Cancer Chemother Pharmacol (2003) 51: 58–66
DOI 10.1007/s00280-002-0536-1

ORIGINAL ARTICLE

**Anne O'Donnell · Cornelis J.A. Punt · Ian Judson
Lydia van Maanen · A. Benjamin Suttle
Philip Ertel · Philip Beale**

A study to evaluate the pharmacokinetics of oral 5-fluorouracil and eniluracil after concurrent administration to patients with refractory solid tumours and varying degrees of renal impairment (FUMA1005)

Received: 15 March 2002 / Accepted: 17 September 2002 / Published online: 20 November 2002

Abstract *Background*: Eniluracil is an inactivator of dihydropyrimidine dehydrogenase, the first enzyme in the catabolic pathway of 5-fluorouracil (5-FU). Concurrent administration of oral eniluracil with oral 5-FU not only increases the bioavailability of 5-FU, owing to elimination of first-pass metabolism, but can change the route of elimination of 5-FU from hepatic metabolism to renal excretion. An open-label study was performed to determine the effect of renal impairment on the pharmacokinetics of 5-FU in the presence of eniluracil. *Methods*: Enrolled in the study were 17 patients with refractory solid tumours (Karnofsky performance status ≥70%; age 31–74 years; 12 male, 5 female). The patients were separated into two groups based upon creatinine clearance (CLCr): group A had "normal" renal function arbitrarily defined as CLCr ≥50 ml/min ($n=8$), and group B had moderate renal impairment, i.e. CLCr < 50 ml/min ($n=9$). Treatment was separated into test and treatment periods. During the test period all patients received eniluracil 50 mg orally on days 1–3 and 5-FU 10 mg/m^2 together with pharmacokinetic measurements. During the treatment period, all patients received eniluracil 50 mg orally on days 1–7 with 5-FU at a standard dose of 20 mg/m^2 for those in group A or a dose individualized according to the pharmacokinetic parameters in the test period for those in group B. *Results*: The clearance of both eniluracil and 5-FU was decreased in patients with renal impairment compared to those with normal renal function. A linear relationship was observed between 5-FU CL/F and CLCr in patients with renal impairment, but not in those with normal renal function. 5-FU dose modification, on the basis of the test dose pharmacokinetic data for the patients with renal function impairment, accurately resulted in drug exposure in the potentially therapeutic range. Toxicity was not increased. *Conclusions*: Eniluracil increases the oral bioavailability of 5-FU and results in a switch from hepatic metabolism to renal elimination. A standard dose of this combination can be administered safely to patients with CLCr > 50 ml/min. The combination can also be given to patients with renal impairment using a test dose and pharmacokinetic measurements to predict the appropriate dose of 5-FU. It is expected that sufficient information will be available from this and other studies to allow accurate prediction of the appropriate 5-FU dose modifications required in patients with renal impairment.

Keywords Eniluracil · 5-Fluorouracil · Renal impairment · Pharmacokinetically guided dosing

Abbreviations *5-FU:* 5-fluorouracil · *ALT:* alanine transaminase · *AST:* aspartate transaminase · *AUC:* area under concentration × time curve · C_{max}: maximum concentration · *CLCr:* creatinine clearance · *CL/F:* plasma clearance · *CLr:* renal clearance · *DPD:* dihydropyrimidine dehydrogenase · *FBAL:* α-fluoro-β-alanine · *ULN:* upper limit of normal

This study was supported by GlaxoWellcome (now GlaxoSmith-Kline).

A. O'Donnell (✉) · I. Judson · P. Beale
Clinical Pharmacology, E Block, Institute of Cancer Research, 15 Cotswold Road, Belmont, Surrey SM2 5NG, UK
E-mail: anneo@icr.ac.uk
Tel.: +44-208-6426011
Fax: +44-208-6427979

C.J.A. Punt · L. van Maanen
University Medical Centre, St Radboud, Nijmegen, The Netherlands

A.B. Suttle · P. Ertel
GlaxoWellcome Inc., Research Triangle Park, North Carolina, USA

Present address: P. Beale
Royal Prince Alfred Hospital, Sydney, Australia

Introduction

5-Fluorouracil (5-FU, Fig. 1) is an antimetabolite with a well-established role in the treatment of many malignancies but particularly in the treatment of

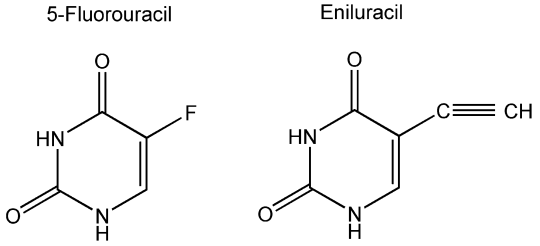

Fig. 1 Structures of 5-fluorouracil and eniluracil

gastrointestinal cancers such as carcinoma of the colon, rectum, stomach and pancreas. The potential efficacy of 5-FU is in part limited by its pharmacokinetics. Although variable, in normal circumstances up to 80% of the systemically available 5-FU is catabolized through the DPD pathway in the liver and other tissues. The remainder is cleared by renal excretion [12]. Eniluracil [2,4(1H,3H)-pyrimidinedione 5-ethynyl, Fig. 1] has been developed as an irreversible inhibitor of DPD, the first, and rate-limiting enzyme in this catabolic pathway. The concomitant administration of eniluracil and 5-FU has been shown in preclinical and clinical studies to change the dominant mode of elimination of 5-FU from catabolism to renal excretion [2, 4, 6, 20, 21]. In animal models, pretreatment with eniluracil also significantly increases the bioavailability of oral 5-FU presumably through inactivation of first-pass metabolism pathways dependent upon DPD activity [2, 6, 21].

Initial phase I studies with eniluracil and 5-FU were performed in patients with near-normal renal function (estimated creatinine clearance, CLCr, ≥50 ml/min) [4, 20]. However, even in these studies a relationship between renal function and pharmacokinetic parameters could be demonstrated. CLCr and serum creatinine correlated well with 5-FU systemic clearance suggesting that, as expected in the presence of eniluracil, the principal means of 5-FU elimination is via renal excretion rather than hepatic metabolism [4].

