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ORIGINAL ARTICLE

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Effect of renal impairment on the pharmacokinetics and tolerability of capecitabine (Xeloda) in cancer patients

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Abstract *Purpose*: The primary objective of this study was to investigate the influence of renal impairment on the pharmacokinetics of capecitabine and its metabolites in cancer patients. Capecitabine (Xeloda) is an orally administered precursor of 5′-deoxy-5-fluorouridine (5′-DFUR), which is preferentially activated to 5-fluorouracil (5-FU) in tumors. *Methods:* A total of 27 patients were enrolled, of whom 24 were evaluable for pharmacokinetics (6 with normal renal function, 8 with mild, 6 with moderate, and 4 with severe renal impairment at baseline). Patients received capecitabine orally at the standard dosing regimen (1250 mg/m^2 capecitabine twice daily for 2 weeks followed by a 1-week rest period). On study days 1 and 14, blood samples were collected to evaluate the pharmacokinetics of capecitabine and its metabolites. The relationship between the area under the plasma concentration-time curve (AUC) and creatinine clearance (CL_{CR}) was assessed by log-linear regression analysis. *Results:* The primary pharmacokinetic parameter with respect to the effect of renal dysfunction was systemic exposure to 5′-DFUR, 5-FU and FBAL determined on study day 14. Renal impairment led to an increase in the systemic exposure to 5′-DFUR and FBAL (23% and 109% increase in AUC, respectively) for a 50% reduction in CL_{CR}. By contrast, renal impairment may lead to decreased exposure to 5′-DFCR. There was no evidence for an effect of renal impairment on systemic exposure to 5-FU or capecitabine. Renal impairment did not have a major effect on peak concentration (C_{max}) or elimination half-life ($t_{1/2}$) of capecitabine, 5′-DFCR, 5′-DFUR, and 5-FU. However, in the case of FBAL, moderate or severe renal impairment caused up to a twofold increase in C_{max} and prolongation of $t_{1/2}$. All patients with severe renal impairment (four patients) had drug-related grade 3 or 4 adverse-events (AEs) and serious AEs. Patients with moderate renal impairment experienced a similar number of grade 3 or 4 AEs (six of nine patients) but had a higher incidence of serious AEs (three of nine patients) when compared with those with normal renal function (four of six patients and one of six patients, respectively). A similar effect was seen in patients with mild renal dysfunction (grade 3 or 4 AEs in four of eight patients; serious AEs in three of eight patients). The relationship between systemic exposure to capecitabine or its metabolites and safety was investigated using logistic

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regression. This exploratory analysis showed a strong positive relationship between AUC of 5′-DFUR and treatment-related grade 3 or 4 AEs, whereas there was no relationship with exposure to capecitabine, 5′-DFCR, 5-FU or FBAL. *Conclusions:* Renal impairment has no effect on the pharmacokinetics of capecitabine or 5-FU, but leads to an increase in the systemic exposure to 5′-DFUR and FBAL. However, only the AUC of 5′-DFUR is correlated with safety. Based on the safety results in patients with severe renal impairment, a dose modification cannot be recommended for these patients and they should not be treated with capecitabine. Additional data from the clinical safety database and pharmacokinetic results from the present study support the recommendation that patients with moderate renal impairment should be treated with 75% of the recommended standard starting dose to achieve systemic exposure comparable to that in patients with normal renal function.

Keywords Capecitabine · Pharmacokinetics · Renal impairment · Adverse events

Abbreviations *5′-DFCR:* 5′-deoxy-5-fluorocytidine · *5′-DFUR:* 5′-deoxy-5-fluorouridine · *5-FU:* 5-fluorouracil · *AEs:* adverse events · *AUC:* area under the plasma concentration versus time curve · CL_{CR}: creatinine clearance · C_{max}: maximum plasma concentration · *FBAL:* α-fluoro-β-alanine · $t_{1/2}$: elimination half-life · t_{max}: time to occurrence of maximum plasma concentration

Introduction

The novel fluoropyrimidine carbamate capecitabine (Xeloda) is an orally administered precursor of 5′-deoxy-5-fluorouridine (5′-DFUR), which is preferentially activated to 5-fluorouracil (5-FU) in tumor tissue [1, 2]. After oral administration, capecitabine is extensively absorbed and passes through the intestinal mucosa as the intact molecule, thus avoiding the direct release of 5-FU within the small intestine [3]. This was expected to reduce the dose-limiting toxicities seen with orally administered fluoropyrimidines with the potential for improvement in the therapeutic index [4]. Capecitabine is first metabolized in the liver to 5′-deoxy-5-fluorocytidine (5′-DFCR), which is then converted to 5′-DFUR by cytidine deaminase, principally located in the liver and tumor tissue [1, 3]. Further catalytic activation of 5′-DFUR to 5-FU then occurs preferentially in the tumor by the tumor-associated angiogenic factor thymidine phosphorylase [5], thereby minimizing the exposure of normal tissues to 5-FU. Subsequently, 5-FU is further metabolized to dihydrofluorouracil and then FBAL [3].

Capecitabine is currently approved in over 50 countries, including the USA and the European Union, for patients with taxane-refractory breast cancer and as first-line monotherapy for patients with metastatic colorectal cancer. The recommended dose of capecitabine is 1250 mg/m^2 twice daily, administered orally for 2 weeks followed by a 1-week rest period, given in 3-week cycles.

