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ORIGINAL ARTICLE

Phase I clinical and pharmacokinetic study of oxaliplatin, irinotecan and capecitabine

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Abstract
Purpose To determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of the combination of weekly oxaliplatin × 4, weekly irinotecan × 4 and capecitabine Monday through Friday for 4 weeks of every 6 week cycle in patients with solid tumors; to determine the pharmacokinetic profile of these agents in this combination; to observe patients for clinical anti-tumor response.
Methods Twenty-two patients with metastatic solid tumors received oxaliplatin 60 mg/m^2 weekly × 4, irinotecan beginning at a dose of 40 mg/m^2 weekly × 4, and capecitabine Monday through Friday for 4 weeks of every 6 week cycle, initially at 1,000 mg twice daily (bid).
Results The MTD was oxaliplatin 60 mg/m^2 weekly × 4, irinotecan 50 mg/m^2 weekly × 4 and capecitabine 450 mg bid Monday through Friday for 4 weeks of every 6 week cycle. One of six patients at this dose level developed DLT of nausea, vomiting, and diarrhea. Among patients treated with a constant capecitabine dose of 450 mg bid, there was a higher mean AUC of 5-FU in women than in men (mean ± SD: 892 ± 287 nM h vs. 537 ± 182 nM h; Mann–Whitney two-tailed, $P = 0.02$). There was one complete response in a patient with gastric cancer.
Conclusion The novel schedule of weekly oxaliplatin, weekly irinotecan, and capecitabine Monday through Friday, all administered for 4 weeks of every 6 week cycle, evaluated in this phase I trial is well-tolerated and demonstrated activity in a patient with gastric cancer.

Keywords Irinotecan · Oxaliplatin · Capecitabine · Phase I study · Chemotherapy

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Introduction

Our study was designed to create a triplet regimen of oxaliplatin, irinotecan, and capecitabine that could be highly active as initial therapy of colorectal cancer and other gastrointestinal malignancies, given the differing mechanisms of action of these chemotherapeutic agents and their efficacy as single-agents and doublets [1–8]. The addition of irinotecan to 5-fluorouracil (5-FU) and leucovorin demonstrated improved response rates and survival compared to 5-FU and leucovorin in phase III studies of first-line therapy of metastatic colorectal cancer, although preclinical studies of irinotecan and 5-FU demonstrated conflicting results with regard to synergy [9–12]. Preclinical data demonstrated synergistic cytotoxic effects of oxaliplatin and 5-FU against colon cancer cell lines and xenografts [13]. The combination of oxaliplatin with 5-FU and leucovorin in patients with advanced colorectal cancer that was refractory to 5-FU demonstrated response rates ranging from 21 to 58%, suggesting synergy between oxaliplatin and 5-FU [5, 7, 8]. Phase III comparisons of 5-FU, leucovorin and oxaliplatin compared to 5-FU and leucovorin as first-line therapy of advanced colorectal cancer demonstrated improved response rates and time to progression with the addition of oxaliplatin [14, 15].

Oxaliplatin is a 1,2 diaminocyclohexane (DACH) platinum compound that forms bulky DACH–platinum DNA adducts, which interfere with DNA synthesis and transcription. The affected DNA must first be unwound before the damaged nucleotides can be excised [16]. Thus there is interest in the combination of oxaliplatin with the topoisomerase inhibitor irinotecan [17]. Preclinical data demonstrated that the combination of oxaliplatin and SN-38, the active metabolite of irinotecan, resulted in synergistic cytotoxicity in human colon adenocarcinoma cells, particularly when oxaliplatin was administered first [18].

A schedule of weekly intravenous (IV) oxaliplatin and irinotecan for 4 weeks every 6 weeks was selected for this study. This schedule was consistent with the irinotecan dosing in the irinotecan, 5-FU and leucovorin (IFL) regimen, which was the standard first-line therapy for metastatic colorectal cancer in the USA at the time this study was designed [10]. The administration of weekly oxaliplatin 1 h prior to weekly irinotecan was selected in attempt to maximize synergy between the two agents [18]. Weekly oxaliplatin at a dose of 60 mg/m^2 in combination with weekly high dose 5-FU and leucovorin had demonstrated efficacy in the German FUFOX regimen in patients with metastatic colorectal cancer resistant to 5-FU and leucovorin [19, 20]. We chose to administer capecitabine twice daily (bid) Monday-through-Friday for the first 4 weeks of the 6 week cycle, in attempt to simulate the efficacy of continuous IV 5-FU, which results in higher response rates in the treatment of metastatic colorectal cancer than does bolus 5-FU [21].