The current study was designed to determine the pharmacokinetics and safety of the combination of oral eniluracil and oral 5-FU in patients with varying degrees of renal impairment. The intention was in the first place to evaluate the use of test dose pharmacokinetics to allow prediction of the safe dose of 5-FU and secondly add to the knowledge of 5-FU renal clearance in the presence of total DPD inhibition in patients with CLCr < 50 ml/min.

Methods

Patient population

Patients for the study were required to have histologically confirmed solid malignancy no longer responsive to standard therapy or for which no standard therapy was available. They were required to be 18 years of age or over, with a life expectancy of at least 12 weeks and a Karnofsky performance status of 70% or higher. Eligibility was further restricted to patients capable of swallowing and retaining oral medication, and patients with any evidence of malabsorption, gastric or small-bowel resection or disease significantly affecting gastrointestinal function were excluded. Patients were ineligible if they had clinically relevant ascites, pleural effusion or peripheral oedema. Eligibility criteria also included: (a) no surgery, wide-field radiotherapy or chemotherapy within 4 weeks of treatment (6 weeks for those previously treated with nitrosoureas or mitomycin C), (b) adequate haematological indices (haemoglobin > 9.0 g/dl, white cell count $> 2.0\times10^9$/l, platelets $> 120\times10^9$/l), (c) adequate hepatic indices (total bilirubin < 1.25 times ULN, AST/ALT < 3 times ULN) and stable renal function. Stable renal function was not strictly defined in the protocol, but patients were only included if the CLCr was essentially unchanged over the 4 weeks prior to study entry. Concomitant medications were closely reviewed and drugs which were considered potentially nephrotoxic or which may have altered or modulated either the activity or the pharmacokinetics of either 5-FU or eniluracil (such as dypyridamole, allopurinol, trimethoprim or folinic acid) were prohibited [9]. All patients gave their full written informed consent prior to treatment. The study was performed under the guidelines set out in The Declaration of Helsinki (September 1989) and was reviewed by the Research Ethics Committee of both participating institutions.

Investigational agents

Both investigational agents were supplied by GlaxoWellcome (now GlaxoSmithKline). Eniluracil was supplied as 10-mg tablets and 5-FU as 1-mg, 5-mg and 25-mg tablets. The tablets were stored at room temperature and were protected from light.

Study design

The study was an open label pharmacokinetic study. Patients were assigned to one of two groups depending upon renal function. Group A were those considered to have normal renal function, with an estimated CLCr of ≥50 ml/min, and group B were those with impaired renal function, with an estimated CLCr of < 50 ml/min. Renal function was estimated using the formula derived by Cockcroft and Gault [8] and by ^{51}Cr-labelled EDTA clearance.

Dosage and administration

Treatment was divided into two periods. During the test period, all patients received a single 50 mg oral dose of eniluracil daily for 3 days after a 2-h fast. Fasting was continued for 2 h after treatment. Each dose was taken with a small amount (180 ml) of water. On day 2 a dose of 5-FU was administered orally immediately after the eniluracil.

The dose of 5-FU was 10 mg/m^2 for both patients in group A (normal renal function) and for those in group B (impaired renal function). At the time of initiation of this trial the recommended phase II dose for oral 5-FU plus eniluracil had not been clearly established. The test dose of 10 mg/m^2 was chosen in light of the available pharmacokinetic, toxicity and efficacy data from the phase I programme. Pharmacokinetic studies of eniluracil and oral 5-FU in these phase I studies had shown that the $AUC_{0-\infty}$ for a single 20-mg/m^2 dose of oral 5-FU when given with eniluracil is similar to the AUC_{0-60} of a 600-mg/m^2 dose of 5-FU alone, when administered by intravenous bolus. A dose of 20 mg/m^2 oral 5-FU on days 1–5 with 50 mg eniluracil on days 1–7 had already been proven safe (and 25 mg/m^2 would subsequently be used as the recommended dose in phase II evaluations). Furthermore, there had been evidence of antitumour activity (tumour shrinkage and clinical improvement) at doses of oral 5-FU as low as 10 mg/m^2 when given for 5 days in combination with eniluracil. Body surface area in metres squared was calculated using the DuBois formula [10].

Patients entered the treatment period up to 3 weeks after the final dose of study drug in the test period, and thereafter treatment was scheduled every 28 days (unless pharmacokinetic parameters

from the test period dictated otherwise). In the treatment period patients received eniluracil 50 mg orally daily on days 1–7, again under limited fasting conditions. 5-FU was administered orally directly after the eniluracil on days 2–6. For patients in group A, the 5-FU was given at 20 mg/m^2. Patients in group B received individualized dosing based on their test dose pharmacokinetic parameters in order to allow exposure to safe but potentially efficacious dose levels of 5-FU. The dose chosen was estimated to achieve an AUC for each patient in group B that would not exceed that of a patient with normal renal function receiving 20 mg/m^2. In the event that a patient had a CLCr of $\leq$ 20 mg/m^2, it was planned that the estimated AUC of the chosen dose should not exceed 60% of that of a patient with normal renal function receiving 20 mg/m^2. However, no such patients were recruited into the study. Courses were repeated until disease progression or the onset of unmanageable toxicity.

Pharmacokinetic sampling

Sampling for the determination of the pharmacokinetics of uracil, eniluracil and 5-FU was performed on day 2 of the test period and on days 6 and 7 of course one in the treatment period. Blood samples were collected into heparinized tubes before drug administration and at 8, 15, 30, 45, 60 and 90 min and 2, 4, 6, 8, 12, 16 and 24 h following administration. During the test period further specimens were also collected at 48 and 72 h, while in the treatment period a final sample was collected at 36 h. Samples were immediately placed on ice and the plasma was then isolated using a refrigerated centrifuge within 20 min of specimen collection, placed in inert plastic tubes and frozen at –20°C until analysed.

