Cancer Chemother Pharmacol (2007) 60:733–739
DOI 10.1007/s00280-007-0419-6

ORIGINAL ARTICLE

Weekday on-weekend off oral capecitabine: a phase I study of a continuous schedule better simulating protracted fluoropyrimidine therapy

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Received: 31 October 2006 / Accepted: 4 January 2007 / Published online: 28 February 2007

Abstract
Background Although protracted intravenous 5-fluorouracil is superior to bolus regimens in terms of tumour exposure to the drug during DNA synthesis as well as activity and safety, the oral fluoropyrimidine capecitabine is administered intermittently. In this phase I study, we investigated an alternative, dose-intense continuous regimen.
Materials and methods Oral capecitabine was administered twice daily continuously with weekend breaks, in patients with advanced solid tumours refractory to standard therapy. Dose escalation proceeded from 1,331 to 2,510 mg/m^2 daily. Dose limiting toxicity (DLT) consisted of any grade-3 or 4 adverse event except for alopecia and skin toxicity resolving within 7 days.
Results Twenty-five heavily pretreated patients participated in the study. No DLT occurred in the first four cohorts. Two out of four patients developed grade III diarrhoea in the fourth week of capecitabine at 2,510 mg/m^2 (DLT). The most common toxic episodes during all cycles of treatment were grade 1–2 fatigue, skin erythema, abdominal cramps, nausea, constipation and neutropenia. Disease regression was seen in three and stabilisation with clinical benefit in ten patients (clinical benefit response 54%). Pharmacokinetic studies of capecitabine and metabolites in four patients at 2,250 mg/m^2 daily showed rapid absorption, short plasma half-lives with the exception of FBAL and absence of accumulation or conversion saturation during the course of therapy. At this dose, administered dose intensity in eight patients was 99.3% of the planned one.
Conclusions Weekday on-weekend off capecitabine maximizes cytotoxic impact on tumour cells during S-phase by safely simulating protracted fluoropyrimidine therapy at a recommended dose (2,250 mg/m^2) close to that of the intermittent schedule and clearly higher than the continuous one of 1,331 mg/m^2.

Keywords Capecitabine · Fluoropyrimidine · Pharmacokinetics · Phase I trials

This study was supported by a research grant from Roche Hellas, Athens, Greece.

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Introduction

5-Fluorouracil (5-FU) is an antimetabolite, widely used in the management of patients with upper gastrointestinal tract, colon and head and neck carcinomas. 5-FU and its cytotoxic intracellular metabolite, deoxy-fluorouridine monophosphate (FdUMP), are most active

when taken up by malignant cells during DNA synthesis in the S-phase of the cell cycle. The plasma half-life of 5-FU is short (5–15 min) whereas tissue half-life has been reported to range from 20–130 min for 5-FU and as long as 20 h for FdUMP [1, 2]. Tumour retention of 5-FU anabolites results in thymidylate synthase (TS) binding and inhibition of DNA synthesis during S-phase. Protracted 5-FU infusion results in more prolonged 5-FU uptake by tumour tissue and has the advantage of exposing a larger malignant cell population to effective FdUMP concentrations during the most "vulnerable" phase of nucleosynthesis [3]. These pharmacodynamic considerations seem to be confirmed by clinical data in several tumour types that establish superior efficacy as well as improved tolerance of either protracted or intermittent 48-h 5-FU infusion as opposed to bolus administration via enhanced 5-FU malignant tissue retention [4, 5]. Capecitabine is a convenient, oral fluorocarbamate preferentially metabolised in malignant tissues to cytotoxic FdUMP that showed remarkable activity against breast and colon cancer [6]. As efforts at continuous capecitabine administration were hindered by excessive toxicity and low cumulative administered dose, the "14-days-on, 7-days-off" regimen at 2,510 mg/m^2 daily has been established as standard [7]. However, this schedule represents a significant distancing from the therapeutic principle of prolonged exposure of malignant cells to an S-phase specific cytotoxic drug, as the 1-week break may allow for tumour repopulation [8]. In this phase I study, we investigated the pharmacokinetics, toxicity and maximal tolerated dose (MTD) of a "5-days-on, 2-days-off" continuous capecitabine regimen that may better simulate protracted fluoropyrimidine therapy without compromising dose intensity.

