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A Phase I Study of an Oral Simulated FOLFOX with High Dose Capecitabine

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Abstract

Background—A phase I study of high-dose capecitabine given over 2 days, along with oxaliplatin, bolus 5FU and leucovorin (LV), was designed to simulate FOLFOX6 without the need for infusional 5FU.

Methods—Schedule A included oxaliplatin 100 mg/m^2, 5FU 400 mg/m^2, and LV 20 mg/m^2 (all given IV on days 1 and 15, 28 day cycle). Capecitabine was administered orally every 8 hours × 6 doses, days 1 and 15. Schedule B excluded 5FU and LV, maintaining oxaliplatin and capecitabine. Pharmacokinetics were performed for capecitabine for 6 patients on each schedule.

Results—36 patients were treated. The dose-limiting toxicities seen included nausea, dehydration, fatigue, hypotension and confusion. Minimal palmar-plantar erythrodysesthesia was seen. Myelosuppression was common, but not a dose limiting toxicity. The pharmacokinetic parameters for capecitabine were unaltered.

Conclusion—Using capecitabine to mimic FOLFOX6 is feasible and well tolerated with a toxicity profile that differs from standard 14-day capecitabine dosing, with less palmar-plantar erythrodysesthesia. The phase II dose for capecitabine in combination with oxaliplatin, 5FU, and LV is 1500 mg/m^2/dose or 2250 mg/m^2/dose in the absence of bolus 5FU/LV.

Keywords

Capecitabine; oxaliplatin; 5-FU; chemotherapy; phase I

Introduction

5-fluorouracil based chemotherapy has been the mainstay of treatment for advanced colorectal cancer since the 1960s. Regimens involving a continuous infusion of 5FU result in an improved side effect profile [1-3] and may be moderately more effective than bolus schedules [1-3]. Addition of leucovorin to intermittent infusion 5FU yields increased toxicity without apparent benefits to overall survival [4,5]. Oxaliplatin combined with leucovorin as well as bolus and infusion 5FU over two days (FOLFOX4) has demonstrated clinical efficacy in multiple

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Statement of efforts: Drs. Mulkerin, Thomas and Wilding conceived of and designed and wrote the trial, and also accrued patients to this study. Ms. Alberti, Oliver and Feierabend performed clinical and regulatory management of this study. Dr. LoConte was involved in enrolling patients on this study, and in writing the manuscript. Dr. Kolesar contributed to trial design and supervised the performance of pharmacokinetics. Dr. Marnocha contributed to trial design and supervised the research pharmacy for this study. All involved participated in revision of this manuscript and interpretation of results.

randomized trials [6,7] and is considered a standard of care for colorectal cancer. The FOLFOX6 regimen consists of a higher dose of oxaliplatin (100 mg/m^2 on D1), and a simplified 5FU/LV administration schedule with bolus 5FU/LV given on D1 only, followed by a higher dose 46 hour continuous infusion of 5FU[8].

Capecitabine is an oral prodrug that is converted to fluorouracil via a 3 step enzymatic process. The conversion of capecitabine to 5′-deoxy-5-fluorocytidine (5′-DFCR) occurs primarily in the liver limiting the gastrointestinal exposure to 5FU. 5′-DFCR is subsequently converted to 5′-deoxy-5-fluorouridine (5′-DFUR). The next step yields 5FU and is mediated by thymidine phosphorylase which is preferentially expressed in tumor tissue. Bioavailability of capecitabine is both predictable and high, and there is potential selective intratumoral conversion to 5FU [9-11]. For these reasons and others, capecitabine may have an improved therapeutic index over intravenous 5FU. In colorectal cancer patients, capecitabine has demonstrated superior response rates, equivalent overall survival, and improved toxicity profile in comparison to 5 daily doses of bolus 5-FU/LV over 4 weeks [12,13]. Palmar-plantar erythrodysesthesia, or hand-foot syndrome, is one side effect seen more commonly with capecitabine than with bolus 5FU.