Urine for 5-FU, eniluracil, uracil and α-fluoro-β-alanine (FBAL, the principal metabolite of 5-FU) levels was collected in 6-h time periods for 48 h commencing after 5-FU administration on day 2. After measurement of both urine volume and pH, a 25-ml sample from each collection was removed to a polyethylene vial and stored at –20°C until analysis. Analysis was completed with gas chromatography/mass spectrometry (GCMS) using validated methods [4, 20]. The pharmacokinetics of 5-FU, eniluracil, uracil and FBAL were determined using noncompartmental methods of analysis in WinNonlin Pro v1.5. Renal excretion parameters were calculated using Microsoft EXCEL.

The AUC was calculated using the logarithmic trapezoidal rule. The AUC was extrapolated to infinity by dividing the last measured concentration by the terminal rate constant λ_z, which was determined from the slope of the terminal phase of a semi-logarithmic plot of the drug concentration-versus-time curve. The following relationships were used to calculate other pharmacokinetic parameters: $t_{1/2}$ was calculated as $\ln(2)\lambda_z$, the apparent oral clearance as dose/$AUC_{0-\infty}$ for test dose data (single dose) and as dose/AUC_{0-24} for treatment period data (steady-state assumed). CL/F is reported in both millilitres per minute and millilitres per minute per kilogram. For each study drug Spearman's rank-order, regression analysis and Pearson's correlation coefficients with their 95% confidence intervals were computed to assess the degree of linear association of the calculated CLCr and CL/F for 5-FU in both the test and treatment periods. These analyses were performed on the entire set of patients as well as by patient group. Finally, one-way analysis of variance (ANOVA) on each of the CL/F values and on each of the CLr values was performed to compare renal function patient groups by period/course for each study drug.

Pretreatment and follow-up evaluations

Prior to study entry each patient had a baseline documentation of medical history, physical examination, performance status, laboratory testing (haematological, renal, hepatic and urinalysis), ECG and assessment of glomerular filtration rate (GFR) by ^{51}Cr-EDTA clearance as a check on the estimated CLCr. Once on-study patients were reviewed weekly when clinical assessment of adverse events and concurrent illness was made and changes in concomitant therapy recorded. A complete blood count and differential were performed weekly and biochemistry, urinalysis every 2 weeks. A complete ocular examination (visual acuity, intraocular pressure, and examination of the cornea, lens, optic disc and retina) was performed at baseline and after every two cycles of therapy, as ocular toxicity is a known, albeit extremely infrequent, consequence of 5-FU treatment. Coagulation studies were performed prior to study entry and reviewed weekly (or more frequently if indicated in patients on anticoagulants). Toxicity was graded according to SWOG criteria and formal tumour response evaluation was performed after every two cycles (8 weeks) of treatment, again measured by SWOG criteria [11].

Results

Seventeen patients were enrolled in this study, 8 in the normal renal function group and 9 in the renal impaired group (one patient repeated the test dose due to an elevated CLCr); their characteristics are displayed in Table 1. Group A (normal renal function) had a median CLCr of 77.9 ml/min (range 62.5–97.0 ml/min) prior to the test period which remained consistent through to the treatment period with a median of 81.1 ml/min (range 60.1–95.6 ml/min). Group B had a median CLCr of 42.0 ml/min (range 22.9–49.1 ml/min) prior to the test period which rose to 46.9 ml/min (range 24.3–51.1 ml/min) prior to the treatment period.

Pharmacokinetic results

Samples from all patients were evaluable for pharmacokinetics. The mean plasma 5-FU concentration-time and eniluracil concentration-time profiles are shown in Fig. 2. Summaries of the mean pharmacokinetic parameters of 5-FU are shown in Table 2. Mean 5-FU clearance and terminal half-life values were similar during the test and treatment periods for both patient groups, suggesting that across the study period no significant time-dependent changes occurred in either group. Renal impairment markedly decreased the renal elimination of 5-FU. Mean CLr was 54.3 ml/min in group A patients and only 19.1 ml/min in group B patients (ANOVA, using least squares mean, significant to 90% confidence interval). Further, in group B a linear relationship between CLCr and 5-FU CL/F was seen in both the test (r^2 0.67) and treatment (r^2 0.59) periods. The relationship between CLCr and 5-FU CL/F is presented for all patients, in both test and treatment periods, in Fig. 3.

Renal impairment also resulted in decreased systemic clearance of 5-FU. The mean $\pm$ SD 5-FU CL/F for group A in the test period was 79.8 $\pm$ 22.3 ml/min compared to 39.5 $\pm$ 10.4 ml/min for group B (Table 2) (ANOVA, using least squares mean, significant to 90% confidence interval).

Table 3 shows the doses of 5-FU given to the patients in group B in the treatment period based on the pharmacokinetic data from the test period. No patients were recruited with a CLCr of less than 20 ml/min and only

Table 1 Demographic characteristics for all patients included in the study

	Normal renal function (CLCr ≥50 ml/min)	Impaired renal function (CLCr < 50 ml/min)
No. of patients	8	9
M:F	7:1	5:4
Karnofsky performance status (%)		
70	1	7
80	2	1
90	2	1
100	3	0
Age (years)		
Median	52	59.7
Range	45–62	31–74
Tumour types		
Adenocarcinoma, cervix		1
Adenocarcinoma, colon		1
Adenocarcinoma, gall bladder	1	
Adenocarcinoma, renal		1
Breast	1	
Gastric	1	
Leiomyosarcoma		1
Uveal melanoma	1	
Non-small-cell lung cancer		1
Pancreas	1	
Spindle cell sarcoma		1
Squamous cell carcinoma, head and neck	1	1
Transitional cell carcinoma, bladder	1	1
Transitional cell carcinoma, kidney		1
Urothelial	1	