Capecitabine has been investigated extensively in clinical trials. Capecitabine monotherapy is an established treatment option for patients with anthracycline- and taxane-pretreated metastatic breast cancer [6, 7] and is active in patients with metastatic colorectal cancer [8, 9, 10]. Two large, phase III trials have demonstrated that as first-line therapy for metastatic colorectal cancer, capecitabine achieves significantly superior response rates, equivalent time to disease progression, and equivalent survival compared with 5-FU/leucovorin [9, 10]. A prospectively planned, integrated analysis of the efficacy and safety data from these trials has been conducted to obtain information on a large patient population (>1200). The results of the integrated analysis confirmed the results of the individual trials [11].

The influence of CL_{CR} (down to values of 35 ml/min) on C_{max} and AUC of capecitabine and its metabolites was assessed in the phase 1 studies by meta-analysis and by individual analyses (data on file at Hoffmann-La Roche). These revealed no effect of CL_{CR} on the AUC of intact drug, 5′-DFCR or 5′-DFUR. However, results with respect to 5-FU were inconsistent and for FBAL a marked increase in AUC was found in patients with a low CL_{CR}. Therefore, the current study was designed with the primary objective of investigating the effect of renal impairment on the pharmacokinetics of capecitabine and its metabolites in patients with various degrees of renal impairment. Since the AUC and C_{max} of 5-FU increase with repeated administration of capecitabine [12], the effect of renal function was investigated on day 1 and also on day 14 at steady-state. Secondary objectives of this study were to explore the effect of renal function on safety and to investigate the relationship between safety and the systemic exposure to capecitabine and its metabolites.

Materials and methods

Study design and patients

This was an open-label pharmacokinetic and safety study with a parallel design including three groups of patients with mild, moderate, and severe renal impairment and one group with normal renal function.

All patients were ambulatory with histologically/cytologically confirmed solid tumors of various origins, had a life expectancy of at least 12 weeks, a normal hepatic function, and no standard treatment available. They were assigned to the following groups based on CL_{CR} estimated at screening using the Cockroft and Gault equation [13]: group A (normal renal function, defined as CL_{CR} >80 ml/min); group B (mild renal impairment, CL_{CR} 51–80 ml/min); group C (moderate renal impairment, CL_{CR} 30–50 ml/min); group D (severe renal impairment, CL_{CR} <30 ml/min). All patients received capecitabine orally at the approved dose of 1250 mg/m^2 twice daily for 14 days, followed by 7 days rest. The treatment was repeated every 21 days until progression of the disease or intolerability.

According to the study protocol, six patients evaluable for pharmacokinetics were to be studied in each group. If the patients did not complete the first 14 days of the study that included the pharmacokinetic assessments, they were replaced. The sample size of six per group was based on statistical calculations using the variability observed in a previous regression analysis with the same variables.

The trial was conducted in full agreement with the principles of the Declaration of Helsinki III (as amended in Tokyo, Venice, and Hong Kong). The trial protocol was approved prior to commencement by the Ethical Review Board of the participating institutions. Written informed consent was obtained from each patient before the start of the study. Screening before the start of the study included physical examination, recording of vital signs (blood pressure, pulse rate, body temperature, body weight, Karnofsky performance status), laboratory safety tests (hematology, blood chemistry, urinalysis), tumor assessment, ECG and a 24-h urine collection for the estimation of CL_{CR}. Adverse events (AEs) were recorded at baseline, throughout the study, and up to 28 days after the last dose. Vital signs and laboratory tests were repeated on days 1 and 14 and follow-up; physical examination was also repeated at follow-up. Standard exclusion criteria taking into account the stage of the disease, the current medical status and life expectancy of the patients were applied in order to obtain evaluable clinical and pharmacokinetic data.

Blood sampling

On study days 1 and 14, blood samples of 5 ml were collected predose and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 h after dosing using Vacutainers containing EDTA as anticoagulant. Blood samples were centrifuged at 1500 *g* for 10 min, and the plasma removed and stored in plastic tubes at –20°C until analysis.

Drug assay

Plasma concentrations of capecitabine and its metabolites were determined by validated liquid chromatography with mass spectrometry detection as described previously [3].

Pharmacokinetic parameters

Estimation of the pharmacokinetic parameters was performed according to standard non-compartmental methods [14], using SAS, Version 6.12 for Windows/NT [15]. The pharmacokinetic parameters of capecitabine and its metabolites (5′-DFCR, 5′-DFUR, 5-FU and FBAL) were calculated for each patient from the concentration-time data on days 1 and 14. Maximum plasma concentration (C_{max}) and time (t_{max}) to reach this value were taken directly from the observed values. Apparent half-life ($t_{1/2}$) was estimated from $\ln 2/\lambda$. The apparent rate constant of elimination (λ) was estimated using linear regression on the logarithm of the plasma concentration versus time data. Area under the plasma concentration time curve from time 0 to infinity ($AUC_{0-\infty}$) was estimated using the sum of AUC_{0-t} and C_{tlast}/k. AUC_{0-t} was the area under the curve from time 0 to the last sampling time (t_{last}) at which a concentration above the limit of quantification was measured (C_{tlast}). AUC_{0-t} was estimated using the linear trapezoidal rule.

Statistical analysis

The primary pharmacokinetic parameter for the investigation of the effect of renal impairment was $AUC_{0-\infty}$ of 5′-DFUR and 5-FU, and AUC_{0-12} of FBAL determined on day 14. A log-linear regression analysis was performed with the dependent log-transformed parameter AUC and the independent parameter log of the estimated CL_{CR} on day 14. This model is equivalent to the multiplicative model:

$$AUC = \mu * CL_{CR}^{\beta}$$

where μ denotes the general mean of the transformed variable and β the slope for the logarithmically transformed parameter CL_{CR}.

The primary statistical analysis was performed using CL_{CR} estimated according to Cockroft and Gault. A secondary analysis was conducted using CL_{CR} estimated from urinary and serum creatinine concentrations to check the consistency with the results obtained from the primary analysis.