The use of capecitabine in combination with oxaliplatin has been extensively investigated. Most studies to date have added oxaliplatin to currently utilized capecitabine regimens rather than attempting to mimic the FOLFOX schedules. Cassidy and colleagues investigated the "XELOX" regimen (oxaliplatin 130 mg/m^2 every 3 weeks with capecitabine 1000 mg/m^2 twice daily days 1 to14) in a phase II trial involving 96 patients with metastatic colorectal cancer. They reported an overall response rate of 55%, median time to disease progression and overall survival of 7.7 and 19.5 months respectively. XELOX safety was similar to the previously observed FOLFOX 4 regimen, except that myelosuppression was less common with XELOX (grade 3 or 4 neutropenia 7% vs. 40-45%) [14]. The incidence of palmar-plantar erythrodysesthesia in this trial was 36%. Scheithauer and colleagues reported a randomized Phase II trial involving a high dose intensity regimen (oxaliplatin 85 mg/m^2 every two weeks with capecitabine 1750 mg/m^2 twice daily for 7 days every two weeks) versus conventional XELOX dosing, in 89 patients with advanced colorectal cancer. Those patients allocated to the high dose intensity capecitabine arm had a higher response rate (54.5% vs. 42.2%) and significantly longer median progression free survival (10.5 vs. 6.0 months) than those treated with conventional dosing. Safety profiles were similar between arms [15]. The incidence of palmar-plantar erythrodysesthesia was 31% in the high dose intensity group. These data suggest a benefit for dose intensified capecitabine in combination with oxaliplatin.

We sought to more closely replicate a FOLFOX6 schedule by substituting the infusional 5FU with high dose capecitabine given over 2 days. In a phase I format, we tested two schedules: one schedule that infused oxaliplatin with leucovorin, followed by a bolus of 5FU and increasing doses of capecitabine every 8 hours over 2 days and another where the oxaliplatin was infused without LV or 5FU followed by increasing doses of capecitabine every 8 hours over 2 days.

Methods

All participants had advanced or metastatic solid tumors. Main eligibility requirements included: no limit imposed on prior therapy; leukocytes ≥3,000/μl, absolute neutrophil count ≥1,500/μl, platelets ≥100,000/μl, total bilirubin ≤ 1.5 mg/dL, AST(SGOT)/ALT(SGPT) ≤ 2.5 × institutional upper limit of normal, and creatinine clearance ≥50 mL/min as calculated by the Cockroft-Gault formula; ECOG PS of 0-2; no CTC grade 2 or worse neuropathy on enrollment; and at least 12 week life expectancy. Exclusion criteria included: prior radiotherapy or chemotherapy within 4 weeks before study entry, known brain metastases, concurrent

investigational treatment, history of allergy to platinum compounds, pregnancy, nursing, highly active antiretroviral therapy (HAART) therapy for HIV infection, and uncontrolled ongoing illness. Patients who had received prior fluoropyrimidine chemotherapy were eligible. All patients gave informed consent according to institutional guidelines before study registration, and the study was approved by the institutional review board at the University of Wisconsin.

Treatment Plan

The treatment schedule consisted of capecitabine administration concomitant with the beginning of the oxaliplatin administration. Oxaliplatin was prepared in a 5% dextrose solution and delivered intravenously over 2 hours at a dose of 100 mg/m2 on days 1 and 15. For patients treated with 5FU and LV, these agents were administered by intravenous bolus immediately following oxaliplatin administration on days 1 and 15 at a dose of 400mg/m2 and 20mg/m2, respectfully. Capecitabine was dosed based on body surface area and continued every 8 hours for a total of six doses beginning on days 1 and 15. Each dose was rounded to the nearest 150 mg. A cycle was defined as 28 days. Prophylactic administration of dolasetron plus dexamethasone at standard doses was routinely used before chemotherapy administration, followed by additional anti-emetic medications as needed. Treatment was continued until clinical or radiographic progression of disease, development of unacceptable toxicity, withdrawal of consent, or clinical condition of the patient (as judged by the treating clinician) prohibited further therapy on study. The initial doses of drugs were determined according to the escalation schedule listed in Table 1. A minimum of three patients were entered at each dose level. Before escalating to the next dose level, all three patients received at least one cycle of treatment and were observed for acute toxicity until day 29. If one of three patients at a given dose level developed a DLT, then at least three more patients were entered at the same dose level.

Continuation of therapy beyond cycle 1 required an absolute neutrophil count of at least 1,500/μL, platelets of at least 75,000/μL, complete resolution of stomatitis or diarrhea, and resolution of all other toxicities to at least a CTC grade 1 excepting up to grade 2 paresthesia/dysesthesia. A dose modification scheme was implemented requiring modification of the probably or definitely related agent or agents causing grade 3 or higher toxicity.