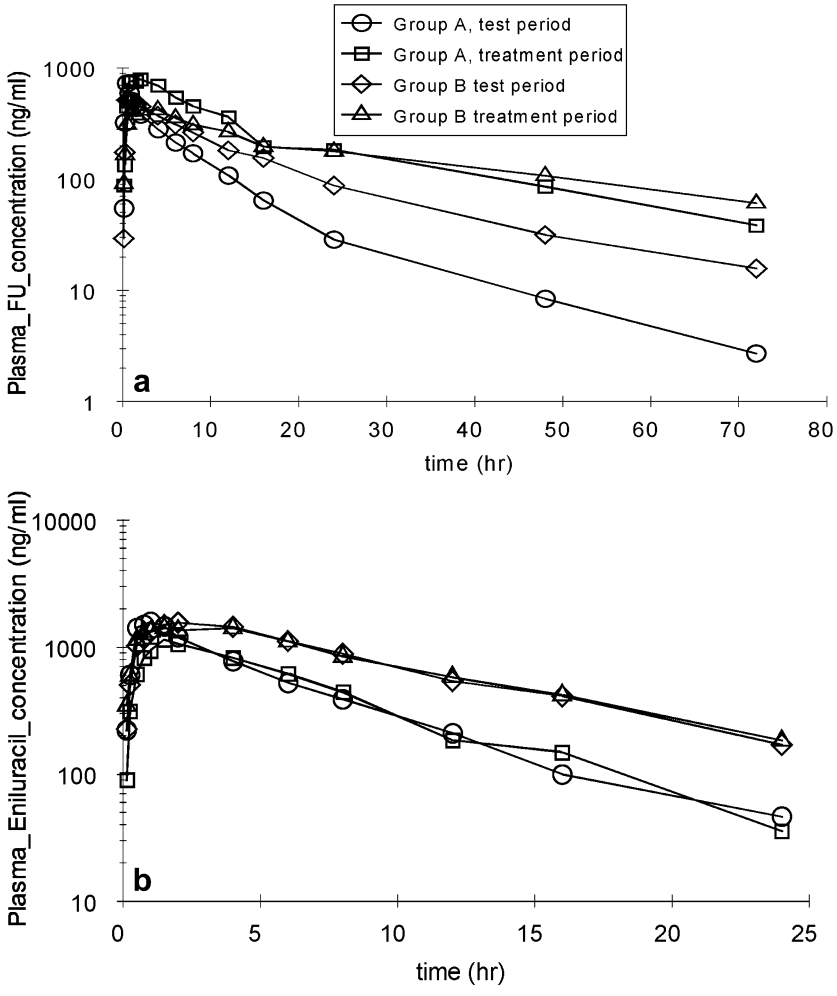

Fig. 2 Mean plasma 5-fluorouracil (**a**) and eniluracil (**b**) concentration vs time profiles for group A (normal renal function) and group B (impaired renal function) during the test and treatment periods

Table 2 5-FU pharmacokinetic parameters in patients with normal renal function (group A) and renal impairment (group B) for both the test period and cycle one of the treatment period. Results are given as means ± SD unless otherwise specified (*Cl/F* apparent oral clearance, *CLr* renal clearance, $T_{1/2}$ terminal elimination half-life, f_e fraction of dose eliminated unchanged in urine, C_{max} maximum plasma concentration, T_{max} time to peak plasma concentration, $AUC_{0-\infty}$ area under the plasma concentration time curve from time zero to infinity, *NC* not calculated)

Parameter	Test period		Treatment period	
	Group A	Group B	Group A	Group B
CL/F (ml/min)	79.8 ± 22.3	39.5 ± 10.4	78.8 ± 24.8	38.1 ± 13.9
CL/F (ml/min/kg)	1.10 ± 0.37	0.65 ± 0.19	1.08 ± 0.41	0.60 ± 0.14
CLr (ml/min)	54.3 ± 23.6	19.1 ± 9.6	NC	NC
$T_{1/2}$ (h)	5.68 ± 1.30	9.72 ± 2.99	8.73 ± 1.97	13.5 ± 3.5
f_e (% of dose)	67.3 ± 12.5	43.7 ± 15.2	NC	NC
C_{max} (ng/ml)	738 ± 153	595 ± 165	1042 ± 308	522 ± 220
T_{max} (median) (h)	0.50	0.80	0.63	0.52
$AUC_{0-\infty}$ (ng·h/ml)	4244 ± 1408	7544 ± 2150	7348 ± 2276	5416 ± 1323