The relationship between systemic exposure to capecitabine or its metabolites and safety was investigated using logistic regression with the dependent variable occurrence (yes/no) of any related grade 3 or 4 AE over the entire study period of 54 weeks and the independent variable logAUC on day 14:

$$p = \exp(\alpha+\beta \ln[x_{hi}])/(1 + \exp(\alpha+\beta \ln[x_{hi}]))(h = 1, ...4, i = 1, ...N_h)$$

where p is the predicted probability for the occurrence of a related grade 3 or 4 AE given the independent variable $\ln(x_{hi})$, and α and β are the parameters of the model to be estimated from (binary) data.

To explore the effect of renal impairment on safety, a logistic regression analysis was performed with occurrence (yes/no) of any related grade 3 or 4 AE (dependent variable) and the log of CL_{CR} (independent variable).

Safety analysis

All patients who received at least one dose of capecitabine and had follow-up safety data were included in the safety analysis. Clinical AEs and laboratory parameters were recorded up to 28 days after last dose of capecitabine and assessed according to the National Cancer Institute of Canada common toxicity criteria (NCIC CTC) grading system. Those toxicities not listed on the NCIC CTC grading system were classified by the investigators as mild, moderate, severe or life-threatening.

Results

A total of 27 patients (19 females, 8 males; age range 38–74 years) entered the study. Their weight ranged between 48 and 95 kg, with body surface area between 1.4 and 2.1 m^2. There were 24 and 21 patients evaluable for pharmacokinetics on days 1 and 14, respectively. Descriptive statistics of the pharmacokinetic parameters of capecitabine and its metabolites estimated on days 1 and 14 in the four groups with differing renal function are presented in Tables 1 and 2, respectively. The AUC of 5′-DFUR, 5-FU, and FBAL determined on day 14 were the primary pharmacokinetic endpoints of the study.

Effect of renal impairment on systemic exposure to capecitabine

Only small increases in AUC of capecitabine were observed in patients with reduced renal function amounting to 13% in group C and 19% in group D on day 1 and to 12% in group C on day 14 (Tables 1 and 2).

Log-linear regression analysis with log-transformed AUC and CL_{CR} provided no evidence for an effect of CL_{CR} (estimated according to Cockroft and Gault) on systemic exposure to intact drug on either study day (Table 3). A reduction in CL_{CR} by 50% resulted in a

Table 1 Descriptive statistics of the pharmacokinetic parameters of capecitabine and its metabolites estimated on day 1 after the morning dose of capecitabine (1250 mg/m^2) in the four groups with different renal functions. Geometric means (geometric %CV) are reported for C_{max}, $AUC_{0-\infty}$ and AUC_{0-12}; median values (min-max) are reported for t_{max}; and arithmetic means (%CV) are reported for $t_{1/2}$

	Group A (normal renal function, $n=6$)	Group B (mild renal impairment, $n=8$)	Group C (moderate renal impairment, $n=6$)	Group D (severe renal impairment, $n=4$)
Capecitabine				
C_{max} (μg/ml)	4.63 (52%)	3.47 (102%)	4.10 (121%)	5.07 (40%)
t_{max} (h)	1.00 (0.25–4.08)	2.03 (0.25–3.10)	2.51 (0.48–3.03)	1.23 (0.48–2.00)
$AUC_{0-\infty}$ (μg·h/ml)	5.95 (35%)	5.40 (50%)	6.73 (75%)	7.06 (51%)
$t_{1/2}$ (h)	0.56 (68%)	0.46 (20%)	0.48 (32%)	0.50 (44%)
5′-DFCR				
C_{max} (μg/ml)	5.20 (24%)	5.15 (32%)	4.65 (93%)	6.23 (27%)
t_{max} (h)	1.03 (0.97–4.08)	2.03 (0.48–4.00)	2.51 (1.12–3.03)	1.54 (1.02–2.00)
$AUC_{0-\infty}$ (μg·h/ml)	11.0 (35%)	12.2 (19%)	11.4 (83%)	11.9 (17%)
$t_{1/2}$ (h)	0.79 (23%)	0.80 (10%)	0.71 (10%)	0.83 (19%)
5′-DFUR				
C_{max} (μg/ml)	6.55 (33%)	6.22 (36%)	7.74 (45%)	12.5 (13%)
t_{max} (h)	1.03 (0.97–4.08)	2.05 (0.48–4.00)	2.98 (1.12–3.03)	1.54 (1.02–2.00)
$AUC_{0-\infty}$ (μg·h/ml)	13.5 (19%)	13.4 (26%)	18.2 (42%)	23.0 (21%)
$t_{1/2}$ (h)	0.72 (39%)	0.61 (12%)	0.62 (9%)	0.68 (20%)
5-FU				
C_{max} (μg/ml)	0.424 (82%)	0.259 (39%)	0.307 (52%)	0.541 (47%)
t_{max} (h)	1.03 (0.70–4.08)	2.03 (0.48–3.10)	2.98 (1.12–3.03)	1.54 (1.02–2.00)
$AUC_{0-\infty}$ (μg·h/ml)	0.796 (43%)	0.549 (30%)	0.723 (45%)	1.01 (41%)
$t_{1/2}$ (h)	0.78 (46%)	0.64 (11%)	0.65 (8%)	0.71 (12%)
FBAL				
C_{max} (μg/ml)	7.34 (10%)	6.39 (19%)	7.76 (19%)	11.2 (17%)
t_{max} (h)	2.57 (1.83–5.15)	3.00 (2.98–5.00)	5.01 (4.00–5.05)	3.50 (2.93–5.07)
$AUC_{0-\infty}$ (μg·h/ml)	37.5 (36%)	35.2 (27%)	69.5 (37%)	133 (46%)
$t_{1/2}$ (h)	3.07 (25%)	3.38 (28%)	4.42 (38%)	7.29 (28%)