The objectives of the study were to determine the maximum tolerated dose (MTD) and dose limiting toxicity (DLT) of the combination; determine the pharmacokinetic profiles of the three chemotherapeutic agents, and observe patients for antitumor response. Special attention was paid to toxicity in women during the study design because of data suggesting that women experience greater toxicity from 5-FU than do men, and a report of a phase I study of capecitabine and oxaliplatin, in which women experienced excessive toxicity when compared to men [22–24]. We chose to enroll at least one female at each dose level in order to decrease the likelihood of dose escalation to levels with unacceptable toxicity for women versus men.

Patients and methods

This study was approved by the Cancer Therapy Evaluation Program at the National Cancer Institute (NCI) and the Institutional Review Board of University Hospitals Case Medical Center.

Patients

Patients were required to have measurable or evaluable metastatic solid tumors for which there was no curative treatment. Eligibility criteria included age $\geq$ 18 years; ECOG performance status $\leq$2; no large-field radiation therapy within 4 weeks; no anti-cancer therapy within 3 weeks; and adequate end-organ function (WBC $\geq$ 4,000/μL, neutrophils $\geq$ 1,500/μL, platelets $\geq$ 100,000/μL, hemoglobin > 10.0 g/dL), hepatic function (bilirubin $\leq$ 1.5 mg/dL, AST and ALT < 2 times upper limit of normal), and renal function (serum creatinine $\leq$ 1.5 mg/dL and/or serum creatinine clearance > 60 mL/min/1.73 m^2). Signed informed consent was required. Patients with New York Heart Association classification III or IV heart disease, brain metastases or primary brain tumors, and those who were pregnant or lactating were excluded.

Study design, dosage, and drug administration

Oxaliplatin (NSC 266064) was provided by the Division of Cancer Treatment, Diagnosis and Centers, NCI, (Bethesda, MD, USA). Commercially available irinotecan and capecitabine were used.

Oxaliplatin and irinotecan were administered IV weekly, for 4 weeks, followed by a 2-week rest. Oxaliplatin was administered as a 2-h 60 mg/m^2 infusion followed 1 h later by a 30-min infusion of irinotecan. Capecitabine was administered orally bid Monday through Friday for 4 weeks, followed by a 2-week rest. Cycles were repeated

every 6 weeks. Patients were treated until disease progression or unacceptable toxicity occurred.

The following parameters were required in order for a patient to receive weekly treatment: granulocytes > 1,500/μL and platelets > 100,000/μL. In order for a patient to begin a subsequent cycle of chemotherapy, the following parameters were required on day 1 of that cycle: granulocytes > 1,500/μL, platelets > 100,000/μL, liver and renal function returned to baseline, no major end organ toxicity, treatment-related toxicities returned to baseline levels or ≤ grade 1. A 2-week delay between weeks of treatment was permitted for myelosuppression and mucositis/diarrhea. A 3-week delay at the start of a new cycle was allowed for myelosuppression, mucositis/diarrhea and other treatment-related toxicities. If a cycle was complicated by grade 3 or 4 mucositis or diarrhea, grade 4 myelosuppression, or febrile neutropenia, the next cycle would be administered at the preceding dose level. Patients who encountered such toxicity in the initial dose level (1A) were treated subsequently with capecitabine 500 mg po bid.

A female patient was required to be enrolled at each dose level. Patients were escalated in cohorts of three until DLT was observed. DLT was defined as any treatment-related grade 3 non-hematological or treatment-related grade 4 hematological toxicity. Elevations in gamma glutamyl transpeptidase were not considered DLT. The occurrence of one DLT in the first three patients at a dose level required the enrollment of up to three more patients, including at least one more female patient, to that dose level. Two occurrences of DLT in a cohort of three to six patients at a given dose level resulted in a halt in dose escalation. The MTD was defined as the highest dose level at which six patients were treated with ≤1 patient experiencing DLT. Three patients would be added to a dose level if necessary to establish the MTD. DLT encountered at the initial dose level (1A) resulted in the amendment of subsequent dose levels to levels 1–4 (Table 2).