Toxicity and Disease Assessment

Toxicities were graded using the National Cancer Institute Common Toxicity Criteria version 2.0, except peripheral sensory neuropathy, which was graded according to a specific grading system (grade 1 = short-term paraesthesia/dysesthesia with complete resolution before next cycle; grade 2 = persistent paraesthesia/dysesthesia between cycles without functional impairment; and grade 3 = persistent paraesthesia/dysesthesia between cycles with pain or functional impairment that interferes with activities of daily living).

The maximum-tolerated dose (MTD) was defined as the highest dose that resulted in a DLT for fewer than 2 of 6 patients during the first 28 days of treatment. Dose-limiting toxicities (DLT) were defined as a toxicity which occurred during the first cycle. Further, a DLT was defined as any grade 3 non-hematologic adverse event or grade 4 neutropenia considered probably or definitely related to therapy. Additional DLT rules included: grade 3 or higher neuropathy not resolving prior to the next cycle of therapy, grade 3 or higher nausea or vomiting occurring despite maximal antiemetic therapy, grade 3 or higher diarrhea occurring despite patient compliance with loperamide therapy, grade 3 thrombocytopenia with bleeding or grade 4 thrombocytopenia, grade 4 neutropenia of any duration with fever, or of 5 days duration without fever, and treatment delay of 4 or more weeks.

Cohorts were expanded on each schedule at one dose level below the maximum administered dose to allow for pharmacokinetic analysis of capecitabine and its metabolites. Disease assessment was required every 2 cycles. Objective responses were recorded according to RECIST (Response Evaluation Criteria in Solid Tumors) [16]. Responses had to be confirmed after at least 4 weeks.

Pharmacokinetics

Sample collection and preparation—Heparinized blood samples for evaluation of capecitabine, 5FU, DFUR and DFCR were collected on Days 1 and 15 for individuals enrolled in Level 2 and Day 1 for those on level 4a at baseline, and 0.25, 0.5, 1, 1.5, 2, 4, 6,and 8 hours. Immediately following collection, samples were centrifuged at approximately 2500 g for at least 5 min at 4°C to separate plasma. Plasma (4.0 ml) was transferred to a cryovial and placed in a -70C freezer until analysis.

5FU, Capecitabine, DFCR and DFUR—5FU, Capecitabine, DFCR and DFUR plasma concentrations were evaluated with a Spectra Physics P2000 HPLC as previously described (Reigner, 1998). For 5FU, the standard curve was linear from 0.019 to 20 μg/ml, r2 = 0.999, with an intraday variability ranging from 4.49%-5.52% over the standard curve. Interday variability over 2 weeks ranged from 4.33-5.42% over the standard curve and the lower limit of quantitation (LLOQ) was 0.0195 μg/ml. For capecitabine, the standard curve was linear from 0.019 to 20 μg/ml, r2 = 0.999, with intraday variability ranging from 1.2-7.8% and interday variability from 7.6-13.9% over 3 months and a LLOQ of 0.019 μg/ml. The standard curves for DFCR and DFUR were both linear from 0.625 to 40 ug/ml, r2 = 0.999, with an intraday variability ranging from 4.21%-4.66% and 0.74%-2.08%, interday variability over 4 weeks ranging from 3.45%-6.36% and 4.24-6.45% and LLOQ of 0.312 μg/ml and 0.0195 μg/ml, respectively.

Pharmacokinetic variables were determined by noncompartmental methods with WinNonlin Pro version 4.0 (Pharsight Corporation, Cary, N.C.). Area under the plasma concentration–time curve was estimated using the trapezoidal rule from time 0 to peak concentration and the log-trapezoidal rule from the peak concentration to the last measurable plasma concentration (AUClast). $AUC_{(0-\infty)}$ was then calculated from the time of dosing and extrapolated to infinity. Pharmacokinetic parameters were summarized by standard descriptive statistics in terms of means and standard deviations. The comparisons of mean AUC values between dose levels were performed using a two-sample t-test. Changes in mean AUC values between day 1 and day 15 assessments were evaluated using a paired t-test. For these comparisons, AUC values were log-transformed in order to meet normality and heterogeneity of variances assumptions. A significance level of 5% was used for all comparisons.

Results

Patients

Thirty-six patients were entered in total; 21 on schedule A (with a 5-FU and LV bolus) and 15 on schedule B (without a 5-FU and LV bolus). All treated patients were assessable for toxicity and efficacy. A summary of patient characteristics is included in Table 2. Due to the known activity of these drugs in gastrointestinal cancers, accrual was predominantly in such patients (83%).