Table 2 Descriptive statistics of the pharmacokinetic parameters of capecitabine and its metabolites estimated on day 14 after the morning dose of capecitabine (1250 g/m^2) the four groups with different renal functions. Geometric means (geometric %CV) are reported for C_{max}, $AUC_{0-\infty}$ and AUC_{0-12}; median values (min-max) are reported for t_{max}; and arithmetic means (%CV) are reported for $t_{1/2}$ (*NC* not calculated)

	Group A (normal renal function, $n=6$)	Group B (mild renal impairment, $n=7$)	Group C (moderate renal impairment, $n=6$)	Group D (severe renal impairment, $n=2$[a])
Capecitabine				
C_{max} (μg/ml)	5.05 (44%)	3.80 (93%)	3.32 (81%)	2.25/2.61
t_{max} (h)	1.50 (0.55–2.00)	1.00 (0.25–3.00)	2.00 (0.25–2.25)	2.00/0.48
$AUC_{0-\infty}$ (μg·h/ml)	6.46 (31%)	6.13 (52%)	7.23 (54%)	3.88/3.98
$t_{1/2}$ (h)	0.37 (26%)	0.48 (23%)	0.56 (30%)	0.50/0.58
5′-DFCR				
C_{max} (μg/ml)	6.26 (20%)	5.38 (31%)	2.71 (73%)	3.37/3.95
t_{max} (h)	1.51 (1.00–2.00)	1.07 (1.00–3.13)	2.13 (1.00–3.05)	3.00/1.02
$AUC_{0-\infty}$ (μg·h/ml)	11.4 (27%)	12.0 (16%)	7.26 (79%)	7.40/9.74
$t_{1/2}$ (h)	0.72 (11%)	0.78 (14%)	0.74 (12%)	0.59/0.92
5′-DFUR				
C_{max} (μg/ml)	11.2 (41%)	7.91 (49%)	9.02 (64%)	12.3/9.79
t_{max} (h)	1.51 (1.00–2.00)	2.00 (1.00–4.00)	2.63 (2.00–4.00)	3.00/1.02
$AUC_{0-\infty}$ (μg·h/ml)	18.8 (24%)	15.4 (17%)	23.2 (43%)	22.5/22.7
$t_{1/2}$ (h)	0.56 (14%)	0.58 (9%)	0.67 (17%)	0.54/0.70
5-FU				
C_{max} (μg/ml)	0.956 (52%)	0.581 (101%)	0.469 (68%)	0.754/0.390
t_{max} (h)	1.51 (1.00–2.00)	1.07 (1.00–3.13)	2.63 (2.00–5.00)	3.00/1.02
$AUC_{0-\infty}$ (μg·h/ml)	1.53 (32%)	1.09 (46%)	1.18 (46%)	1.456/0.966
$t_{1/2}$ (h)	0.60 (18%)	0.69 (8%)	0.75 (17%)	0.58/0.72
FBAL				
C_{max} (μg/ml)	6.55 (28%)	7.80 (31%)	8.93 (31%)	19.6/17.1
t_{max} (h)	3.00 (2.08–3.00)	2.00 (2.00–5.00)	4.02 (3.05–6.00)	5.00/3.12
AUC_{0-12} (μg·h/ml)	36.5 (43%)	44.8 (33%)	63.9 (31%)	163/NC
$t_{1/2}$ (h)	3.88 (41%)	3.25 (24%)	5.45 (29%)	8.85/NC

[a]Individual values for the two patients

13% increase in AUC on day 1 and a 13% decrease on day 14 ($P=0.43$ and 0.47 for the log-linear regression test, respectively). Similar results were obtained when CL_{CR} was estimated from urine collection ($P=0.86$ for the log-linear regression test).

Effect of renal impairment on systemic exposure to 5′-DFCR

There was no evidence for an increase in AUC of 5′-DFCR on day 1 in patients with renal impairment

Table 3 Parameter estimate for the influence of estimated CL_{CR} on the AUC of the primary and secondary analytes on day 14

Analyte	Parameter	μ	β	*P*-value	% change in AUC for a 50% reduction in CL_{CR} (95% CI)
Capecitabine	$AUC_{0-\infty}$	2.87	0.194	0.47	–13 (–40, 28)
5′-DFCR	$AUC_{0-\infty}$	0.752	0.642	0.013	–35 (–54, –10)
5′-DFUR	$AUC_{0-\infty}$	63.5	–0.300	0.11	23 (–5, 60)
5-FU	$AUC_{0-\infty}$	0.646	0.162	0.51	–11 (–37, 27)
FBAL	AUC_{0-12}	3658	–1.06	< 0.0001	109 (54, 183)

(Tables 1 and 2). However, on day 14, AUC appeared to be 36% lower for patients in group C compared to those in group A. Similarly, lower AUC values were also found for patients in group D.

On day 1, regression analysis provided no evidence for an effect of CL_{CR} (Cockroft and Gault) on systemic exposure to 5′-DFCR ($P = 1.00$). On day 14, the AUC of 5′-DFCR was reduced by 35% ($P = 0.013$) when CL_{CR} decreased by 50% (Table 3). The results obtained on day 14 were similar when using CL_{CR} estimated from urine collection (27% decrease in AUC, $P = 0.042$).

Effect of renal impairment on systemic exposure to 5′-DFUR

AUC values of 5′-DFUR were higher in group C by 35% on day 1 and 23% on day 14, and by 70% in group D on day 1 (Tables 1 and 2).