Pretreatment and follow-up studies

Patient history, physical examination and laboratory studies consisting of complete blood count (CBC) with differential and platelets, and chemistry panel were performed within 7 days of beginning cycle 1 and on day 1 of each subsequent cycle. A pregnancy test was performed within 7 days of beginning cycle 1. A CBC with platelets and differential was measured each week. Patients were questioned for neurologic symptoms, and an appropriate neurological examination was performed before each oxaliplatin dose. Patients were provided with a diary in which to record the timing of capecitabine doses as well as comments. The diary was reviewed by the study coordinator at each visit.

Tumor measurements were performed every two cycles. Toxicities were graded according to the NCI Common Toxicity Criteria version 2.0.

Plasma sampling and assays

Blood samples for oxaliplatin pharmacokinetics were collected at the following time points on day 1 of the first cycle: pre-infusion; 1 h (half-way through infusion); 1 h 55 min (just before end of infusion); 2 h 5 min; 2 h 30 min; 3, 4, 6, 8, 12–18, 24, 72, 168, and 336 h after the start of the infusion. The samples were collected in one 5-mL green-top vacutainer (heparin anticoagulant) at each of the specified times. Immediately after collection, each sample was gently inverted to mix completely and then placed into an ice bath. Within 1 h after collection, each sample was centrifuged at approximately $1{,}000 \times g$ to separate cellular elements from plasma. The plasma was transferred to polypropylene, screw-cap vials and frozen at −70°C. All plasma samples for oxaliplatin pharmacokinetics were shipped to and analyzed at the University of Pittsburgh Cancer Institute.

Blood samples for irinotecan and SN-38 pharmacokinetic studies were drawn at the following times on day 1 of the first cycle: pre-infusion; end of infusion; 2.5 h (after end-of-oxaliplatin infusion = 1 h after end-of-irinotecan); 3.5, 5.5, and 24 h. The samples were collected in 5-mL purple-top vacutainers (EDTA anticoagulant). The tubes were immersed in an ice water bath for 3 min, centrifuged at $2{,}000 \times g$ at 4°C for 10 min, and the resulting plasma was transferred to cryogenic storage tubes. Specimens were stored frozen at −70°C until analysis.

Blood samples for capecitabine and metabolite pharmacokinetic studies were obtained at the following times: just before oral dosing and then at 30 min and 1, 1.5, 2, 3, 4, 5, 6, and 8 h after dose administration on day 5 of weeks 1 and 4 of cycle 1. The samples were obtained and processed for storage as described above for irinotecan and SN-38 determination.

Pharmacokinetic analysis

Amicon CF25 ultrafiltration devices were used to separate free platinum from protein-bound platinum in plasma. Total and ultrafilterable platinum were assayed by flameless atomic absorption spectrometry according to published methods [25]. Irinotecan and SN-38 were measured via solid-phase extraction and high performance liquid chromatography according to published methods [26, 27]. Capecitabine and its metabolites 5′-deoxy-5-fluorocytidine (5′-DFCR), 5′-deoxy-5-fluorouridine (5′-DFUR), and 5-FU were measured by solvent extraction and reverse phase high performance liquid chromatography with detection by

electrospray ionization tandem mass spectrometry according to modifications of published methods [28–30].

Platinum concentration versus time data were analyzed non-compartmentally, using the Langrange function as implemented by the Langran computer program [31]. Compartmental pharmacokinetic modeling of irinotecan plasma concentration versus time data was carried out upon 15 evaluable data sets with the computer program PKAnalyst (Micromath, Salt Lake City, UT, USA). SN-38 AUC and half-life were calculated using the Excel program (Microsoft, Redmond, WA, USA). Peak measured capecitabine and metabolite concentrations were read directly from the capecitabine and metabolite data sets. Capecitabine and metabolite AUC and half-life calculations were made using the Excel program.

Statistical analyses

Descriptive statistics were used to summarize pharmacokinetic parameters. Arithmetic mean and standard deviation (SD) values for area under the curve (AUC), peak concentration (*C*max) and clearance were calculated. Correlations between continuous variables were evaluated using Pearson's (r) or Spearman's rank (r_s) correlation coefficients. The study was not powered to rule-out correlations between variables, and statements regarding a lack of correlation between variables are observational. Spearman's rank (r_s) correlation coefficient and a paired-samples t test were used to compare capecitabine pharmacokinetics at week 4 versus week 1. For patients treated with a uniform dose of capecitabine, the Mann–Whitney test was used to compare the mean AUC of capecitabine and metabolites with gender. Interpatient variation in pharmacokinetic parameters was calculated as a coefficient of variation (CV), equivalent to the (SD/mean) × 100. Statistical calculations were performed using SPSS Version 8.0 (Chicago, IL, USA).