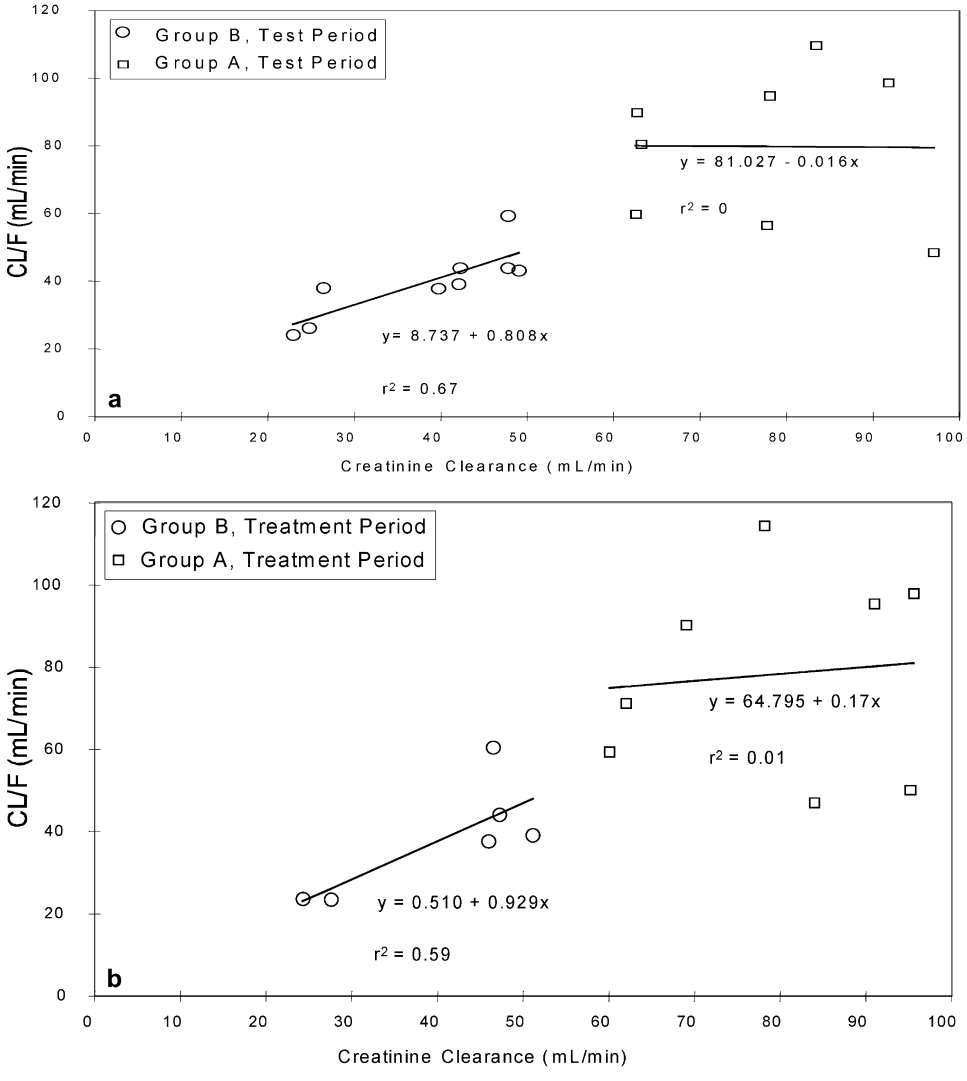

Fig. 3 The relationship between 5-fluorouracil and renal clearance for patients with normal renal function (group A) and those with impaired renal function (group B) during the test period (**a**) and the treatment period (**b**) (r^2 is the correlation coefficient for the least squares regression line of best fit given by *y*)

two patients in the study with a CLCr less than 40 ml/min completed one or more cycles in the treatment period. As patients in group A received significantly higher doses of 5-FU, the mean C_{max} was correspondingly higher in this group than in those in group B.

As shown in Table 4, mean plasma eniluracil clearance values were 30–45% less in the renal impaired groups with a corresponding increase in $t_{1/2}$. The fraction of the 5-FU dose recovered in the urine as FBAL from individual patients ranged from 0.8% to 2.7%.

Table 3 Doses of 5-FU in the treatment period in group B as based on creatinine clearance

Patient number	Period one completed	Estimated GFR (ml/min)	5-FU dose (mg/m^2)	Number of cycles
1b	Yes	22.9	2.5	2
2b	Yes	47.7	8	1
3b	Yes	39.7	Not dosed	0
4b	Yes	42.2	Not dosed	0
5b	Yes[a]	26.4	5	0
6b	Yes	49.0	10	4
7b	Yes	42.0	8	4
8b	Yes	24.7	6	2
9b	Yes	47.8	10	3

[a]Period one repeated

There was no significant difference between the fraction recovered from the patients with renal impairment (median fraction of 0.9% in the normal group) and those with normal renal function (median fraction 1.2%). Mean plasma uracil $AUC_{0\text{-}24}$ was greater in those with renal impairment but the plasma levels achieved were consistently elevated in all patients (Table 5).

Toxicity

In general the toxicity experienced by patients in this study was mild to moderate and was representative of the previous experience with this combination [4, 20]. Although 14 patients (82%) experienced a drug-related adverse event, the overwhelming majority were grade 1 or 2 and only one patient developed a drug-related nonhaematological serious adverse event (cardiac toxicity). There were no toxic deaths on-study, but one patient died of progressive disease within 28 days of receiving the final dose of drug.

Haematological toxicity

The haematological toxicities observed during this treatment programme are presented in Table 6. Bone marrow suppression was generally mild (overall only three patients experienced grade 3/4 toxicity) and was less commonly associated with cycle one than subsequent cycles. One patient (from the normal renal function group) required a temporary treatment delay as a result of unresolved bone marrow toxicity. This affected both cycles two and four of the treatment period (as opposed to the test period).

Nonhaematological toxicity

The principal nonhaematological toxicities seen were nausea, vomiting, mild fatigue, diarrhoea and mucositis. Mild nausea and vomiting was common but not different in the two treatment groups, similarly the incidence of diarrhoea, mucositis and fatigue were not influenced by renal impairment. These results are summarized in Table 6.

Only two patients (one from each group) developed palmar/plantar erythema during the treatment period. A single patient reported dry eyes suggestive of conjunctival irritation, although no treatment-related abnormalities were detected in any patient on ophthalmological

Table 4 Eniluracil pharmacokinetic parameters in patients with normal renal function (group A) and renal impairment (group B) for both the test period and cycle one of the treatment period. Results given as means ± SD unless otherwise specified (Cl/F apparent oral clearance, $T_{1/2}$ terminal elimination half-life, f_e fraction of dose eliminated unchanged in urine, C_{max} maximum plasma concentration, T_{max} time to peak plasma concentration, $AUC_{0\text{-}\infty}$ area under the plasma concentration time curve from time zero to infinity, *NC* not calculated)

Parameter	Test period		Treatment period	
	Group A	Group B	Group A	Group B
CL/F (ml/min)	95.4 ± 16.4	53.6 ± 12.8	102 ± 20	55.9 ± 20.1
CL/F (ml/min/kg)	1.31 ± 0.28	0.859 ± 0.150	1.41 ± 0.37	0.875 ± 0.149
$T_{1/2}$ (h)	3.94 ± 0.82	6.63 ± 1.73	4.04 ± 0.70	6.27 ± 1.37
f_e (% of dose)	52.9 ± 10.7	30.5 ± 10.1	NC	NC
C_{max} (ng/ml)	1723 ± 295	1583 ± 518	1289 ± 268	1632 ± 310
T_{max} (median) (h)	1.03	1.60	1.78	2.51
$AUC_{0\text{-}\infty}$ (ng·h/ml)	9007 ± 1840	16,593 ± 4197	8431 ± 1720	16,365 ± 5110