Log-linear regression analysis revealed that CL_{CR} (Cockroft and Gault) had a significant effect on the AUC of 5′-DFUR on day 1 with a 35% increase in AUC when CL_{CR} was reduced by 50% ($P = 0.0034$). On day 14, the direction of the change in exposure was the same with a 23% increase in AUC when CL_{CR} was reduced by 50%, but the relationship was no longer statistically significant ($P = 0.11$). When using CL_{CR} estimated from urine collection, the change on day 14 was in the same direction but less pronounced (11% increase in AUC when CL_{CR} was reduced by 50%; $P = 0.25$).

Effect of renal impairment on systemic exposure to 5-FU

An increase of 27% in systemic exposure to 5-FU occurred in group D on day 1. All other groups experienced no substantial changes in AUC (Tables 1 and 2).

There was no statistically relevant influence of CL_{CR} (Cockroft and Gault) on AUC of 5-FU on days 1 and 14. On day 1, the increase was 23% for a 50% reduction in CL_{CR} ($P = 0.13$), while on day 14, a decrease in AUC of 11% was observed for a 50% reduction in CL_{CR} ($P = 0.51$; Table 3). A similar result was obtained on day 14 with a 10% decrease in AUC when using CL_{CR} estimated from urine collection ($P = 0.41$).

Effect of renal impairment on systemic exposure to FBAL

On both study days, the AUC values of FBAL were markedly higher in patients in groups C and D compared to those in group A. There was no increase, or only a slight increase, for patients in group B compared with those in group A (Tables 1 and 2). On day 1, the increase in AUC amounted to 85% in group C and 255% in group D. Similar increases in AUC were observed on day 14: 75% in group C and of 347% in group D (only one assessable patient) compared with group A.

Statistical analysis revealed that CL_{CR} (Cockroft and Gault) had a statistically significant influence on the AUC of FBAL on both day 1 ($P < 0.0001$) and day 14 ($P < 0.0001$). The magnitude of the increase in AUC was 114% on day 1 and 109% on day 14 when CL_{CR} was reduced by 50% (Table 3). When using CL_{CR} estimated from urine collection, the increase in AUC on day 14 was 61% ($P = 0.0002$).

Effect of renal impairment on peak plasma concentrations and elimination half-lives

There was no evidence for a clinically relevant increase in C_{max} for capecitabine, 5′-DFCR, or 5-FU in patients with renal impairment on either day 1 or day 14 (Tables 1 and 2). C_{max} values for 5′-DFUR on day 1 appeared to be higher in group D compared with the other groups, but on day 14, peak concentrations were similar in all groups. C_{max} values for FBAL were similar on day 1 in group A, B, and C. However, a 53% increase in C_{max} was observed for group D compared with group A. On day 14, C_{max} values for FBAL were similar in groups A and B. On this occasion, a 36% increase in C_{max} was observed for patients of group C and with an almost twofold increase in the two subjects of group D (compared with group A).

On both study days, renal impairment had no important effect on the $t_{1/2}$ of capecitabine, 5′-DFCR, 5′-DFUR, or 5-FU (Tables 1 and 2). By contrast, the $t_{1/2}$ of FBAL was markedly affected by reduced renal function. On day 1, the mean $t_{1/2}$ was 44% greater in group C and 140% greater in group D compared with group A. Similar increases in $t_{1/2}$ were observed for these two groups on day 14.

Relationship between safety and renal impairment

Mean duration of exposure to capecitabine was 110 ± 71 days for patients in group A, 147 ± 133 days in group B, 68 ± 38 days in group C, and 40 ± 28 days in group D. The most important safety results are summarized in Table 4.

Patients with mild renal impairment (group B). Patients with mild renal impairment appeared to have a similar risk of experiencing treatment-related grade 3 or 4 AEs as the control group (four of eight patients in group B compared to four of six in group A). The incidence of drug-related serious AEs was higher in group B than in group A (three of eight patients and one of six patients, respectively), which may be partly explained by the longer treatment duration in group B. However, only two out of eight patients in group B withdrew from treatment due to AEs.

Patients with moderate renal impairment (group C). Patients with moderate renal impairment also appeared to have a similar number of related grade 3 or 4 AEs when compared with those who had a normal renal function (six of nine patients in group C compared four of six in group A). However, these patients were treated for a shorter period of time than those in group A, so a small increase in the risk of experiencing grade 3 or 4 AEs may have existed but did not result in an increased withdrawal rate. The incidence of drug-related serious AEs appeared higher in group C than in group A (three of nine patients and one of six patients, respectively). Only one of the nine patients with moderate renal impairment withdrew from capecitabine treatment due to AEs.

Patients with severe renal impairment (group D). All four patients with severe renal impairment experienced a serious AE and a treatment-related grade 3 or 4 AE. The median treatment duration was shorter in group D and two out of the four patients were withdrawn from treatment due to AEs. The only death in the study considered by the investigator to be related to treatment occurred in this group. The patient died due to a combination of sepsis and acute on chronic renal failure (both considered probably related to study drug), and deterioration of her general condition due to disease progression (considered unrelated to trial medication). Because of these safety concerns, no further patients with severe renal impairment were recruited.

The results of the statistical analysis (logistic regression) showed that the probability of experiencing a treatment related grade 3 or 4 AE during the study increased with decreasing CL_{CR}, but the relationship was not statistically significant ($P = 0.26$).

