Cancer Chemother Pharmacol (2009) 64:45–51
DOI 10.1007/s00280-008-0844-1

ORIGINAL ARTICLE

Dose-escalation study of fixed-dose rate gemcitabine combined with capecitabine in advanced solid malignancies

Steven Attia · Sherry Morgan-Meadows · Kyle D. Holen · Howard H. Bailey · Jens C. Eickhoff · William R. Schelman · Anne M. Traynor · Daniel L. Mulkerin · Toby C. Campbell · Thomas A. McFarland · Michael S. Huie · James F. Cleary · Amye J. Tevaarwerk · Dona B. Alberti · George Wilding · Glenn Liu

Received: 30 May 2008 / Accepted: 20 September 2008 / Published online: 8 October 2008

Abstract
Purpose To define dose limiting toxicities (DLTs) and the maximum tolerated dose (MTD) of capecitabine with fixed-dose rate (FDR) gemcitabine.
Methods Eligible adults (advanced solid tumor; performance status ≤2) received capecitabine 500 mg/m^2 PO BID days 1–14 and FDR gemcitabine (400–1,000 mg/m^2 escalated by 200 mg/m^2 increments) at 10 mg/m^2/min days 1 and 8 on a 21-day cycle. A traditional 3 + 3 cohort design was used to determine the MTD.
Results Thirty patients (median age 59 years) were enrolled. The predominant grade ≥3 toxicity was myelosuppression, particularly neutropenia. At dose level 4 (1,000 mg/m^2 gemcitabine), two out of five evaluable patients had a DLT (grade 4 neutropenia ≥7 days). At dose level 3 (800 mg/m^2 gemcitabine), one patient had a DLT (grade 3 neutropenia ≥7 days) among six evaluable patients. Therefore, the MTD and recommended phase II dose was designated as capecitabine 500 mg/m^2 PO BID days 1–14 with 800 mg/m^2 FDR gemcitabine days 1 and 8 infused at 10 mg/m^2 per min on a 21-day cycle. Partial responses occurred in pretreated patients with esophageal, renal cell and bladder carcinomas.
Conclusions This regimen was well tolerated and may deserve evaluation in advanced gastrointestinal and genitourinary carcinomas.

Keywords Capecitabine · Gemcitabine · Phase I · Fixed-dose rate

Introduction

The anti-cancer mechanisms of capecitabine (Xeloda; Roche, Basel, Switzerland), an oral pro-drug of 5-fluorouracil (5-FU), include the inhibition of thymidylate synthase and its incorporation into DNA and RNA. Its main toxicities include cytopenias, diarrhea and palmar–plantar erythrodysesthesia (i.e., hand–foot syndrome) [8]. Gemcitabine (Gemzar; Lilly, Indianapolis, Indiana), a nucleoside analog, incorporates into DNA and inhibits ribonucleotide reductase. Myelosuppression is its dose-limiting toxicity [1].

5-Fluorouracil and gemcitabine are synergistic in vitro [20]. By inhibiting ribonucleotide reductase, gemcitabine depletes the intracellular pool of deoxyuridine monophosphate. This results in enhanced binding of 5-fluorodeoxyuridine monophosphate to thymidylate synthase. Cancer cells contain higher concentrations than healthy cells of thymidine phosphorylase, an enzyme that catalyzes the last step in the conversion of capecitabine to 5-FU [9, 19]. As a result, capecitabine selectively produces relatively higher intratumoral 5-FU levels. Thus, administering capecitabine,

The results of this research appeared as abstract ID 13509 at the 2008 American Association of Clinical Oncology meeting in Chicago, IL, USA.

S. Attia · K. D. Holen · H. H. Bailey · J. C. Eickhoff · W. R. Schelman · A. M. Traynor · D. L. Mulkerin · T. C. Campbell · T. A. McFarland · M. S. Huie · J. F. Cleary · A. J. Tevaarwerk · D. B. Alberti · G. Wilding · G. Liu (✉)
University of Wisconsin Paul P. Carbone Comprehensive Cancer Center Madison, 600 Highland Avenue, Box 5669, Madison, WI 53792, USA
e-mail: gxl@medicine.wisc.edu

S. Attia
e-mail: attia@wisc.edu

S. Morgan-Meadows
Gulf Coast Minority-Based Clinical Oncology Program, Mobile, AL 36607, USA

rather than 5-FU, with gemcitabine may enhance this synergism. Phase II studies of gemcitabine (30-min bolus infusion) with capecitabine have shown activity in advanced breast [2], pancreatic [3, 5, 11], biliary [7, 13] and renal cell [22, 26] carcinomas.

