oral fluoropyrimidine carbamate: capecitabine. J. Clin. Oncol., *16:* 1795–1802, 1998.

7. McKean, M., Planting, A., Twelves, C., Schellens, J., Allman, D., Osterwalder, B., Kaye, S., and Verweij, J. A Phase 1 study of intermittent twice daily oral therapy with capecitabine in patients with advanced and/or metastatic solid cancer. J. Clin. Oncol., *16:* 2977–2985, 1998.

8. Dirix, L. Y., Bissett, D., Van Oosterom, A. T., Allman, D. S., Osterwalder, B., and Cassidy, J. A Phase I Study of capecitabine in combination with oral leucovorin in patients with advanced and/or metastatic tumors. Ann. Oncol., *7* (Suppl. 5)*:* 124, 1996.

9. Villalona-Calero, M., Moczygemba, J., Atkins, I., Thurman, A., Rodriguez, G., McCune, D., Drengler, R., Griffin, T., Osterwalder, B., and Von Hoff, D. Paclitaxel-capecitabine. Results of a dual escalation Phase 1 and pharmacokinetic (PK) study. Ann. Oncol., *7* (Suppl. 5)*:* 127, 1996.

10. Vasey, P. A., Pronk, L., Twelves, C., Sparreboom, A., Wilson, P., Gordon, R. S., Osterwalder, B., and Verweij, J. Phase I and pharmacokinetic study of Xeloda™ (capecitabine) in combination with Docetaxel. Eur. J. Cancer, *33:* S8, 1997.

11. Chase, J. L., Ignoffo, R. J., and Stagg, R. J. *In:* J. G. DiPiro, R. L. Talbert, P. E. Hayes, G. C. Yee, and L. M. Posey, (eds.), Gastrointestinal Cancers in Pharmacotherapy: A Pathophysiologic Approach, pp. 1384–1394. New York: Elsevier, 1988.

12. Reigner, B., Verweij, J., Dirix, L., Cassidy, J., Twelves, C., Allman, D., Weidekamm, E., Roos, B., Banken, L., Utoh, M., and Osterwalder, B. Effect of food on the pharmacokinetics of capecitabine and its metabolites following oral administration in cancer patients. Clin. Cancer Res., *4:* 941–948, 1998.

13. Reigner, B., Jodrell, D., Clive, S., Cassidy, J., Schulz, R., Rowland, J., Goggin, T., Banken, L., Roos, B., Utoh, M., Mulligan, T., and Weidekamm, E. Influence of the antacid Maalox® on the pharmacokinetics of capecitabine in cancer patients. Cancer Chemother. Pharmacol., *43:* 309–315, 1999.

14. Gibaldi, M., and Perrier, D. (eds.). Pharmacokinetics, Ed. 2. New York: Marcel Dekker Inc., 1982.

15. Pelkonen, O., Kärki, N. T., and Larmi, T. K. I. Liver drug metabolism in tumor-bearing surgical patients. Chir. Gastroenterol., *7:* 436–443, 1973.

16. Weisburger, J. H., Grantham, P. H., Vanhorn, E., Steigbigl, N. H., Rall, D. P., and Weisburger, E. K. Activation and detoxification of *N*-2-fluorenylacetamide in man. Cancer Res., *24:* 475–479, 1964.

17. Benjamin, R. S., Wiernik, P. H., and Bachur, N. R. Doxorubicin chemotherapy—efficacy, safety, and pharmacologic basis of an intermittent single high-dose schedule. Cancer (Phila.), *54:* 19–27, 1973.

18. Twelves, C. J., Dobbs, N. A., Gillies, H. C., James, C. A., Rubens, R. D., and Harper, P. G. Doxorubicin pharmacokinetics: the effect of abnormal liver biochemistry tests. Cancer Chemother. Pharmacol., in press, 1999.

19. Bruno, R., Hille, D., Thomas, L., Riva, A., and Sheiner, L. B. Population pharmacokinetics/pharmacodynamics of docetaxel (Taxotere) in Phase II studies. Proc. Am. Soc. Clin. Oncol., *14:* 457, 1995.

20. Pugh, R. N. H., Murray-Lyon, I. M., Dawaon, J. L., Pietroni, M. C., and Williams, R. Transection of the oesophagus for bleeding oesophageal varices. Br. J. Surg., *60:* 646–649, 1973.

21. Gillies, H. C., Rogers, H. J., Ohashi, K., Liang, R., Harper P. G., and Rubens, R. D. Correlation between elimination of indocyanine and doxorubicin or idarubicin. Proc. Am. Soc. Clin. Oncol., *5:* 56, 1986.

22. Dobbs, N. A., Twelves, C. J., Rizzi, P., Warwick, J. D., Metivier E. M., Williams, R., and Johnson, P. J. Epirubicin in hepatocellular carcinoma: pharmacokinetics and clinical activity. Cancer Chemother. Pharmacol., *34:* 405–410, 1994.

23. Twelves, C. J., Dobbs, N. A., Michael, Y., Summers, LA, Gregory, W., Harper, P. G., Rubens, R. D., and Richards, M. A. Clinical pharmacokinetics of epirubicin: the importance of liver biochemistry tests. Br. J. Cancer, *66:* 765–769, 1992.

24. Twelves, C., Budman, D. R., Creaven, P. J., Schellens, J. H. M., Kuruma, I., Dumont E., Osterwalder, B., and Reigner, B. G. Pharmacokinetics and pharmacodynamics of capecitabine in two Phase 1 studies. Proc. Am. Soc. Clin. Oncol., *15:* 476, 1996.

25. Moore, M. J., and Theissen, J. J. Cytotoxics and irreversible effects. *In:* C. J. van Boxtel, N. H. G. Holford, and M. Danhof (eds.), The *In Vivo* Study of Drug Action, pp. 379–400. Amsterdam: Elsevier, 1992.

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