Relationship between systemic exposure and safety

The relationship between systemic exposure to capecitabine and its metabolites on day 14 and the likelihood of treatment-related grade 3 or 4 AEs over the entire study period was investigated using univariate logistic regres-

Table 4 Number of patients with clinically relevant AEs, serious AEs, or deaths in the four groups with different degrees of renal impairment over the entire study duration

	Group A (normal renal function: CL_{CR} >80 ml/min)	Group B (mild renal impairment: CL_{CR} 51–80 ml/min)	Group C (moderate renal impairment: CL_{CR} 30–50 ml/min)	Group D (severe renal impairment: CL_{CR} <30 ml/min)
Number of patients evaluable for safety	6	8	9	4
Duration of treat-ment (median days)	114	159	74	35
Number of patients with related grade 3 or 4 AEs	4	4	6	4
Number of patients who withdrew due to AEs	1	2	1	2
Number of patients with related serious AEs	1	3	3	4
Number of deaths unrelated to treat-ment[a]	0	1	1	1
Number of deaths related to treat-ment[a]	0	0	0	1
Number of patients with selected AEs				
Diarrhea (all intensities)	5	5	6	3
Hand-foot syndrome (all intensities)	6	5	2	1
Stomatitis (all intensities)	2	1	2	1
Neutropenia (grade 3 or 4)	0	0	0	1
Leucopenia (grade 3 or 4)	0	1	0	1

sion. The data obtained in this study were particularly suited to this type of statistical analysis because the proportion of patients with a treatment-related grade 3 or 4 AE was high (66%) and the ranges of the AUCs were large, especially for FBAL.

Descriptive summary statistics for AUC in patients with and without related grade 3 or 4 AEs are presented in Table 5. The estimated logistic regression relationships for 5′-DFUR and FBAL are shown in Fig. 1. There was a statistically significant relationship for 5′-DFUR ($P = 0.013$, slope 1.25) but not for the parent drug ($P = 0.631$, slope –0.13), 5′-DFCR ($P = 0.091$, slope –0.69), 5-FU ($P = 0.710$, slope 0.11), or FBAL ($P = 0.934$, slope –0.02).

Discussion

The primary objective of this study was to investigate the effect of renal impairment on the pharmacokinetics of capecitabine and its metabolites in patients with various degrees of renal impairment. Secondary objectives were to explore the effect of renal function on safety and to investigate the relationship between safety and the systemic exposure to capecitabine or its metabolites.

Influence of renal impairment on systemic exposure

The pharmacokinetic parameters determined on day 1 in patients with normal renal function were similar to those previously reported following administration of identical doses to patients with comparable renal function [3]. The present study provided no evidence for an effect of renal impairment on the systemic exposure to capecitabine on either study day. A similar result was obtained for 5′-DFCR on day 1, but a decrease in systemic exposure was observed on day 14 in patients with renal impairment. The current results are difficult to interpret because of the lack of consistency between day 1 and day 14.

For 5-FU, no evidence for an influence of renal impairment on the systemic exposure to this active metabolite was found. The results obtained in the present study were expected because after administration of capecitabine, urinary excretion is a minor pathway of elimination for 5-FU (only approximately 0.5% of dose is recovered in urine as 5-FU [3]).

Renal impairment caused a moderate but clear increase in the systemic exposure to 5′-DFUR. This is in contrast to two previous investigations that have shown no evidence for an effect of renal impairment on the AUC of 5′-DFUR (data on file at Hoffmann-La Roche). From a clinical point of view, this moderate increase in the AUC of 5′-DFUR in the current study was considered relevant because of the relationship between systemic exposure to 5′-DFUR and safety (Fig. 1a).

Renal impairment also caused a major increase in systemic exposure to FBAL. This result was expected because approximately 50% of the capecitabine dose is excreted in the urine as FBAL [3]. From a clinical point of view, however, the effect of renal impairment on the AUC of FBAL is not considered to be relevant because FBAL does not have antiproliferative activity and there is no relationship between the AUC of FBAL and safety (Fig. 1b).

For capecitabine and its metabolites, the plasma protein binding is relatively low (54%, 10%, 60% and 10% for capecitabine, 5′-DFCR, 5′-DFUR and 5-FU respectively) and is not concentration-dependent [3]. Possible changes in protein binding in patients with renal impairment might therefore be of minor relevance to explain the observed pharmacokinetic changes.

Relationship between systemic exposure and safety

Following administration of capecitabine, 5′-DFUR is the direct precursor of 5-FU, the pharmacologically active compound. Intact drug, 5′-DFCR, 5′-DFUR and FBAL are themselves not cytotoxic. The positive correlation between plasma AUC of 5′-DFUR and safety suggests that plasma concentrations of 5′-DFUR can serve as a marker of the exposure of the healthy tissues to 5-FU, and 5′-DFUR should be considered as the most important metabolite of capecitabine.

The lack of relationship between plasma AUC of 5-FU and the occurrence of treatment-related grade 3 or 4 AEs suggests that 5-FU concentrations in plasma did not reflect the exposure of normal tissues to 5-FU. This is probably due to the metabolism of 5-FU in situ since dihydropyrimidine dehydrogenase is present in many different tissues of the body. 5-FU is metabolized in normal tissues and never comes back to the systemic circulation as 5-FU. The absence of a correlation between systemic exposure to FBAL and safety suggests that FBAL did not cause adverse effects and that its concentrations in plasma did not reflect the extent of exposure of normal tissues to 5-FU. In the absence of renal impairment, plasma concentrations of FBAL might be considered as a potential marker of tissue exposure to 5-FU. However, in the present study, high plasma levels of FBAL in plasma were primarily observed in patients with low CL_{CR} and not in patients who were exposed to high concentrations of 5-FU in normal tissues.

Influence of renal impairment on safety

Due to the small number of patients in this clinical pharmacology study, no firm conclusion concerning the impact of renal impairment on safety is possible. The increase in the incidence of clinically relevant AEs (serious AEs and grade 3 or 4 AEs) in patients with moderate and severe renal impairment may have pharmacokinetic and pharmacodynamic explanations.