Gemcitabine incorporation into DNA requires its conversion to an active triphosphate form, 2′,2′-difluordeoxycytidine triphosphate (dFdCTP). Prolongation of gemcitabine infusion to 10 mg/m^2 per min maximizes intracellular concentrations of dFdCTP [1, 4]. A phase II study comparing FDR gemcitabine and bolus gemcitabine in patients with advanced pancreatic carcinoma suggested benefit for the FDR regimen [24]. However, there was no difference in survival in a phase III study of FDR gemcitabine vs. bolus gemcitabine versus gemcitabine/oxaliplatin [12].

Two phase I studies evaluating FDR gemcitabine (10 mg/m^2 per min) in combination with capecitabine have been reported. In the first study, Rini et al. [14] did not find a maximum tolerated dose (MTD) in nine patients with metastatic renal cell carcinoma. The first dose level consisted of FDR gemcitabine at 600 mg/m^2 on days 1, 8 and 15 with capecitabine at 830 mg/m^2 PO BID days 1–21 on a 28-day cycle. Two DLTs (grade 3 hand–foot syndrome and persistent grade 2 hand–foot syndrome) occurred in the first six patients. Patients were then enrolled to a regimen of FDR gemcitabine at 600 mg/m^2 on days 1, 8 and 15 with capecitabine at 415 mg/m^2 PO BID days 1–21 on a 28-day cycle. Two of five patients at this dose level experienced a DLT (grade 3 neutropenia and delay in treatment ≥14 days due to infection). These toxicities precluded further evaluation. In the second phase I trial, conducted contemporaneously with ours, Santini et al. [17] found an MTD of capecitabine 650 mg/m^2 PO BID days 1–14 with FDR gemcitabine 800 mg/m^2 on days 1 and 8 of a 21-day cycle in patients with advanced solid tumors. Predominant grade ≥3 toxicities were hematologic. Partial responses (PRs) occurred in patients with periampullary and pancreatic carcinomas.

Based on the clinical activity of capecitabine with bolus gemcitabine and our hypothesis that FDR gemcitabine would improve this activity, the University of Wisconsin conducted a phase I study of FDR gemcitabine and capecitabine in patients with advanced solid malignancies. Our primary objective was to define the MTD for this combination. Secondary objectives were to assess tolerability and response.

Materials and methods

Patient selection

Eligible patients were, at baseline, ≥18 years old; had an Eastern Cooperative Oncology Group performance status (PS) ≤2 [10]; had biopsy-confirmed locally advanced, unresectable or metastatic solid malignancy; had adequate major organ function [absolute neutrophil count (ANC) >1,500/μL, hemoglobin ≥10 g/dL, platelet count >100,000/μL, estimated creatinine clearance >50 mL/min, total bilirubin <1.5 times the upper limit of normal (ULN), aminotransferases <2.5 times the ULN (or <5 times the ULN in the case of liver metastasis), alkaline phosphatase <2.5 times the ULN (or <5 times the ULN in the case of liver metastasis or <10 times the ULN in the case of bone metastasis)]; had received ≤3 chemotherapy regimens; had ≥1 non-irradiated measurable lesion; and had a life expectancy ≥12 weeks. At least 4 weeks had passed from prior treatment (6 weeks in the case of prior mitomycin C or nitrosoureas).

Exclusion criteria included pregnancy or breastfeeding, brain metastasis, other malignancy within 5 years, severe allergic reaction to 5-FU or gemcitabine, intestinal malabsorption, surgery within 4 weeks, need to continue warfarin therapy, unstable coronary artery disease, uncontrolled cardiac arrhythmias and myocardial infarction within the previous year. The Institutional Review Board of the University of Wisconsin approved the study protocol prior to its implementation. Patients provided written informed consent prior to enrollment.

Study parameters and tumor assessment

Baseline laboratory and imaging studies were performed within 2 and 4 weeks prior, respectively, of enrollment. Subsequent lab studies were performed on day 1 of each cycle. A complete blood count was drawn weekly. Measurable disease was reimaged and graded using Response Evaluation Criteria in Solid Tumors [25] every two cycles. Cycle length was 21 days.

Treatment

Roche provided capecitabine tablets. Gemcitabine was obtained commercially as an intravenous injection. We used pill counts to monitor capecitabine compliance.

Capecitabine at 500 mg/m^2 was given orally twice daily days 1 through 14 with increasing concentrations of FDR gemcitabine (400, 600, 800 and 1,000 mg/m^2; dose levels 1–4, respectively) on days 1 and 8 infused at a rate of 10 mg/m^2 per min. The dose of capecitabine was rounded to the nearest amount that could be administered in 150 and 500 mg tablets. These doses were adapted from the MTDs determined in studies of capecitabine with bolus gemcitabine [6, 18]. Patients were asked to take capecitabine at least 10 h prior to gemcitabine, with at least 10 h between capecitabine doses. Patients continued treatment until progressive disease (PD), treatment intolerance, treatment

delay >14 days of either drug or withdrawal of consent occurred.