Patients and methods

This was a phase I non-randomised study that took place in the Departments of Medical Oncology of Ioannina University Hospital and Papageorgiou General Hospital, Greece, from January 2004 until January 2006. The study was approved by the local research ethics committees and all patients gave written informed consent.

Eligibility criteria and treatment

All patients enrolled in the study had histologically or cytologically confirmed inoperable malignant solid tumours refractory to standard palliative treatment. Eligibility criteria included ECOG performance status 0–2, estimated life expectancy >12 weeks and adequate bone marrow (absolute neutrophil count ANC $\geq$ 1.5 $\times$ 10^9/l, platelet count PLT $\geq$ 100 $\times$ 10^9/l), hepatic (AST, ALT, Alkaline phosphatase < 2.5 $\times$ upper limit of normal, bilirubin < 1.5 $\times$ upper limit of normal) and renal (glomerular filtration rate GFR $\geq$ 50 ml/min as measured by the Cockroft-Gault formula) function.

Capecitabine was administered orally as 500-mg capsules twice daily 30 min after food intake for 5 consecutive days each week, followed by a weekend break. Dose escalation proceeded in cohorts consisting of a total daily dose of 1,331, 1,665, 2,000, 2,250, 2,510, 2,750 mg/m^2. The starting dose represented the dose recommended by Budman et al., in their continuous regimen while the highest dose was 10% higher than the standard dose of the intermittent 14-day schedule [6, 14]. Dose escalation proceeded in cohorts of 3–6 patients and was allowed only after all patients in the previous dose level had completed 6 weeks of chemotherapy. Intrapatient dose escalation was not allowed. The daily patient dose was rounded up based on body surface area and availability of the drug in 500-mg capsules.

Dose escalation and evaluation of toxicity

Chemotherapy toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC version 3.0), assessed every 2 weeks or daily upon appearance of severe side effects. Dose escalation, determination of dose-limiting toxicity (DLT) and MTD, occurred on the basis of toxicity during the first 6 weeks of therapy only. Three patients entered each cohort and in the absence of DLT, escalation to the next dose was allowed in a new patient cohort. If one DLT episode occurred, the initial cohort was expanded with another three patients (total of six) and escalation continued if no additional DLT events occurred. Occurrence of DLT in two or more out of three to six patients defined identification of the MTD. DLT was defined as any grade 3 or 4 side-effects except for any resolving to grade 0–1 within two days without loss of more than four capecitabine doses, any skin toxicity resolving to grade 0–1 within seven days without loss of more than six capecitabine doses [13]. Any side effect causing treatment delay for more than 2 weeks was also considered DLT. The MTD was defined as the capecitabine dose causing DLT in one-third or more of treated patients. Once the MTD had been reached, the previous dose level was defined as the recommended dose and four additional patients were enrolled to expand clinical experience and to perform pharmacokinetic studies. Patients who did not complete 6 weeks of therapy for

reasons other than toxicity, were replaced to determine DLT and MTD. Cumulative toxicity was also recorded for all subsequent chemotherapy cycles at all dose levels in all patients. Patient therapy could continue beyond 6 weeks until disease progression, unacceptable toxicity or withdrawal of consent.

Dose intensity, dose modification and activity

Dose modifications were performed on the basis of toxicity observed, following capecitabine-specific recommendations already published [6]. The total capecitabine dose administered during the first 6 weeks of therapy was calculated in the eight patients who received the recommended dose of 2,250 mg/m^2 and dose-intensity was expressed as a percentage of the planned drug dose to be administered per square meter of body surface area per week. Although not a formal endpoint in a phase I study, response was evaluated after 6 weeks of treatment using the RECIST criteria. At the same time, clinical benefit response, defined as absence of disease progression with simultaneous symptom palliation and improved performance status, was recorded. Symptom palliation was evaluated by patient completion of a simplified analog scale representing severity of tumour and treatment-induced complaints (0–10) every 2 weeks. Time to disease progression was measured from start of capecitabine therapy until first evidence of malignant progression or death, while objective response duration from documentation of tumour regression until progression. The duration of stable disease was measured from the start of treatment until disease progression, while that of clinical benefit response until disease progression or worsening of symptoms or performance status. All toxicity and activity analyses were on an intention-to-treat basis.