Table 5 Descriptive statistics of AUC values on day 14 in patients with and without related grade 3 or 4 AEs during the whole study (*Q1*, *Q3* first and third quartiles, respectively)

Analyte	Grade 3 or 4 AEs	Number of patients	AUC (μg·h/ml)		
			Q3	Median	Q1
Capecitabine	No	7	10.64	6.61	5.47
	Yes	14	8.07	6.52	3.98
5′-DFCR	No	7	13.34	11.81	11.44
	Yes	14	12.03	9.53	8.21
5′-DFUR	No	7	18.26	14.57	13.07
	Yes	14	24.14	22.22	17.07
5-FU	No	7	1.59	1.15	0.84
	Yes	14	1.59	1.31	0.97
FBAL	No	7	66.09	49.89	36.82
	Yes	13	62.94	53.72	32.02

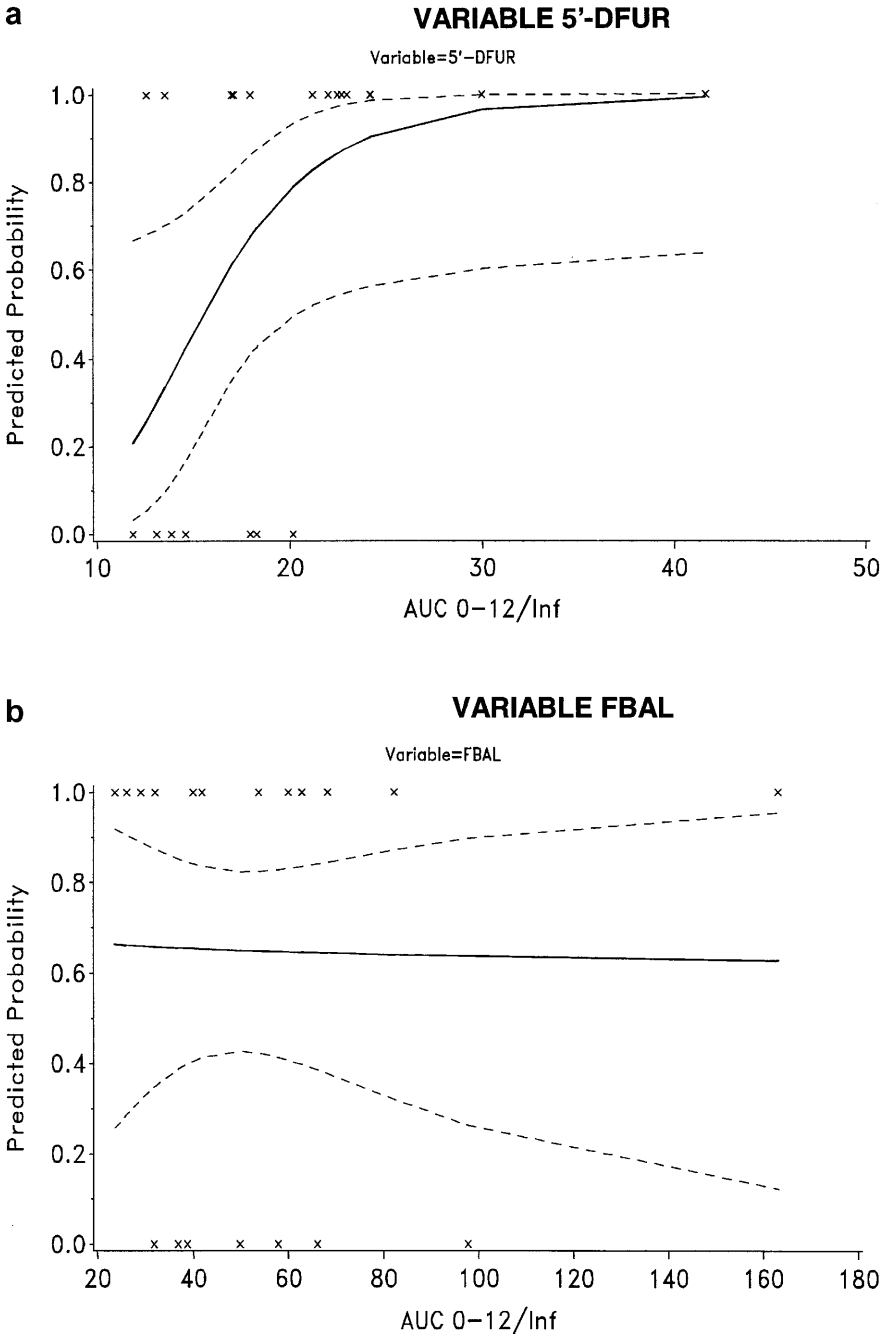

Fig. 1a, b Relationship between the AUCs of 5′-DFUR (**a**) and FBAL (**b**) and the probability of treatment-related grade 3 or 4 AEs ($n = 21$). The *solid lines* represent the logistic regression curves and the *dotted lines* the 95% confidence intervals. *Crosses* are individual patient values

In patients with severe and moderate renal impairment, the AUC of 5′-DFUR was higher than in patients with normal renal function. The changes in 5′-DFUR pharmacokinetics may partially explain the increased incidence of clinically relevant AEs. 5′-DFUR is considered the most important metabolite because of its demonstrated relationship with safety (Fig. 1a) and because it is the direct precursor of 5-FU, the pharmacologically active compound. Moreover, it is possible that patients with moderate or severe renal impairment are pharmacodynamically more sensitive to the side effects of chemotherapy with 5-FU. The patients enrolled in this study were very sick, due to the combined effects of their advanced cancer and renal impairment. Patients who are pharmacodynamically more sensitive to 5-FU may be at greater risk of clinically relevant AEs than a less-sensitive group, even if systemic exposure to 5-FU is the same for both groups.