Results

Patient characteristics and treatment administration

Twenty-two patients were enrolled onto this study from November, 2000 through October, 2003 (Table 1). A total of 60 cycles of chemotherapy were administered. All patients were evaluable for toxicity. Five patients received less than one cycle of therapy due to rapid progression of disease (one patient) or DLT as described below (four patients). The median number of cycles administered was 2 (range 0.5–6).

Dose-limiting toxicity

The starting dose level was oxaliplatin 60 mg/m^2; irinotecan 40 mg/m^2; and capecitabine 1,000 mg bid (Table 2).

Table 1 Patient characteristics

Characteristic	Number of Patients
Total number enrolled	22
Age (years)	
Median	60
Range	38–80
Gender	
Male	13
Female	9
ECOG performance status	
0	9
1	10
2	3
Number of prior chemotherapy regimens	
Median	2
Range	0–6
Tumor types	
Colorectal	11
Gastric	2
Lung	2
Pancreatic	2
Adenocarcinoma, unknown primary	1
Breast	1
Esophageal	1
Hepatocellular	1
Sarcoma	1

ECOG Eastern Cooperative Oncology Group

Two of four patients treated at the initial level (1A) developed DLT in the form of grade 3 diarrhea, which resulted in a revision of capecitabine dosing for subsequent dose levels (1–4), starting at 300 mg bid. In these two patients DLT began during weeks 2 and 3. There was no further DLT until dose level 3, which involved an increase of irinotecan to 50 mg/m^2. At this level during the fourth week of cycle 1, one (male) of six patients developed grade 3 nausea, vomiting and diarrhea, all of which were DLT. At the final level, which was oxaliplatin 60 mg/m^2, irinotecan 60 mg/m^2, and capecitabine 450 mg bid, all three patients treated developed DLT of grade 3 diarrhea during the first cycle (two females and one male). The onset of the grade 3 diarrhea was in weeks 2, 3, and 4 in these three patients. Thus the MTD of this regimen is oxaliplatin 60 mg/m^2, irinotecan 50 mg/m^2, and capecitabine 450 mg bid.

Non-hematologic toxicity

The incidence of non-hematologic toxicities in the first cycle is listed in Table 3. There were no occurrences of capecitabine-related hyperbilirubinemia or palmar–plantar erythrodysesthesia. Neurosensory toxicity, primarily in the

Table 2 Dose escalation scheme and DLT

Level	Oxaliplatin (mg/m^2)	Irinotecan (mg/m^2)	Capecitabine (mg PO BID)	Number of patients	Gender	Type of DLT and Gender
1A	60	40	1,000	4	3 M/1F	2 grade 3 diarrhea (1 M/1F)
1	60	40	300	3	1 M/2F	None
2	60	40	450	6	4 M/2F	None, see note
3	60	50	450	6	4 M/2F	1 grade 3 nausea, vomiting, diarrhea (1 M)
4	60	60	450	3	1 M/2F	3 grade 3 diarrhea (1 M/2F)

Transient grade 3 hyponatremia in 1 patient led to cohort expansion but was subsequently determined not to be DLT

M male, *F* female

Table 3 Treatment-related non-hematologic and hematologic toxicity in Cycle 1 (worst grade per patient)

Dose level	Ox (mg/m^2)	Irino (mg/m^2)	Cape mg bid	No. of Pts	Non-hematologic Toxicity and grade																							
					Diarrhea				Nausea				Vomiting				Neurosensory				Anorexia				Fatigue			
					1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
1A	60	40	1,000	4	0	1	2	0	2	1	1	0	2	1	1	0	3	0	0	0	3	0	0	0	1	1	0	0
1	60	40	300	3	2	0	0	0	3	0	0	0	1	0	0	0	2	0	0	0	2	0	0	0	3	0	0	0
2	60	40	450	6	4	0	0	0	2	0	0	0	2	0	0	0	6	0	0	0	1	0	0	0	3	1	0	0
3	60	50	450	6	2	0	2	0	2	0	2	0	0	1	2	0	2	0	0	0	3	0	0	0	0	3	0	0
4	60	60	450	3	0	0	3	0	1	0	0	0	0	0	0	0	2	0	0	0	0	1	0	0	1	2	0	0