Table 5 Uracil pharmacokinetic parameters for patients with normal renal function (group A) and impaired renal function (group B) during the test period. Results are presented as mean ± SD (C_{max} maximum plasma concentration, $AUC_{0\text{-}24}$ area under the plasma concentration time curve from time zero to 24 h)

Parameter	Test period		Treatment period	
	Group A	Group B	Group A	Group B
C_{max} (ng/ml)	4,527 ± 1,813.3	8,215 ± 2,209.5	5,441 ± 2,875.3	11,517 ± 4,764.0
$AUC_{0\text{-}24}$ (ng·h/ml)	92,879 ± 34,834.9	160,391 ± 39,564.2	116,670 ± 61,697	250,754 ± 38,316.8

Table 6 Summary of proliferative toxicities experienced by patients with normal renal function (group A) and impaired renal function (group B) for both the test and treatment periods, presented as the number of patients with each toxicity. Toxicity gradings according to the SWOG Common Toxicity Criteria (*Gd* grade)

	n	Granulocytopenia				Anaemia				Thrombocytopenia				Diarrhoea				Mucositis			
		Gd 1	Gd 2	Gd 3	Gd 4	Gd 1	Gd 2	Gd 3	Gd 4	Gd 1	Gd 2	Gd 3	Gd 4	Gd 1	Gd 2	Gd 3	Gd 4	Gd 1	Gd 2	Gd 3	Gd 4
Test period																					
Group A	8	0	0	0	0	2	1	0	0	0	0	0	0	1	0	0	0	1	0	0	0
Group B	9	0	0	0	0	1	2	0	0	1	1	0	0	1	0	0	0	1	1	0	0
Treatment period																					
Group A	8	4	3	0	1	3	3	0	0	6	0	0	0	3	1	1	0	2	1	0	0
Group B	7	1	0	2	0	1	0	2	1	3	1	0	0	2	0	0	0	2	1	0	0

examination. Three patients (one group A, two group B) developed grade 3/4 hyperbilirubinaemia, but this was a reflection of progression of the underlying malignant disease in each case. Three patients (one group A, two group B) developed mild (grade 1) and transient elevations in liver transaminases (both AST and ALT) attributed to the study drugs. One patient (in group A with normal renal function) experienced an acute myocardial infarction after eight cycles of therapy was admitted to hospital and withdrawn from the study. The patient made a full recovery, but in line with previous experience with 5-FU and its derivatives the investigators considered that there was a reasonable possibility that this event was in part related to the study drug.

Response

Of the 17 patients enrolled, 8 were considered to have evaluable disease. One partial response was confirmed in a patient with pancreatic cancer and one patient with colon cancer achieved stable disease. There was also evidence of significant activity in a patient with breast cancer with an overall 92% reduction in size of one of two marker lesions. However, as the final measurement of this lesion was not taken, this patient was considered not evaluable.

Discussion

Eniluracil reliably causes complete inhibition of DPD, the initial rate-limiting enzyme in the catabolic elimination of 5-FU. This enhances the oral bioavailability of 5-FU and overcomes interpatient variability in pharmacokinetic behaviour, which can limit the efficacy of the drug. In addition when administering 5-FU with eniluracil, one can confidently dose the 5-FU, no longer needing to take account of those patients with the rare inherited deficiency of DPD expression who are otherwise considered at risk of unpredictable severe, life-threatening 5-FU toxicity. Several studies have demonstrated encouraging benefits for protracted venous infusion of 5-FU over bolus schedules with fewer side effects and a higher response rate, particularly in the setting of colorectal cancer [17]. An oral 5-FU therapy is thus particularly attractive, as protracted infusion schedules require the placement of central venous catheters with their accompanying risk of infection and thrombosis. Unfortunately, wide interpatient variations in first-pass metabolism normally result in unpredictable oral 5-FU bioavailability. Concomitant administration of oral 5-FU with eniluracil offers a strategy to provide steady-state levels of 5-FU comparable with those achieved using protracted venous infusion. Adjei et al. have recently suggested, based upon a carefully designed pharmacokinetic study, that a higher dose of oral 5-FU than that recommended for protracted phase II use, may be required to achieve steady-state equivalence with infusional 5-FU regimens. The authors themselves acknowledge that at present "the clinical significance of achieving plasma levels similar" to protracted infusion 5-FU is unclear and pharmacokinetic considerations may not be entirely responsible for the efficacy relationships of compounds of this family [1].

As the major pathway of elimination of 5-FU in the presence of eniluracil is renal clearance, dosing guidelines for 5-FU are required for patients with renal impairment who are at risk from increased drug exposure. Similarly, as the clearance of eniluracil is predominantly renal, it can be proposed that theoretically eniluracil may require dose adjustment in this patient group. Dose modification of eniluracil was not undertaken in this study since although the eniluracil was probably administered at a supramaximal dose with respect to DPD inhibition it does not, of itself, cause significant toxicity.

The plasma clearance of oral 5-FU decreased in proportion to a decrease in CLCr over the range 20–50 ml/min. Owing to insufficient data, we were unable to demonstrate a similar relationship in the group with CLCr $>$ 50 ml/min. As seen in Table 2, in the patients in this study, there was a marked difference between the apparent oral clearance (CL/F, dose/$AUC_{0-\infty}$ test dose, dose/AUC_{0-24} treatment period, steady-state assumed) and true renal clearance (CLr, the ratio of the amount excreted in the urine and $AUC_{0-\infty}$). It is likely that this is a consequence of incomplete oral absorption. In a phase I study of patients with advanced malignancy, Baker et al. found the apparent oral bioavailability of oral 5-FU given as a solution, in an eniluracil/5-FU combi-

nation to be variable, ranging from 72% to 122% [4]. Absorption may have also been influenced by the characteristics of the tablet formulation used in the current study, which may be less well absorbed than when the drug is given as a solution.