Dose modifications

Dose modifications were permanent. Both drugs were held for a day 1 or day 8 ANC <1,000/mm^3 and restarted when the ANC had recovered to ≥1,500/mm^3 with a 25% (first occurrence) or 50% (second occurrence) reduction from the original dose. Both drugs were held for a day 1 or 8 platelet count <90,000/mm^3 and restarted when recovered with a 25% dose reduction. Both drugs were held for a hemoglobin <8 g/dL and restarted when the hemoglobin was ≥8 g/dL with a 25% dose reduction. Packed red blood cell transfusions were permitted. The dose of capecitabine was held for grade ≥2 hand–foot syndrome and restarted when recovered to grade ≤1 with a 25% (first occurrence) or 50% (second occurrence) reduction from the original dose. For persistent nausea and vomiting despite maximal supportive measures, capecitabine was reduced by 25% (grades 2/3) or 50% (grade 4) from the original dose. For diarrhea, the dose of capecitabine was held and, once recovered to grade ≤1, reduced by 25% (first grade 2/3 event) or 50% (first grade 4 event or second grade 2/3 event) from the original dose for a first occurrence. For other non-hematologic toxicity, the dose of capecitabine was held and reduced by 25% (first grade ≥2 events) or 50% (second grade ≥2 events) from the original dose. The dose of capecitabine was reduced by 50% from the second dose reduction for a third grade 2 occurrence of non-hematologic toxicity.

Dose-limiting toxicity, dose escalation, and maximum tolerated dose

Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0. DLT was defined as any of the following cycle 1 grade ≥3 toxicities deemed probably or definitely treatment-related: neutropenia ≥7 days or associated with fever (≥38.1°C) or infection; thrombocytopenia ≥7 days; mucositis; nausea; vomiting; hand–foot syndrome; diarrhea and non-hematologic toxicity. Patients who did not complete all planned cycle 1 treatment were unevaluable for a DLT and were replaced.

We utilized a traditional "3+3" dose escalation design [21, 23] to determine the MTD. If one patient experienced a DLT at a given dose level, a total of six patients were entered at that level. If two of six patients experienced DLT, then the MTD would be exceeded and additional patients enrolled at the next lowest dose level. The MTD of the combination was defined as the highest dose level at which less than two of six patients experienced a DLT.

Statistical analysis

Standard descriptive statistics were used to evaluate demographics, baseline variables, toxicities and responses. Toxicities were summarized by dose level and for all dose levels combined. The Wilsons' score interval method was used to construct 95% confidence intervals for the proportion of patients with a response and the proportion of patients with stable disease (SD). Patients who had received treatment were evaluable for toxicity analysis. Patients completing at least two cycles were evaluable for response.

Results

Baseline patient characteristics

Table 1 summarizes the baseline characteristics of the 30 patients enrolled between March 2004 and March 2008.

Dose escalation, dose limiting toxicity and maximum tolerated dose

Patients received capecitabine at 500 mg/m^2 PO BID days 1–14 with varying concentrations of FDR gemcitabine (400–1,000 mg/m^2 escalating by 200 mg/m^2 increments) infused at 10 mg/m^2 per min on days 1 and 8 on a 21-day cycle (Table 2). More than six patients enrolled per dose level. This occurred because patients who did not complete all planned cycle 1 treatment were unevaluable for DLT and were replaced. At dose level 3 (800 mg/m^2 gemcitabine), there was one DLT (grade 3 ANC ≥7 days) among six evaluable patients. At dose level 4 (1,000 mg/m^2 gemcitabine), two patients had DLT (grade 4 thrombocytopenia ≥7 days and grade 4 ANC ≥7 days in one patient, and grade 4 ANC ≥7 days in another patient) out of five evaluable patients. Therefore, the MTD and recommended phase II dose was designated as capecitabine 500 mg/m^2 PO BID days 1–14 with 800 mg/m^2 FDR gemcitabine days 1 and 8 infused at 10 mg/m^2 per min on a 21-day cycle.