Dose level	Ox (mg/m^2)	Irino (mg/m^2)	Cape mg bid	No. of Pts	Hematologic toxicity and grade															
					Hemoglobin				Leukopenia				Neutropenia				Platelets			
					1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
1A	60	40	1,000	4	2	2	0	0	1	0	1	0	0	0	0	1	1	0	1	0
1	60	40	300	3	3	0	0	0	2	0	0	0	0	0	0	0	1	0	0	0
2	60	40	450	6	3	2	1	0	3	1	0	0	0	1	1	0	2	0	0	0
3	60	50	450	6	4	2	0	0	3	2	1	0	0	0	3	0	2	0	0	0
4	60	60	450	3	2	1	0	0	1	0	2	0	0	0	1	1	1	0	0	0

Ox oxaliplatin, *Irino* irinotecan, *Cape* capecitabine, *Pts* patients

form of grade 1 cold-induced paresthesias, developed in 14 of 22 patients in cycle 1. Among all cycles, 15 patients developed neurosensory toxicity, which was of maximal intensity of grade 2 in 2 patients. Neurosensory toxicity most commonly presented as cold-induced paresthesias, but also included paresthesias not related to cold exposure, jaw pain, and eye pain. No neuromotor toxicity was observed.

Hematologic toxicity

The worst grade hematologic toxicities observed in cycle 1 are listed in Table 3. Neutropenia was dose-limiting in one patient at the initial dose level (1A) and one patient at the final dose level (4). Fever with neutropenia (grade 3) occurred in one patient at the final dose level but was not associated with documented infection. At the MTD (level 3), three of six patients developed grade 3 neutropenia.

Pharmacokinetics

Full platinum pharmacokinetic data were available for 20 patients, all of whom were treated with 60 mg/m^2 oxaliplatin weekly, weeks 1–4 of every 6 week cycle (Table 4). The mean ultrafilterable platinum AUC was 7.29 μg/mL h (SD = 6.41 μg/mL h) and the mean peak ultrafilterable platinum concentration at the end of infusion was 0.83 μg/mL (SD = 0.29 μg/mL). At the end of the 2 h oxaliplatin infusion, 39.5% (SD = 14.1%) of the platinum was ultrafilterable.

Pharmacokinetic data for SN-38 were available for all 22 patients and for irinotecan from 17 patients (Table 5).

Table 4 Ultrafilterable platinum pharmacokinetics

	Dose level				
	1A	1	2	3	4
No. of patients	3	3	6	6	3
Oxaliplatin	60 mg/m^2	60 mg/m^2	60 mg/m^2	60 mg/m^2	60 mg/m^2
Irinotecan	40 mg/m^2	40 mg/m^2	40 mg/m^2	50 mg/m^2	60 mg/m^2
Capecitabine	1,000 mg bid	300 mg bid	450 mg bid	450 mg bid	450 mg bid
Free platinum Cmax Mean (SD, CV %)	0.85 (0.15,18)	0.65 (0.15, 23)	0.72 (0.16, 22)	0.76 (0.19, 25)	1.34 (0.42, 31)
Free Platinum AUC Mean (SD, CV %)	8.5 (2.2, 26)	11.0 (10.3, 94)	9.2 (10.8, 117)	3.4 (2.4, 71)	7.3 (3.2, 44)
Free Platinum Cl (mL/min) Mean (SD, CV %)	120.3 (41.1, 34)	144.2 (89.8, 62)	198.1 (118.4, 60)	294.5 (116.3,40)	142.2 (97.0, 68)

Table 5 Irinotecan Pharmacokinetics

Dose level	No. of patients	Oxaliplatin (mg/m^2)	Capecitabine (mg bid)	Irinotecan (mg/m^2)	Irinotecan *C*max (ng/ml) mean (SD)	Irinotecan AUC (nM h) mean (SD)	Clearance Irinotecan L/h/m^2 mean (SD)	SN38 *C*max (ng/ml) mean (SD)	SN38 AUC$_{(0\text{-}t)}$ (nM h) mean (SD)
1A	4	60	1,000	40	273.3 (82.9)	2,136 (1,228)	19.0 (10.7)	9.6 (5.1)	79.6 (38.8)
1	3	60	300	40	415.2 (205.0)	1,785 (218)	20.5 (3.7)	11.1 (2.7)	92.2 (69.0)
2	6	60	450	40	427.4 (231.0)	2,338 (645)	15.6 (3.6)	13.0 (4.1)	109.0 (33.7)
3	6	60	450	50	736.3 (399.0)	2,388 (510)	20.3 (4.1)	11.5 (3.4)	87.16 (19.71)
4	3	60	450	60	544.1 (302.2)	1,984 (423)	26.3 (3.4)	11.4 (3.3)	91.70 (39.72)