Eniluracil clearance was also decreased in those with renal impairment but, although a linear relationship could be shown across the entire group of patients on study, the linearity of this relationship could not be confirmed when each study group was analysed on its own. Although normal renal function was defined arbitrarily as those with CLCr greater than or equal to 50 ml/min, no patients enrolled in this study actually had a CLCr between 50 and 60 ml/min. Therefore, although the results of this study suggest that patients with impaired renal function require adjustments of oral 5-FU when administered with eniluracil, the threshold for CLCr below which such adjustments are indicated has not been absolutely defined.

Plasma uracil levels have been shown to be a reliable surrogate marker of effective inactivation of DPD. In practice, due to the ubiquitous nature of this enzyme in human tissues, it has been shown that over 90% of DPD must be inhibited before elevated levels of substrates such as uracil may be detected. Uracil is eliminated by renal clearance and therefore levels of uracil would be expected to be (and indeed were) higher in the patients with renal impairment relative to those with normal renal function. As the levels were consistently elevated in all patients, we can be confident that adequate inhibition of DPD did occur in both groups [3, 22].

The fraction of 5-FU dose recovered in the urine as FBAL ranged from 0.8% to 2.7%. In the presence of eniluracil the fraction of 5-FU dose recovered in the urine as FBAL (the principal metabolite of 5-FU) would be expected to be low, thus confirming effective inhibition of the formation of 5-FU catabolites at these dose levels of eniluracil. As the catabolites in turn determine in large part the non-antiproliferative toxicity profile of 5-FU (neurotoxicity, cardiotoxicity, etc.), this is concordant with the favourable toxicity results also observed in the patients in this study [14, 17, 21, 22].

The toxicity in patients with normal renal function was consistent with the previously reported phase I experience with 5-FU in combination with eniluracil [4, 20]. In addition, the toxicity described by the patients with renal impairment was not dissimilar to those with normal renal function, indicating that successful dose modification of 5-FU on the basis of renal clearance can be performed using test dose pharmacokinetics. In previous phase I studies, the infrequent occurrence of plantar/palmar erythema with the 5-FU/eniluracil combination as compared to 5-FU given by protracted venous infusion has been noted [16]. In the current trial only two patients experienced a palmar/plantar rash. The pharmacokinetic parameters of both these patients were not dissimilar from those of the other patients in their groups.

A single patient in the normal renal function group developed a myocardial infarction following protracted treatment, and was taken off study. Cardiotoxicity is a well-recognized but infrequent side effect of 5-FU, usually manifest as ischaemia, which has been variably considered to be the result of vasospasm, a direct cytotoxic effect, or to be mediated by metabolites of the cytotoxic. In this patient, the pharmacokinetic evaluations were in line with those of the other patients with normal renal function. It is difficult to predict how frequently ischaemic changes occur, as there are few large prospective studies, but estimates range from 1.2% to 18% [5]. This event was thus considered to be within the expected toxicity spectrum.

The pharmacokinetic results demonstrate that similar exposure to 5-FU was successfully achieved in both groups of patients. The antitumour activity seen in this study correlated well with the documented spectrum of activity of 5-FU. One partial response was confirmed in a patient with pancreatic cancer previously treated with a platinum/5-FU combination. It is recognized that further response to 5-FU given as a protracted venous infusion may occur in patients previously treated with bolus schedules [16].

Alternative approaches have been taken to the problem of 5-FU bioavailability. These include: UFT, a combination of the 5-FU precursor tegafur and uracil, a competitive inhibitor of DPD; S1, a fixed mixture of tegafur and two biomodulators, 5′-chloro-2,4-dihydroxypyridoxine and oxonic acid; and capecitabine, arguably the most successful, a rationally designed oral fluoropyrimidine carbonate which is converted to active 5-FU via a three-step enzymatic conversion largely confined to tumour. The randomized phase III trials completed to date (including those with eniluracil) have demonstrated equivalence for these innovative approaches compared to 5-FU, when considering the traditional endpoints of response and survival [7, 13, 15, 18, 23, 24]. There are, however, treatment-related quality of life and cost-effectiveness issues which make oral therapy a worthwhile objective to pursue.

Turning to the needs of the specific patient group explored in this protocol, a study of capecitabine in patients with renal impairment has shown a moderate increase in systemic exposure to 5′-deoxy-5-fluorouridine (5′-DFUR) in patients with renal impairment which was considered relevant because of the relationship between 5′-DFUR levels and safety. Dose modification was proposed for patients with moderate renal impairment (CLCr 30–50 ml/min) but Poole et al. concluded that it was not possible to recommend a dose modification for patients with severe renal impairment (CLCr < 30 ml/min) and they should not be treated with capecitabine [19]. The results of the current investigation appear more robust. With pharmacokinetically guided dosing, it should be possible to offer such patients a second generation fluoropyrimidine (5-FU and eniluracil) with the confidence of a predictable therapeutic window.

In conclusion, the combination of eniluracil and 5-FU can be safely and successfully delivered to patients with varying degrees of renal impairment. Patients with

a CLCr below 50 ml/min should be carefully monitored as dose adjustments are indicated. This study validates the use of a test dose and pharmacokinetic analysis to predict a safe and effective dose of 5-FU. We anticipate that these data will make a substantial contribution to the generation of a nomogram specifying the appropriate dose adjustment of 5-FU/eniluracil in the presence of renal impairment.