Pharmacokinetic analysis

PK studies were performed at the recommended dose level on days 1, 19 and 22 of therapy at time points $t = 0$, 1, 2, 3, 6, 12 h from the morning capecitabine ingestion. Five milliliters of venous blood was collected and plasma was divided into two aliquots and stored at −80°C until analysis.

Capecitabine, 5′-DFCR and 5′-DFUR concentrations were measured by a reverse- phase high-pressure liquid chromatography, as previously described [9]. The retention times for capecitabine, 5′-DFCR, 5′-DFUR were 25.9, 6.7 and 10.1 min, respectively. Calculation of capecitabine concentration and its metabolites was based on standard calibration curves using standard solutions over the analytical range 0.05–55.55 μg/ml with good linearity ($r^2 \geq 0.998$, 0.999 and 0.999 for apecitabine, 5′-DFCR and 5′-DFUR, respectively). The limit of quantification was 0.05 μg/ml for all of the compounds, using 0.5 ml plasma specimen. The procedure for sample preparation for analysis of 5-FU and FBAL was performed by gas-chromatography mass spectrometry similar to that reported by Anderson [10]. The concentrations of the analytes were estimated using standard calibration curves ($r^2 \geq 0.984$ and 0.978) from human plasma standards spiked with 5-FU or FBAL at concentrations of 0.0, 50, 100, 200, and 500 ng/ml.

The concentration-time data for both the drug and its metabolites were fitted to a noncompartmental model using WinNonlin™ software, standard version 2.1 (Pharsight Corporation, Palo Alto, CA, USA). The maximum plasma concentration (C_{max}) and the time of occurrence of C_{max} (T_{max}) were the observed values. The area under the concentration versus time curve (AUC_{all}) was calculated using the linear trapezoidal method with extrapolation of the curve to the last time-point (at 12 h). Terminal half-life ($t_{1/2}$) was calculated as 0.693/k, and total body clearance (CL) expressed as "dose/AUC".

Results

A total of 25 patients (11 males, 14 females) received a median of 12 weeks of therapy (range 2–52 weeks). Most patients were mildly to moderately symptomatic and moderately to heavily pretreated. Three chemonaive patients entered the study, two with tumours for which no standard effective treatment exists (cholangiocarcinoma, metastatic hepatoma) and one elderly patient with breast cancer refusing intravenous chemotherapy. The most common primaries were breast, gastric, pancreatic, colorectal carcinomas and cancer of unknown primary with metastatic spread commonly occurring in the liver, lymph nodes and bone. Patient characteristics are summarised in Table 1.

Toxicity

The regimen was tolerated exceptionally well up to doses of 2,510 mg/m^2 daily, with absence of myelosuppression, fever, severe diarrhoea or skin toxicity. The median number of treatment weeks given without any dose reduction was six (range 2–40 weeks). The most common toxic manifestations in all treatment cycles were fatigue, palmar-plantar erythema, nausea/vomiting, abdominal cramps, constipation, diarrhoea and anemia. These side effects were mild (grade 1–2) and easily managed with appropriate measures not necessi-