Treatment Exposure and Safety

The median number of cycles administered per patient was 3 (range 1-13). Nineteen patients (53%) received more than 2 cycles, and 10 patients (28%) received more than 4 cycles. The most frequently observed cycle 1 grade 3 or 4 toxicities by patient were neutropenia without

fever (9 of 36 patients; 25%), nausea and/or vomiting (2 of 36, 6%), and diarrhea (1 of 36; 3%). During the entire course of therapy for all patients, fatigue and nausea/vomiting were common (5 and 7 patients, respectively). Two patients experienced grade 3 confusion which was thought possibly related to chemotherapy treatment. One patient was in their second cycle, the other was in their third cycle. One additional patient developed grade 1 confusion which was thought to not be related to the chemotherapy. There were no treatment-related deaths. Table 3 lists the most common grade 3 to 4 toxic episodes per patient.

Grade 3 to 4 neuropathy was not observed, although only 10 pts received cumulative oxaliplatin doses greater than 800 mg/m^2. There was no dose reduction or treatment discontinuation due to peripheral neuropathy. There was only one case of significant palmar-plantar erythrodysesthesia which was a grade 3 event occurring in the second cycle of therapy in a patient treated at dose level 2.

Fourteen patients had received prior fluoropyrimidine-based chemotherapy, 22 had not (see Table 4). As seen in the table, those with prior fluropyrimidine exposure had roughly the same incidence of DLT (14% for those with prior fluropyrimidine and 18% for those without).

Determination of MTD

On schedule A, dose level 2, one patient experienced grade 3 hyperglycemia and confusion (table 3). At dose level 3, the DLT was grade 3 nausea (2 patients, one of whom also had grade 3 dehydration, hypotension, and weakness). Therefore, the second dose level (capecitabine 1500mg/m^2) was considered the MTD with one of the 12 patients exhibiting a DLT. On schedule B, the fourth dose level was determined to be the MTD (2250mg/m^2 of capecitabine), as DLTs were observed in 2 of 4 patients treated at dose level 5. One of these DLTs was a grade 4 fatigue and grade 3 confusion, and the other was grade 4 neutropenia requiring dose delay. Thus, further dose escalation of capecitabine was possible with the discontinuation of bolus 5-FU/LV.

Anti-tumor effect

There was 1 complete response (gastric cancer) and 3 partial responses (colon, esophageal, and gastric adenocarcinomas). Additionally, prolonged stabilization of disease with improvement in tumor markers was seen in two patients (4 months and 6 months) with gemcitabine refractory pancreatic cancer.

Pharmacokinetics

On schedule A, dose level 2, capecitabine 1500mg/m^2 every 8 hours for 6 doses was administered on days 1-2 and days 15-16 of a 28 cycle. The capecitabine AUC for dose level 2 did not vary between day 1 and 15, with a day 1 AUC of 11.90 ±6.17 (μg/mL) × hours and 9.51 ±3.75 (μg/mL) × hours on day 15, suggesting no accumulation. Patients in schedule B, dose level 4 received 2250mg/m^2 of capecitabine every 8 hours for 6 doses on days 1-2 and days 15-16 of a 28 cycle, however, blood sampling was performed on day 1 only. As expected, the capecitabine AUC varied between dose level 2 and 4. The day 1 AUC for dose level 4 was 17.34±4.72 compared to 11.90 ±6.17 (μg/mL) × hours for dose level 2, day 1, (p=0.02, one sided t-test). As expected, the 5-FU AUC also varied between dose level 2 and 4, with a day 1 AUC for dose level 4 of 1.56±0.63 compared to 0.68 ±0.31 (μg/mL) × hours for dose level 2, day 1, (p=0.01, one sided t-test) (Table 4). Plasma 5-FU concentrations were observed within 12 minutes after capecitabine administration suggesting rapid peripheral conversion of capecitabine. In dose level 2, the bolus of 5-FU was administered 2 hours after the capecitabine dose, and is included in the day 15 pharmacokinetic analysis accounting for the increased 5-FU plasma concentrations and AUC. (Table 4). 5′-DFCR and 5′-DFUR exhibited high interpatient variability and did not vary by capecitabine dose.

Discussion

The primary objective of our study was to define the MTD and toxicity profile for oxaliplatin with and without bolus 5-FU/LV along with high dose capecitabine administered every 8 hours for two days. The MTD for schedule A was dose level 2 (oxaliplatin 100 mg/m^2, bolus 5-FU 400 mg/m^2 and leucovorin 20 mg/m^2 with capecitabine 1500 mg/m^2/dose × 6 doses). The corresponding MTD for schedule B was dose level 4 (oxaliplatin 100 mg/m^2 and capecitabine 2250 mg/m^2/dose × 6 doses). We recommend using the MTD of either schedule for future phase II studies.