Irinotecan pharmacokinetics were consistent with a 2-compartment model. The mean half-lives associated with the initial and terminal phases of irinotecan elimination were 1.0 h (SD = 0.6 h) and 9.0 h (SD = 3.7 h), respectively. There was no apparent correlation between the AUC of SN-38 or irinotecan with irinotecan dose. The mean plasma clearance of irinotecan was 20.1 L/h/m^2 (range 12.3–29.7). The CV for the clearance of irinotecan was 27.5%.

Evaluable capecitabine pharmacokinetic data sets were obtained from 22 patients in week 1 and 17 patients in week 4. Peak concentrations and AUC for capecitabine, 5′-DFCR, 5′-DFUR, and 5-FU are listed in Table 6. Among the 15 patients treated with capecitabine at 450 mg bid, the average times to peak concentration (SD) of capecitabine, 5′-DFCR, 5′-DFUR and 5-FU were 1.9 (1.4), 2.4 (1.6), 2.2 (1.4), and 2.2 (1.4) hours, respectively. There was no correlation between the AUC of capecitabine or its metabolites and the dose of capecitabine administered. In the week 1 pharmacokinetic studies, there was a correlation between the AUC of capecitabine and the AUC of 5-FU ($r_s = 0.691$, $P < 0.001$), the AUC of 5′-DFUR ($r_s = 0.636$, $P = 0.001$) but not the AUC of 5′-DFCR. There was a correlation between the AUC of capecitabine at week 1 and week 4 ($r_s = 0.561$, $P = 0.019$). Stronger correlation existed between the AUC of capecitabine metabolites at week 1 and week 4 (5′-DFCR $r_s = 0.662$, $P = 0.01$; 5′-DFUR $r_s = 0.912$, $P < 0.001$; 5-FU $r_s = 0.652$, $P = 0.005$. Using a paired-samples t test ($N = 17$), there was a trend to increased AUC of capecitabine at week 4 versus week 1 (mean capecitabine AUC week 1 = 2,428 nM h, mean AUC capecitabine week 4 = 2,911 nM h, $P = 0.062$) but there was no difference between the weeks 1 and 4 AUCs of 5′-DFCR, 5′-DFUR and 5-FU.

For the 6 women and 9 men treated at dose levels 2–4 (constant capecitabine dose of 450 mg bid), analysis of capecitabine pharmacokinetics measured during week 1 of cycle 1 revealed there was a higher mean AUC of 5-FU in women than in men (mean ± SD: 892 ± 287 nM h vs. 537 ± 182 nM h; Mann–Whitney two-tailed $P = 0.02$). Comparison of the AUC of capecitabine and metabolites measured in week 4 of cycle 1 in the patients treated at dose levels 2–4 revealed similar results.

Pharmacodynamics

In the 13 patients treated at dose levels 1A, 1 and 2 (constant irinotecan and oxaliplatin dose) there was a correlation between earlier onset (measured in days) of diarrhea with increasing peak capecitabine concentration in week 1, $r_s = -0.812$, $P = 0.008$.

Efficacy

Seventeen patients were evaluable for response. Four patients did not complete the first cycle due to DLT and