Table 1 Patient characteristics

Characteristic	Value
Male/female	11/14
Median age (range)	67 (32–77)
Performance status	
0	5
1	10
2	10
Primary tumour	
Breast	8
Gastric	5
Colorectal	2
Cholangiocarcinoma	2
Pancreas	2
Cancer of unknown primary	2
Other	4
Metastatic sites	
Liver	10
Lymph nodes	8
Bone	7
Lung	3
Peritoneum	3
Pleura	2
Prior lines of chemotherapy	
0	3
1	11
2	3
3 or more	8

tating treatment interruption for more than two days. Mild skin and gastrointestinal toxicity tended to occur more often at dose levels 1,665 mg/m^2 and higher after the first 4 weeks of capecitabine therapy. One patient with a medical history of hypertension, coronary artery disease and diabetes, underwent a myocardial infarction 6 weeks after the last dose of capecitabine therapy at a daily dose of 1,331 mg/m^2. The cardiac episode was successfully managed and was not thought to be related to capecitabine. In the same cohort, one patient, hospitalised for symptom palliation due to rapid disease progression, suffered a brief episode of atrial fibrillation (duration < 6 h) 1 week after treatment interruption. One more patient in the expanded pharmacokinetic cohort (2,250 mg/m^2) experienced grade 2 fatigue and colicky abdominal pain in week-3 of treatment along with rapid disease progression and opted to withdraw consent. In 16 patients treated at dose levels of 2,000 mg/m^2 and higher, 13 completed at least 6 weeks and 10 more than 10 weeks of treatment, while ten patients received at least 6 weeks' therapy without dose reductions. Toxicity data are summarised in Table 2.

Dose escalation, DLT and MTD

Out of five and four patients receiving capecitabine at daily 1,331 and 1,665 mg/m^2 respectively, no DLT occurred. The additional patients were recruited due to patient dropout prior to completion of 6 weeks of treatment because of disease progression. All three and four patients receiving 2,000 and 2,250 mg/m^2 of capecitabine respectively tolerated therapy without severe toxicity. In the 2,510 mg/m^2 cohort, grade 3 diarrhoea necessitating hospitalisation for intravenous hydration occurred in two out of four patients. The side-effect occurred in both patients during the fourth treatment week and resolved within 48 h, nevertheless constituted a DLT. The MTD and the recommended dose were defined at 2,510 and 2,250 mg/m^2, respectively. Five additional patients were recruited at the recommended dose of 2,250 mg/m^2 for PK studies without severe side-effects during the 6-week administration of capecitabine, apart from one patient with deterioration of performance status due to disease progression and grade 2 fatigue/abdominal pain, who opted to withdraw consent. In the eight patients who completed 6 weeks of therapy at 2,250 mg/m^2 daily, the administered dose-intensity during that time was 99.3% of the planned one. Dose escalation and DLT are summarized in Table 3.

Table 2 Toxic episodes in all treatment cycles

Toxicity	Grade 1–2	Grade 3–4
Fatigue	10	–
Skin erythema	6	–
Abdominal cramps	5	–
Nausea–vomiting	4	–
Constipation	4	–
Neutropenia	3	–
Diarrhoea	1	2
Anemia	3	–
Fever	2	–
Cardiac	1	2
Anorexia	1	–

A total of 270 weeks of therapy were administered. Number of toxic episodes occurring in all treatment cycles (multiple episodes may occur in the same patient)

Activity

Objective responses were seen in 3 out of 24 evaluable patients (objective response rate, ORR 12%) with disease stabilisation occurring in additional ten patients for a median of 6 months. Thirteen out of 24 patients enjoyed disease stabilisation or regression with symptom palliation and maintenance or improvement of performance status (clinical benefit response, CBR 54%). Among eight breast cancer patients receiving daily capecitabine at doses of 2,000 mg/m^2 or more, seven obtained a clinical benefit response and three a partial remission, with a median (clinical benefit plus

Table 3 Dose escalation and DLT

Cohort (mg/m^2)	Sample size	DLT	Severe toxicity and dropouts
1,331	5	0/5	Two patients dropped out in week 4 due to disease progression. One patient with atrial fibrillation in week-5, 1 week after capecitabine interruption. One patient with myocardial infarction and relevant medical history 6 weeks after completion of capecitabine therapy
1,665	4	0/4	One patient dropped out in week-4 due to progressive disease.
2,000	3	0/3	
2,250	4	0/4	One patient dropped out in week-3 due to progressive disease.
2,510	4	2/4	One patient dropped out in week 5 due to progressive disease. Two patients experienced grade- 3 diarrhoea (DLT) in treatment week 4.
2,250 PK	5	0/5	One patient with grade-2 fatigue/abdominal cramps and PS deterioration who opted to drop out.

objective response) duration of 9 months. The median duration of objective response in all responding patients was 6 months (range 3–13). The median time to progression in all 25 patients was 3 months (95% CI 1.6–4.3). The median TTP of breast cancer patients receiving capecitabine at 2,000 mg/m^2 or higher was 7 months (95% CI 2–17).