Overall, the regimen was well tolerated and it was feasible to administer capecitabine at a higher dose with an abbreviated schedule. Myelosuppression was the major toxicity, perhaps due to the 100 mg/m2 dose of oxaliplatin, or a shift in capecitabine toxicity with this schedule. No patients were hospitalized as a result of the myelosuppression, but did result in frequent dose delays. Nausea and vomiting were within expected degree and severity for these agents, although these were rarely a cause for treatment discontinuation or failure to complete the capecitabine course. Two patients experienced confusion which was a dose limiting toxicity. For both patients the neurologic side effects improved once the chemotherapy was held. Confusion and other central nervous system symptoms have been previously reported as side effects of high dose 5-FU and capecitabine.[17-20] As expected, many patients also experienced grade 1 or 2 cold induced neuropathy, a known dose limiting toxicity of oxaliplatin,[21] as well as grade 1 or 2 fatigue. Notably, only one patient experienced palmar-plantar erythrodysesthesia with our abbreviated capecitabine course, which is in contrast to the frequent appearance of this toxicity in the 7 and 14 day capecitabine schedules.[21,22]

We did not find any evidence of saturation of capecitabine metabolism. Even at near twice standard doses of capecitabine, conversion to 5-FU followed a predictable time course and the AUCs and Cmax of capecitabine, 5′-DFCR, 5′-DFUR, and 5-FU were all within published ranges[23,24]. Thus, higher levels of capecitabine and its metabolites did not account for the side effects seen with this regimen.

This novel combination showed predictable activity in tumor types known to be responsive to oxaliplatin and fluoropyrimidine combinations [25-28]. This included responses for patients with colon cancer, gastric cancer, esophageal cancer, and gemcitabine-refractory pancreas cancer. Based on these results, we are currently conducting a phase II study testing the schedule A regimen for first-line therapy of metastatic colon cancer. This study began before finishing the schedule B accrual. For proposed future studies in gastric and pancreatic cancer we will test schedule B.

Within the past few years, many agents for the treatment of advanced colorectal cancer have been approved by the Food and Drug Administration. Thus far, there does not appear to be a major advantage for initial therapy with either oxaliplatin or irinotecan containing regimens. However, it has become increasingly clear that there is an improved therapeutic index for either oxaliplatin or irinotecan based regimens when the fluoropyrimidine schedule is optimized. Our study attempts to replicate the optimal short–duration, high–dose, infusional 5-FU schedules via a novel schedule of capecitabine. This should continue to allow for the synergistic interaction between oxaliplatin and the fluoropyrimidine while increasing convenience in dosing and improving toxicities. Certainly, the toxicity profile as described here suggests that we have indeed shifted the capecitabine closer to that of a FOLFOX regimen. Other potential advantages of our schedule include enhanced convenience to the patient and physician. There may also be a decreased in the morbidity of chemotherapy administration in that a central line would not necessarily be required. If the efficacy and tolerability of this approach is born out in further phase II testing, the novel schedule of capecitabine may be applicable for combination

with other agents. If similar efficacy is shown with this regimen to other standard capecitabine regimens, this regimen may provide a potential economic advantage given that the total dose of capecitabine is about 20-30% less than other regimens.

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TABLE 1

Heading: Dose escalation schema

Dose Level	Oxaliplatin (mg/m^2) iv over 2 hours on days 1 and 15	Leucovorin (mg/m^2) iv and 5-fluorouracil (mg/m^2) iv bolus on days 1 and 15	Capecitabine (mg/m^2) po q 8 hrs × 6 doses on days 1-2 and 15-16
Level 1	100	20400	1000
Level 2	100	20400	1500
Level 3	100	20400	2250
Level 4	100	00	2250
Level 5	100	00	3375

TABLE 2

Heading: Baseline demographics

Characteristic	N (total = 36)
Median age (years)	63.7 (28-81)
% ECOG PS 0 (n (%))	13 (36)
# male (n (%))	23 (63.9)
Disease site (n (%))	
• Colorectal	7 (19.4)
• Pancreas	7 (19.4)
• Liver/intrahepatic bile duct	5 (13.9)
• Gallbladder	4 (11.1)
• Esophagus	4 (11.1)
• Gastric	3 (8.3)
• Other (non-GI)	4 (11.1)

TABLE 3

Heading: Dose limiting and grade 3 or greater toxicities which occurred at least once per patient.