Safety and tolerability

As of May 2008, 30 patients had received a median three cycles of treatment (130 cycles total; range 0.3–14 cycles). Table 3 summarizes the maximal severity of toxicities per patient without regard to study drug attribution occurring in at least 10% of patients. Twenty of 130 cycles (15.4%) involved a dose reduction. This included 9/61 cycles (14.8%) at dose level 1, 2/27 cycles (7.4%) at dose level 2 (600 mg/m^2 gemcitabine), 4/24 cycles (16.7%) at dose level 3 (i.e., the MTD) and 5/18 cycles (27.8%) at dose level 4. The most frequent reason for dose reduction was

Table 1 Baseline patient characteristics ($n = 30$)

Characteristic	Frequency	
	n	%
Age (years)		
Median	58.5	
Range	35–80	
Gender		
Male	16	53.3
Female	14	46.7
Ethnicity		
Caucasian	30	100
ECOG performance status		
0	11	36.7
1	17	56.7
2	2	6.6
Tumor type		
Renal cell carcinoma	6	20.0
Pancreatic carcinoma	4	13.3
Esophageal carcinoma	4	13.3
Head and neck carcinoma	3	10.0
Biliary tract carcinoma	3	10.0
Soft tissue sarcoma[a]	2	6.7
Non-small cell lung	2	6.7
Bladder carcinoma	2	6.7
Other[b]	4	13.3
Metastatic sites		
Liver	17	56.7
Lung	13	43.3
Lymph node	7	23.3
Other[c]	2	6.7
Prior treatment		
Chemotherapy	23	76.6
Radiotherapy	12	40.0
Surgery	15	50.0

ECOG Eastern Cooperative Oncology Group; *n* number

[a] Includes angiosarcoma and soft tissue sarcoma, not otherwise specified

[b] Includes one of each: uterine, anal, ovarian and rectal carcinomas

[c] One of each: adrenal, bone

myelosuppression, particularly grade ≥3 ANC. However, neutropenic fever did not occur. Dose delays occurred during 9/130 cycles (6.9%), including 3/61 cycles (4.9%) at dose level 1 (grade 2 dyspnea, grade 2 rash and grade 3 rash), 1/27 cycles (3.7%) at dose level 2 (patient request), 1/24 cycles (4.2%) at dose level 3 (grade 3 ANC) and 4/18 cycles (22.2%) at dose level 4 (grade 4 ANC, grade 3 pain, grade 3 thrombocytopenia and hospitalization due to pain). One patient died during treatment secondary to progressive disease and unrelated to the study drugs.

Efficacy

A total of 27 of the 30 enrolled patients were evaluable for response, a secondary study objective. Three patients were not evaluable for response: one patient at dose level 3 and two patients at dose level 4 withdrew during cycle 1 due to declining performance status. There were no complete responses. Four patients (14.8%; 95% CI: 6–32%) had PR for a median 5.5 months (8 cycles). The first patient with a PR had esophageal carcinoma, was treated at dose level 1 and requested to come off study after receiving five cycles to go on vacation. This patient continued the same treatment off study for 3 more months before experiencing PD. Prior treatment for this patient included paclitaxel, doxorubicin, irinotecan and cisplatin. The second patient with a PR had esophageal carcinoma, was treated at dose level 2 and had PD after seven cycles. Prior treatment included cisplatin and irinotecan. The third patient with a PR had renal cell carcinoma, was treated at dose level 1 and had PD after nine cycles. Prior treatment included interleukin-2 and sunitinib in combination with docetaxel. The fourth patient with a PR had bladder carcinoma, was treated at dose level 2 and requested to end treatment after nine cycles due to progressive fatigue. Prior treatment included carboplatin and paclitaxel.

A total of 12 patients (44.4%; 95% CI 28-63%) had SD as a best response (5 patients at dose level 1, 1 patient at dose level 2, 4 patients at level 3 and 2 patients at level 4). The median duration of SD was 4.1 months (6 cycles). Malignancies in which SD was seen include biliary carcinoma (3 patients), renal cell carcinoma (3 patients), anal carcinoma (1 patient), rectal carcinoma (1 patient), pancreatic carcinoma (3 patients) and esophageal carcinoma (1 patient). PD was the best response for 11 patients (40.7%; 95% CI 25–59%).

Discussion

Bolus gemcitabine with capecitabine is an active doublet in a variety of solid tumors [2, 3, 22, 26]. Combining FDR gemcitabine and capecitabine has the potential advantage of producing higher, more efficacious intracellular concentrations of the active metabolite of gemcitabine, dFdCTP. Therefore, we conducted this dose escalation study to find a suitable regimen for phase II testing.