Pharmacokinetics

The PK profile of capecitabine and its metabolites in four patients receiving the recommended daily dose of 2,250 mg/m^2 is summarised in Table 4. Peak plasma concentrations were reached rapidly after oral administration at approximately 1–2 h. The half-lives were short around 1–3 h, except for FBAL, which had a $t_{1/2}$ of 10 h (Fig. 1). At the recommended dose, the AUC for 5-FU was five and nine times lower than its precursor 5′-DFUR on days 1 and 19, respectively. Based on data comparing days 1, 19 and 22, there is no statistically or clinically significant accumulation of capecitabine and its metabolites over time, as judged by C_{max} and AUC_{all} values. Statistically identical pharmacokinetic parameters were seen between days 1, 19 and 22 of all capecitabine metabolites, their values being compatible with those reported in the literature at comparable doses. Wide interpatient and intrapatient variability of pharmacokinetic parameters was seen for capecitabine and its metabolites, as expected by their extensive metabolism involving multiple polymorphic enzymes.

Table 4 Pharmacokinetic parameters

	Day 1	Day 19	Day 22
Capecitabine			
C_{max} (CV)	6.26 (73.7)	6.47 (109.2)	6.60 (37.0)
T_{max} (min–max)	1.25 (1–2)	1.50 (1–2)	1.50 (1–2)
AUC_{all} (CV)	18.33 (97.8)	23.48 (125.5)	21.49 (69.9)
$t_{1/2}$ (CV)	3.24 (53.7)	4.26 (97.5)	1.71 (44.6)
Cl (CV)	263.14 (70.5)	208.45 (57.4)	173.08 (60.2)
5′-DFCR			
C_{max} (CV)	8.51 (41.9)	8.83 (93.9)	7.72 (26.6)
T_{max} (min–max)	1.25 (1–2)	1.75 (1–2)	1.75 (1–2)
AUC_{all} (CV)	18.37 (64.5)	36.37 (118.5)	22.96 (33.3)
$t_{1/2}$ (CV)	1.34 (39.4)	1.54 (42.0)	1.19 (35.6)
Cl (CV)	160.28 (37.5)	189.61 (73.9)	108.70 (31.7)
5′-DFUR			
C_{max} (CV)	10.81 (38.8)	10.10 (54.0)	10.28 (6.0)
T_{max} (min–max)	1.25 (1–2)	1.50 (1–2)	2.0 (1–3)
AUC_{all} (CV)	18.55 (28.5)	36.70 (67.6)	28.25 (12.3)
$T_{1/2}$ (CV)	0.93 (59.6)	1.54 (56.7)	0.67 (19.3)
Cl (CV)	131.99 (26.3)	83.25 (41.2)	84.39 (15.7)
5-FU			
C_{max} (CV)	1.28 (62.9)	1.75 (45.3)	1.53 (50.8)
T_{max} (min–max)	1.0	1.25 (1–2)	1.0
AUC_{all} (CV)	3.70 (62.6)	4.24 (33.8)	4.08 (47.6)
$T_{1/2}$ (CV)	1.52 (28.8)	1.24 (20.6)	1.57 (21.9)
Cl (CV)	0.96 (62.8)	0.62 (34.2)	1.04 (97.8)
FBAL			
C_{max} (CV)	7.24 (18.6)	7.72 (20.8)	6.93 (27.9)
T_{max} (min–max)	2.0	2.0	2.0
AUC_{all} (CV)	52.88 (32.6)	46.19 (27.2)	44.27 (27.0)
$T_{1/2}$ (CV)	10.15 (50.2)	6.94 (39.2)	9.11 (28.1)
Cl (CV)	30.55 (60.7)	37.41 (43.2)	30.64 (23.8)