	CYCLE 1 Number of episodes*		*CYCLE 2+ Number of episodes*		*OVERALL Number of episodes*	
Toxicity	***Grade 3***	***Grade 4***	***Grade 3***	***Grade 4***	***Grade 3***	***Grade 4***
Neutropenia	3	4 (2*)	6	1	9	5
Fatigue	1	1*	3	-	4	1
Nausea	4(2*)	-	-	-	4	-
Vomiting	3(1*)	-	-	-	3	-
Diarrhea	1	-	2	-	3	-
Dehydration	2(1*)	-	1	-	3	-
Thrombocytopenia	1	-	2	-	3	-
Hypotension	1*				1	
Confusion	2(2*)				2	
Hyperglycemia	1*				1	

* = dose limiting toxicity

TABLE 4

Type of cancer, prior chemotherapy and best response to current chemotherapy

Disease Site	Prior fluoropyrimidine?	Number of prior chemotherapy regimens	Best response
Dose Level 1			
Colorectal	yes	2	PD
Colorectal	yes	4	SD
Esophageal	yes	1	SD
Dose Level 2			
Cholangiocarcinoma	yes	3	N/A
Colorectal	yes	1	PD
Colorectal	**yes**	**3**	**N/A**
Unknown	no	0	SD
Pancreas	no	1	SD
Gastric	no	0	PR
Esophageal	no	1	PR
Pancreatic	no	1	PD
Cholangiocarcinoma	no	0	PD
Cholangiocarcinoma	no	0	SD
Colorectal	yes	1	SD
Esophageal	no	1	PD
Dose Level 3			
Pancreas	**no**	**1**	**N/A**
Gallbladder	no	0	SD
Colorectal	no	0	PD
Ovarian	no	4	SD
Pancreas	yes	1	N/A
Pancreas	**no**	**1**	**PD**
Dose Level 4			
Pancreas	no	0	SD
Colorectal	yes	1	SD
Ovarian	no	3	PD
Bladder	no	5	PD
Cholangiocarcinoma	yes	1	SD
Esophageal	no	2	SD
Unknown	yes	2	SD
Cholangiocarcinoma	no	2	PD
Gastric	**yes**	**1**	**SD**
Breast	yes	6	PD
Cholangiocarcinoma	no	1	PD
Dose Level 5			

Disease Site	Prior fluoropyrimidine?	Number of prior chemotherapy regimens	Best response
Pancreas	**no**	**1**	**N/A**
Cholangiocarcinoma	**no**	**2**	**PR**
Gastric	yes	2	CR
Cholangiocarcinoma	no	0	N/A

Bolded text indicates DLT

TABLE 5

Heading: Mean Area Under the Curve (AUC) and Cmax (Concentration Maximum) Values for capecitabine, 5FU, 5′DFCR and 5′-DFUR

AUC $_{(0-\infty)}$ ±SD (μg/mL)*hr								
	Capecitabine		**5FU**		**5′-DFCR**		**5′-DFUR**	
	Day 1	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**
Level 2 (n=6)	**11.90±6.17**	**9.51±3.75**	**0.68±0.31**	**12.65±2.84**	**25.81±10.61**	**12.80±10.61**	**58.53±35.28**	**38.64±22.95**
Level 4 (n=6)	**17.34±4.72**		**1.56±0.63**		**22.66±7.19**		**33.89±6.26**	
Cmax ±SD μg/mL								
	Capecitabine		5FU		5′-DFCR		5′-DFUR	
	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15
Level 2 (n=6)	**8.55±6.96**	**8.03±8.13**	**0.39±0.24**	**22.00±10.45**	**4.95±4.29**	**4.96±3.05**	**11.11±9.11**	**11.73±4.22**
Level 4 (n=6)	**21.16±18.27**		**0.88±0.34**		**12.34±4.63**		**18.93±7.53**	

AUC= Area under the curve; SD= standard deviation; 5FU=5-fluorouracil; 5′-DFCR=5′deoxy-5-5-fluorocytidine; 5′-DFUR= 5′-deoxy-5-fluorouridine

Level 2, Day 1: Capecitabine 1500 mg/m^2 orally

Level 2, Day 15: Capecitabine 1500 mg/m2 orally + Bolus 5FU 400mg/m^2 2 hours after capecitabine administered

Level 4: Capecitabine 2250 mg/m^2 orally

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