Table 6 Capecitabine pharmacokinetics

Dose level	Oxaliplatin (mg/m^2)	Irinotecan (mg/m^2)	Capecitabine (mg bid)	Capecitabine *C*max (nM)	Capecitabine AUC (nM h)	DFCR *C*max (nM)	DFCR AUC (nM h)	DFUR *C*max (nM)	DFUR AUC (nM h)	5FU *C*max (nM)	5FU AUC (nM h)
Week 1											
1A	60	40	1,000								
Mean				3,008	4,990	3,152	6,849	5,899	11,726	466	895
SD				2,478	4,574	1,149	1,713	2,608	5,635	248	557
CV %				82	92	36	25	44	48	53	62
1	60	40	300								
Mean				1,263	1,876	2,630	5,561	2,860	5,481	155	297
SD				698	1,183	2,125	5,079	581	1,114	45	135
CV %				55	63	81	91	20	20	29	45
2	60	40	450								
Mean				2,751	2,854	2,799	7,151	6,368	9,996	422	636
SD				2,567	1,485	2,299	2,398	6,685	7,194	325	217
CV %				93	52	82	34	105	72	77	34
3	60	50	450								
Mean				1,488	2,622	2,581	6,074	3,981	8,647	302	581
SD				854	1,166	2,337	3,351	1,336	2,559	119	236
CV %				57	44	91	55	34	30	39	41
4	60	60	450								
Mean				2,820	3,239	2,534	5,835	7,407	12,658	518	962
SD				706	557	1,332	3,042	1,156	1,159	271	362
CV %				25	17	53	52	16	9	52	38
Week 4											
1A	60	40	1,000								
Mean	Data available from 1 patient only			2,609	2,435	3,251	6,489	6,345	10,816	315	568
SD				NA	NA	NA	NA	NA	NA	NA	NA
CV %				NA	NA	NA	NA	NA	NA	NA	NA
1	60	40	300								
Mean				958	1,815	1,908	4,372	2,298	5,052	148	298
SD				359	834	1,442	3,808	36	1,174	32	112
CV %				37	46	76	87	2	23	22	38
2	60	40	450								
Mean				1,960	3,174	1,848	6,247	3,662	8,867	268	632
SD				1,278	1,014	975	1,919	3,010	5,084	53	113
CV%				65	32	53	31	82	57	20	18
3	60	50	450								
Mean				3,265	3,229	4,566	7,524	6,197	9,399	402	529
SD				1,854	978	2,061	551	4,739	3,763	361	253
CV%				57	30	45	7	76	40	90	48
4	60	60	450								
Mean				1,284	3,212	1,764	5,081	3,529	12,898	188	685
SD				944	2	1,773	4,272	553	2,353	67	15
CV%				74	0	100	84	16	18	36	2

DFCR 5′-deoxy-5-fluorocytidine, *DFUR* 5’-deoxy-5-fluorouridine

NA not applicable

were not considered evaluable for response. One patient declined further participation in the study after cycle 1 and had no radiologic assessment for response. A complete response (CR) was confirmed in one patient, who had gastric cancer previously treated with 5-FU and radiation. Nine patients had stable disease as their best response, and 6 of these patients (5 with colorectal cancer, 1 with esophageal cancer) were treated through at least 4 cycles.

Discussion

In this study, we have demonstrated that the administration of weekly oxaliplatin, weekly irinotecan, and fixed dose capecitabine Mondays through Fridays, all administered for 4 weeks every 6 weeks is feasible at low doses of capecitabine. The MTD and recommended phase II dose is oxaliplatin 60 mg/m^2, irinotecan 50 mg/m^2 and capecitabine 450 mg bid. Diarrhea, nausea, and vomiting were dose-limiting. Minimal myelosuppression was observed, with only two patients experiencing grade 4 neutropenia in cycle 1. At the MTD, three of six patients experienced grade 3 neutropenia. The relatively low dose of capecitabine resulted in no palmar plantar erythrodysesthesia. The minimal neurotoxicity observed reflects the moderate dose of oxaliplatin and the short duration of therapy. The presence of UGT1A1 promoter polymorphisms in our patients was not assessed but may have had an impact on the occurrence of dose-limiting diarrhea induced by irinotecan [32, 33]. However, we observed no relationship between the grade of diarrhea and the AUC of SN-38. Only one of the six patients who experienced DLT (grade 3 diarrhea and grade 3 neutropenia) had demonstrated intermittent elevations in unconjugated bilirubin prior to study entry, suggestive of UGT1A1 deficiency.

In the bloodstream, oxaliplatin is rapidly converted into a number of metabolites, most of which bind to protein and are inactive. Given the large number of metabolites, elemental platinum was measured rather than concentrations of individual metabolites. Non-compartmental methods were used for oxaliplatin pharmacokinetic analysis, given the non-specific nature of the platinum measured. The pharmacokinetics for ultrafilterable platinum are reported as it is this fraction, rather than the protein bound platinum, that contains the active forms of oxaliplatin.

There was no observed increase in the AUC of irinotecan or SN-38 with increasing irinotecan dose. This lack of a dose–response in the AUC of irinotecan and SN-38 was observed by Pitot and colleagues and is attributed to the interpatient variability in irinotecan and SN-38 concentrations and the narrow dose range studied [34]. Differences in UGT1A1 status between patients, which was not assessed in this study, may have contributed to the interpatient variability in irinotecan and SN-38 concentrations. Mathijssen and colleagues reported an inter-individual variability in irinotecan clearance of 32.1%, which is similar to our finding of a 27.5% coefficient of variation for irinotecan clearance [35]. The interpatient variability in irinotecan and SN-38 concentrations, small sample size, and assessment of irinotecan and SN-38 pharmacokinetics on day 1 only preclude an evaluation of capecitabine dose on irinotecan pharmacokinetics in this study.