C_{max}: Geometric mean in μg/ml, T_{max}: Arithmetic median in hours, AUC_{all}: Area under the concentration-time curve, geometric mean in μg × h/ml, $t_{1/2}$: Arithmetic mean $t_{1/2}$ in hours, *Cl* clearance in $L/h/m^2$

CV percentage of coefficient of variation, min–max: minimum to maximum

Discussion

Accumulating evidence established the superior activity and safety of infusional versus bolus 5-FU regimens for both the adjuvant and palliative management of patients with colon-cancer [4–6, 11]. These clinical data are supported by pharmacodynamic principles: 5-FU has a short plasma half-life of less than thirty minutes and its cytotoxic impact on malignant cells is maximal during DNA synthesis. Despite more prolonged reten-

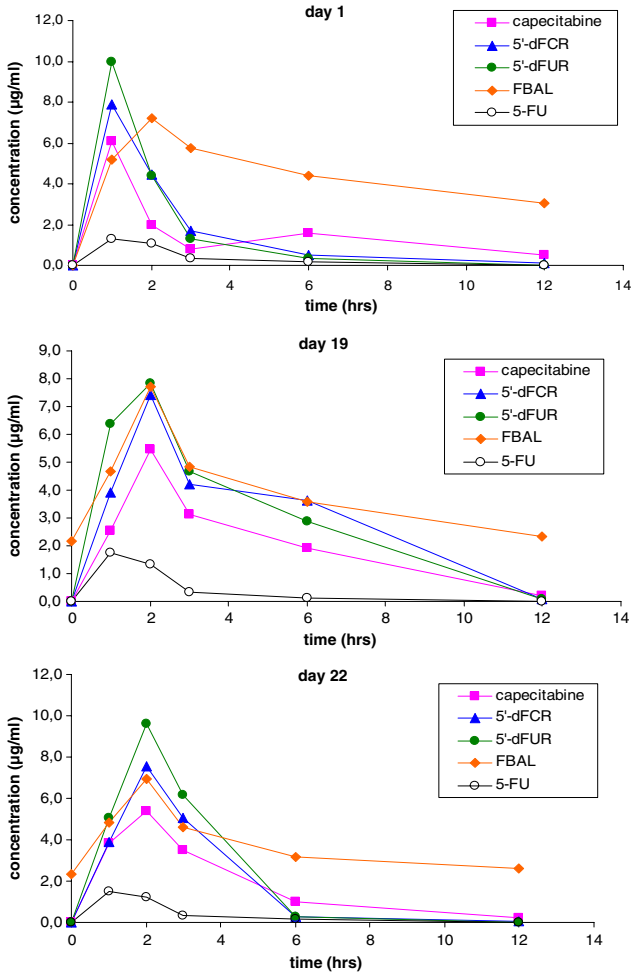

Fig. 1 Median plasma concentrations of capecitabine and metabolites on days 1, 19 and 22 based on four patients treated at a daily dose of 2,250 mg/m^2

tion of 5-FU and anabolites in tumour tissues, two ways to maximise the number of neoplastic cells exposed to 5-FU during S-phase are known: administration of calcium folinate which results in stabilisation of 5-FdUMP-TS complexes and prolongation of 5-FU intravenous infusion [4, 11, 12]. Despite its improved therapeutic index, prolonged 5-FU administration has shortcomings, as it necessitates insertion of indwelling central venous catheters, frequent hospital visits and use of portable pumps. Switching to an oral continuous flurocarbamate schedule of equivalent efficacy would be highly desirable and capecitabine offers promise for such a breakthrough.