Implications for dose recommendations

Severe renal impairment (CL_{CR} *< 30 ml/min*). Based on the high incidence of serious AEs and grade 3 or 4 AEs, patients with severe renal impairment should not be treated with capecitabine.

Moderate renal impairment (CL_{CR} *30–50 ml/min*). The number of patients in the present study was small and no firm conclusions about safety in this group were possible. Additional assessment of safety data from two phase III studies has confirmed the higher incidence of clinically significant AEs in patients with moderate renal impairment compared with the control group [16]. Based on the 25–35% increase in the AUC of 5′-DFUR, patients with moderate renal impairment should be treated with a reduced dose corresponding to 75% of the usual recommended standard starting dose of 1250 mg/m^2 twice daily (2500 mg/m^2 per day). In these patients, the reduced dose should result in systemic exposure to 5′-DFUR comparable to that of the standard dose in patients with normal renal function. This should maintain both the tolerability and antitumor activity of capecitabine.

The increase in the incidence of clinically relevant AEs in patients with renal impairment is not limited to capecitabine. Indeed, in a clinical safety database with results from two phase III studies comparing capecitabine with 5-FU/leucovorin, renal impairment has been shown to lead to a higher incidence of grade 3 or 4 treatment-related AEs in the 5-FU/leucovorin arm, and the incidence of stomatitis was almost doubled in patients with moderate renal impairment who received 5-FU/leucovorin [16]. Furthermore, efficacy was substantially reduced in these patients (response rate of 10% in the 5-FU/leucovorin arm). In contrast, response rates to capecitabine (between 24% and 27%) was not affected by renal function status. [16]. The implications of renal impairment are, if anything, more substantial for patients receiving 5-FU than for those treated with capecitabine. Also, there was no evidence of a direct nephrotoxic effect with capecitabine [16].

Mild renal impairment (CL_{CR} *51–80 ml/min*). Patients with mild renal dysfunction appeared to have an almost identical probability of related grade 3 or 4 AEs as those with normal renal function and no change in the pharmacokinetics of 5′-DFUR. Nevertheless, these patients should be monitored carefully during capecitabine treatment.

References

1. Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, Shimma N, Umeda I, Ishitsuka H (1998) Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumors by enzymes concentrated in human liver and cancer tissue. Eur J Cancer 34:1274–1281
2. Schüller J, Cassidy J, Dumont E, Roos B, Durston S, Banken L, Utoh M, Mori K, Weidekamm E, Reigner B (2000) Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. Cancer Chemother Pharmacol 45:291–297
3. Reigner B, Blesch K, Weidekamm E (2001) Clinical pharmacokinetics of capecitabine. Clin Pharmacokinet 40:85–104
4. Kono A, Hara Y, Sugata S, Karube Y, Matsushima Y, Ishitsuka H (1983) Activation of 5′-deoxy-5-fluorouridine by thymidine phosphorylase in human tumors. Chem Pharm Bull 31:175–178
5. Takebayashi Y, Akiyama S, Akiba S, Yamada K, Miyadera K, Sumizawa T, Yamada Y, Murata F, Aikou T (1996) Clinicopathologic and prognostic significance of an angiogenic factor, thymidine phosphorylase in human colorectal carcinoma. J Natl Cancer Inst 88:1110–1117
6. Blum JL, Jones SE, Buzdar AU, et al (1999) Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. J Clin Oncol 17:485–493
7. Blum JL, Buzdar AU, Dieras V, et al (1999) A multicentre phase II trial of Xeloda™ (capecitabine) in taxane-refractory metastatic breast cancer. Proc Am Soc Clin Oncol 18:107a (abstract 403)
8. Van Cutsem E, Findlay M, Osterwalder B, et al (2000) Capecitabine, an oral fluoropyrimidine carbamate with substantial activity in advanced colorectal cancer: results of a randomized phase II study. J Clin Oncol 18:1337–1345
9. Van Cutsem E, Twelves C, Cassidy J, et al (2001) Oral Xeloda® (capecitabine) compared with intravenous 5-fluorouracil plus leucovorin (Mayo Clinic regimen) in patients with metastatic colorectal cancer patients: results of a large phase III study. J Clin Oncol 19:4097–4106
10. Hoff PM, Ansari R, Batist G, et al (2001) Comparison of oral capecitabine (Xeloda®) v intravenous 5-fluorouracil plus leucovorin (Mayo Clinic regimen) as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. J Clin Oncol 19:2282–2292
11. Hoff PM (2000) Capecitabine as first-line treatment for colorectal cancer (CRC): integrated results of 1207 patients from 2 randomized, phase III studies. On behalf of the Capecitabine CRC Study Group. Ann Oncol 11 [Suppl 4]:60 (abstract 263)
12. Mackean MJ, Planting ASTh, Twelves C, Schellens JHM, Allman D, Osterwalder B, Reigner B, Griffin T, Kaye S, Verweij J (1998) A phase I and pharmacologic study of intermittent twice daily oral therapy with capecitabine in patients

with advanced and/or metastatic cancer. J Clin Oncol 16:2977–2985
13. Cockroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16:31–41
14. Gibaldi M, Perrier D (1982) Pharmacokinetics, 2nd edn. Marcel Dekker, New York
15. SAS Institute (1993) SAS companion for the Microsoft Windows environment, version 6, 1st edn, SAS Institute, Cary
16. Cassidy J, Twelves C, Marshall J, Van Cutsem E, Hoff P, Osterwalder B, Burger U, Schilsky R (2001) First-line capecitabine therapy in metastatic colorectal cancer: a review of the safety profile. Ann Oncol (in press)