Pharmacokinetic parameters of capecitabine and metabolites were similar to previous reports [36, 37]. Capecitabine was rapidly absorbed and converted to metabolites, with peak concentrations of capecitabine and metabolites achieved in approximately 2 h. Similar to an earlier report, large interpatient variations in capecitabine and metabolite concentrations were observed and reflected in the coefficients of variation [37]. At each dose level, the concentrations for 5-FU were approximately 1 log lower than those of 5′-DFCR and 5′-DFUR. A trend to increased AUC of capecitabine but not its metabolites was observed at week 4 compared to week 1, which may have been due to chance. Competition between irinotecan and capecitabine for hepatic carboxyl esterase is unlikely as irinotecan was administered 4 days prior to pharmacokinetic sampling for capecitabine, and no decrease in the AUC of 5′-DFCR was observed at week 4. Prior pharmacokinetic studies with bid dosing of capecitabine have not demonstrated differences in the AUC of capecitabine at day 14 compared to day 1 [36, 38].

Reviews of cooperative group studies of 5-FU for the treatment of colorectal cancer found that women experience an increased incidence of severe toxicities compared with men [22, 23]. In a phase I study of capecitabine administered bid for 2 weeks and oxaliplatin at 130 mg/m^2 every 3 weeks, 4 of 4 female patients developed DLT in cycle 1 or 2 at a median capecitabine dose of 3,600 mg per day, whereas 2 men had $\leq$ grade 2 toxicity at 3,900 mg per day [24]. In light of these data, our study required enrollment of a female patient at each dose level and at least one additional female patient if three additional patients were enrolled to a level following an occurrence of DLT. In our study, female patients demonstrated a higher AUC for 5-FU when compared to those of male patients at week 1 and week 4. We did not observe differences in toxicity between women and men (DLT occurred in six men and six women), which may reflect the conservative dose escalation scheme or small sample size. Although neither of two women treated at the MTD experienced DLT, the MTD in women may not be the same as in men. Treatment of a larger sample of women and men at the MTD would be required to establish that the MTD is the same for women and men.

The only response in this study was a confirmed complete response in a patient with gastric cancer previously treated with 5-FU and radiation. The three agents in this

regimen are active in colorectal cancer. Of the 11 patients enrolled with advanced colorectal cancer, ten were evaluable for response and none had received prior oxaliplatin. Two of these patients experienced disease progression and eight had stable disease as their best response. The lack of responses observed in the patients with colorectal cancer is not unexpected, as nine of the ten patients had received prior 5-FU and irinotecan. The response rates of FOLFOX regimens after irinotecan and 5-FU failure are approximately 9–15% [4, 39, 40].

Most combination studies with capecitabine administer capecitabine bid for 14 days every 3 weeks, as is standard for single agent capecitabine. Interest exists in alternative schedules that facilitate combination with weekly or every-2-week administration of IV chemotherapy [41, 42]. The schedule for our regimen was based upon the IFL regimen, which was a standard first-line therapy for metastatic colorectal cancer in the United States until the N9741 study demonstrated less toxicity and improved time-to-progression, response rate and survival with FOLFOX compared to IFL [43]. Despite the use of capecitabine Monday through Friday, rather than bolus weekly 5-FU, severe gastrointestinal toxicities limited the dosing of capecitabine and irinotecan. The dose of capecitabine at the MTD of 450 mg bid Monday through Friday for 4 weeks every 6 weeks, is considerably lower than the commonly prescribed dose of 2,000 mg/m^2 on days 1–14 every 21 days. However, the synergy between oxaliplatin and 5-FU, oxaliplatin and irinotecan, and recently demonstrated potential synergy between irinotecan and capecitabine suggest that our regimen may be active despite the relatively low doses of irinotecan and capecitabine at the MTD [5, 7, 8, 13, 18, 44]. Activity at the MTD was demonstrated in a patient with gastric cancer. This regimen was subsequently evaluated at our institution in a phase II study for initial therapy of advanced gastro-esophageal junction and gastric cancer (NCI 6449, CASE 1203).

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