When the optimal capecitabine schedule had been investigated in a randomised phase II study, the pharmacodynamically rational continuous schedule suggested by Budman et al., resulted in a strikingly low recommended daily dose at 1,331 mg/m^2, short treatment duration, low total cumulative dose and shorter time to progression in comparison to the intermittent schedule [7, 13, 14]. In human xenograft models, inhibition of tumour growth depended on the total capecitabine dose used [8]. The poor tolerance and low dose-intensity of the Budman schedule were factors that impeded the clinical application of continuous capecitabine administration. This is in keeping with experience from application of very prolonged 5-FU infusions: Dose reductions are occasionally necessary leading to suboptimal inhibition of TS and more easily allowing tumour cells to develop resistance [15].

An alternative approach to mitigating the poor tolerability of continuous capecitabine administration would be to interpose short treatment breaks, as done in our study. Although the terminal half-life of capecitabine and major metabolites(5-DFCR, 5-DFUR, 5-FU) is less than 2 h, in xenograft models the inhibition of the neoplastic molecular target, intracellular thymidylate synthase, persisted at levels higher than 50% for more than 24 h after the last capecitabine dose [8, 16]. On the other hand, capecitabine-induced toxicity has been correlated with healthy tissue exposure to the toxic metabolites 5-DFUR and FBAL, the latter having an elimination half-life ranging from 3 to 33 h. Moreover, in early PK clinical studies, the AUC and plasma concentrations of 5-FU and FBAL increased by 10–60% from day-1 to day-14 during multiple doses, suggesting 5-fluorouracil accumulation [13, 14, 17]. This is due to saturation of the main 5-FU catabolising enzyme, dehydropyrimidine dehydrogenase (DPD), an event reversible upon withholding of as few as to 2–4 capecitabine doses [17, 18]. Accordingly, a short treatment break offers promise for diminution of healthy tissue exposure to toxic moieties via their metabolism/elimination and repair of effected injuries, while FdUMP-induced thymidylate synthase inhibition, necessary for antineoplastic activity, persists in tumour.

Our weekday on-weekend off regimen was characterized by high dose-intensity and excellent tolerability. The recommended dose of 2,250 mg/m^2 was only slightly lower than the monotherapy dose of the intermittent schedule (2,510 mg/m^2), while many US and European oncologists administer intermittent capecitabine at even lower daily doses (2,000 mg/m^2), [19]. Bone marrow, skin and gastrointestinal toxicities were minimal and patient compliance to therapy was optimal due to the convenient weekend break. The optimal safety of the regimen was associated with hints for improved efficacy. Our pretreated cancer patients receiving capecitabine therapy at pharmacodynamically relevant doses (2,000 mg/m^2 or higher) enjoyed a clinical benefit response of 67% and a median time to progression of 5 months, while the equivalent figures for breast cancer patients were 87% and 7 months.

Gastrointestinal absorption of capecitabine and metabolites was rapid and plasma half-lives short, FBAL being the only notable exception [13, 14, 17]. The previously reported high variability in the PK parameters of fluoropyrimidines was confirmed, probably owing to the oral mode of administration and to the varying activity of the multiple enzymes involved in their metabolism [20, 21]. The selective conversion of weakly cytotoxic 5′-DFUR to active 5-FU in the tumour was confirmed by the ninefold lower levels of healthy tissue exposure to 5-FU. No accumulation was evident as systemic exposure to 5′-DFCR and 5′-DFUR was increased on day 19 compared to day 1, but the week-end break prevented accumulation of these substances, as shown by the reduction of the relevant AUC values.

In conclusion, our capecitabine schedule represents a synthesis of previously tested regimens that satisfy prolonged tumour exposure to fluoropyrimine moieties, maximal dose intensity, long treatment duration along with optimal tolerability and encouraging antineoplastic activity. Recently, two groups of investigators administered capecitabine at the weekday on-weekend off schedule in an effort to maximise its radiosensitizing and cytotoxic synergy with pelvic irradiation, either as monotherapy (2,000 mg/m^2) or with oxaliplatin (1,650 mg/m^2), with tolerability being better for monotherapy [22, 23]. Expansion of clinical experience and comparison to the standard intermittent schedule with response, survival and toxicity as endpoints are warranted through development of randomised phase II studies.

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