References

1. Adjei A, Reid J, Diasio R, Sloan J, Smith D, Rubin J, Pitot H, Alberts S, Goldberg R, Hanson L, Atherton P, Ames M, Erlichman C (2002) Comparative pharmacokinetic study of continuous venous infusion fluorouracil and oral fluorouracil with eniluracil in patients with advanced solid tumours. J Clin Oncol 20:1683–1691
2. Baccanari DP, Davis DT, Knick VC, Spector T (1993) 5-Ethynyluracil (eniluracil): a potent modulator of the pharmacokinetics and anti-tumour efficacy of 5FU. Proc Natl Acad Sci 90:11064–11068
3. Baker SD (2000) Pharmacology of fluorinated pyrimidines: eniluracil. Invest New Drugs 18:373–381
4. Baker SD, Peang Khor S, Adjei AA, Doucette M, Spector T, Donehower RC, Grochow LB, Sartorius, Noe DA, Hohnecker JA, Rowinsky EK (1996) Pharmacokinetic, oral bioavailability and safety study of fluorouracil in patients treated with 776C85, an inactivator of dihydropyrimidine dehydrogenase. J Clin Oncol 14:3085–3096
5. Becker K, Erckenbrecht JF, Haussinger D, Freiling T (1999) Cardiotoxicity of the anti-proliferative compound fluorouracil. Drugs 57:475–484
6. Cao S, Rustum YM, Spector T (1994) 5-Ethynyluracil (eniluracil): modulation of 5FU efficacy and therapeutic index in rats bearing advanced colo-rectal carcinoma. Cancer Res 54:1507–1510
7. Carmichael J, Popeila T, Radstone D, Falk S, Fey M, Oza A, Skovsgaad T, Martin C (1999) Randomised comparative study of orzel (oral uracil/tegafur) plus iv versus parenteral 5-FU plus leucovorin in patients with metastatic colorectal cancer (abstract 1015). Proc Am Soc Clin Oncol 18:264a
8. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16:31–41
9. Czejka MJ, Jayer W, Schuller J, Fogl U, Weiss C, Schernthaner G (1993) Clinical pharmacokinetics of 5-fluorouracil: influence of the biomodulating agents interferon, dipyridamole, and folinic acid alone and in combination. Arzneimittelforschung 43:387–390
10. DuBois D, DuBois EF (1916) A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 17:863–871
11. Green S, Weiss GR (1992) Southwest Oncology Group standard response criteria, endpoint definitions and toxicity criteria. Invest New Drugs 10:239–253
12. Grem JL (2000) 5-Fluorouracil: forty-plus and still ticking. A review of its preclinical and clinical development. Invest New Drugs 18:299–313
13. Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, Maroun J, Walde D, Weaver C, Harrison E, Burger H, Osterwalder B, Wong AO, Wong R (2001) Comparison of oral capecitabine versus intravenous 5-fluorouracil plus leucovorin as first line treatment in 605 patients with metastatic colo-rectal cancer. Results of a randomised phase III study. J Clin Oncol 19:2282–2292
14. Lemaire L, Malet-Martino MC, de Forni M, Martino R, Lasserre B (1992) Cardiotoxicity of commercial 5-fluorouracil vials stems from the alkaline hydrolysis of this drug. Br J Cancer 66:119–127
15. Levin J, Schilsky R, Burris H, Wong A, Colwell B, Thirwell R, Ansari R, Bell W, White R, McGuirt P, Hohnecker J, Pazdur R (2001) North American phase III study of oral eniluracil plus leucovorin in the treatment of advanced colo-rectal cancer (abstract 523). Proc Am Soc Clin Oncol 20:132a
16. Meta-analysis Group In Cancer (1998) Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. J Clin Oncol 16:301–308
17. Paff MT, Baccanari DP, Davis ST, Shousong C, Tansik RL, Rustum Y, Spector T (2000) Pre-clinical development of eniluracil: enhancing the therapeutic index and dosing convenience of 5-fluorouracil. Invest New Drugs 18:365–371
18. Pazdur R, Douillard J-Y, Skillings JR, Eisenberg PD, Davidson N, Harper P, Vincent M, Lambersky B, Benner S (1999) Multicentre phase III study of 5-fluorouracil or UFT in combination with leucovorin in patients with metastatic colo-rectal cancer (abstract 1009). Proc Am Soc Clin Oncol 18:263a
19. Poole C, Gardiner J, Twelves C, Johnston P, Harper P, Cassidy J, Monkhouse J, Banken L, Weidekamm E, Reigner B (2002) Effect of renal impairment on the pharmacokinetics and tolerability of capecitabine (Xeloda) in cancer patients. Cancer Chemother Pharmacol 49:225–234
20. Schilsky RL, Hohnecker J, Ratain MJ, Janisch L, Smetzer L, Sol Lucas V, Peang Khor S, Diasio R, Von Hoff DD, Burris HA (1998) Phase I clinical and pharmacologic study of eniluracil plus fluorouracil in patients with advanced cancer. J Clin Oncol 16:1450–1457
21. Spector T, Cao S, Rustum YM (1995) Attenuation of the antitumour activity of 5-fluorouracil by (*R*)-5-fluorou-5,6-dihydrouracil. Cancer Res 55:1234–1241
22. Takimoto CH, Lu ZH, Zhang R, Liang MD, Larson LV, Cantilena LR, Grem JL, Allegra G, Diasio RB, Chu E (1996) Severe neurotoxicity following 5-fluorouracil based chemotherapy in a patient with dihydropyrimidine dehydrogenase deficiency. Clin Cancer Res 2:477–481
23. Van Cutsem E, Sorenson J, Cassidy J, Dancel F, Harper P, Bailey N, Badey N, Peachey M, Somerville M (2001) International phase III study of oral eniluracil plus 5-fluororuracil vs iv 5-fluorouracil plus leucovorin in the treatment of advanced colo-rectal cancer (abstract 522). Proc Am Soc Clin Oncol 20:131a
24. Van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, Bugat R, Findlay M, Frings S, Jahn M, McKendrick J, Osterwalder B, Perez-Manga G, Rosso R, Rougier P, Schmiegel W, Seitz J, Thompson P, Vieitez JM, Weitzel C, Harper P (2001) Oral capecitabine compared with intravenous 5-fluorouracil plus leucovorin in patients with metastatic colo-rectal cancer. Results of a large phase III study. J Clin Oncol 19:4097–4106