Treatment yielded an MTD of capecitabine 500 mg/m^2 PO BID days 1–14 with FDR gemcitabine at 800 mg/m^2 infused at 10 mg/m^2 per min days 1 and 8 on a 21-day cycle. DLTs included, at 400 mg/m^2 of gemcitabine, grade 3 rash (1 patient); at 600 mg/m^2 of gemcitabine, grade 3 thrombocytopenia ≥7 days and grade 3 ANC ≥7 days in the same patient; at 800 mg/m^2 of gemcitabine, grade 3

Table 2 Dose levels, dose-limiting toxicities and cycle 1 dose reductions

Dose level	Dose of gemcitabine (mg/m^2)[a]	No. of patients	No. of patients with DLTs (cycle 1)	Description of DLTs (cycle 1)[b]	No. of patients with dose reduction[c] (cycle 1)	Reason for dose reduction (cycle 1)
1	400	9	1	Grade 3 rash	3	Grade 3 ANC, grade 2 dyspnea and grade 2 rash
2	600	6	1	Same patient: grade 3 thrombocytopenia ≥7 days and grade 3 ANC ≥7 days	0	–
3	800	7	1	Grade 3 ANC ≥7 days	1	Grade 2 rash
4	1,000	8	2	One patient with grade 4 thrombocytopenia ≥7 days and grade 4 ANC ≥7 days; one patient with grade 4 ANC ≥7 days	3	One patient with grade 3 thrombocytopenia, another with grade 3 pain and one patient with grade 3 pain/grade 3 infection

DLT Dose-limiting toxicity; *No* number; *ANC* absolute neutrophil count

[a] Gemcitabine infused at 10 mg/m^2 per min days 1 and 8 with capecitabine 500 mg/m^2 orally twice daily on days 1–14 of a 21-day cycle

[b] National Cancer Institute Common Toxicity Criteria version 3.0

[c] Unevaluable for dose-limiting toxicity

ANC ≥7 days; and, at 1,000 mg/m^2 of gemcitabine, grade 4 ANC ≥7 days and grade 4 thrombocytopenia ≥7 days in one patient and grade 4 ANC ≥7 days in another patient. This regimen was safe and well tolerated. Dose modification occurred in 15.4% (20/130) of cycles, including 16.7% (4/24) of cycles at dose level 3, the MTD. The predominant grade ≥3 toxicity (13/30 patients) and most common reason for dose reduction was myelosuppression, particularly neutropenia. However, neutropenic fever did not occur. Hand–foot syndrome was infrequent (i.e., 2 grade 1 and 1 grade 2 events).

The frequent occurrence of grade ≥3 neutropenia in our patients with the use of FDR gemcitabine was not surprising. FDR gemcitabine is expected to produce more neutropenia than bolus gemcitabine because prolonging the gemcitabine infusion produces higher intracellular concentrations of dFdCTP [1, 4]. Combining capecitabine with FDR gemcitabine is expected to potentiate neutropenia. Because of this, we utilized a dose of capecitabine that was significantly lower than that recommended in studies of bolus gemcitabine/capecitabine [6, 18].

Two other phase I evaluations of FDR gemcitabine with capecitabine have been reported. The first phase I trial was conducted by Rini et al. [14]. The first dose level of the Rini study was FDR gemcitabine at 600 mg/m^2 on days 1, 8 and 15 with capecitabine 830 mg/m^2 PO BID days 1–21 on a 28-day cycle. The second dose level was FDR gemcitabine at 600 mg/m^2 on days 1, 8 and 15 with capecitabine 415 mg/m^2 PO BID days 1–21 on a 28-day cycle. Due to DLTs in the initial dose levels of this study, the MTD was exceeded and the study was stopped. These DLTs included hand–foot syndrome at the first dose level and persistent infection/neutropenia with fever at the second dose level. These toxicities may have occurred because of the use of three weekly doses of gemcitabine as well as 21, rather than 14, continuous days of capecitabine on a 28-day cycle.

Our results are similar to those of a phase I study by Santini et al. [17]. These investigators reported an MTD of capecitabine at 650 mg/m^2 PO BID days 1–14 with gemcitabine at 800 mg/m^2 days 1 and 8 infused at 10 mg/m^2 per min on a 21-day cycle. As in our patients, cytopenias accounted for the majority of grade ≥3 toxicities. In contrast to our study, hand–foot syndrome was more frequent (5 grade 1 events and 1 grade 2 event vs. 2 grade 1 events and 1 grade 2 event) over the same number of cycles (i.e., 130 cycles). This may be attributable to the lower capecitabine dose used in our study (500 vs. 650 mg/m^2 PO BID). Additionally, diarrhea, a toxicity more ascribable to capecitabine than gemcitabine, appears to have been less frequent and less severe in our patients. However, for unclear reasons, nausea/vomiting were more common in our patients. These comparisons are limited by small patient numbers. Ultimately, the difference in capecitabine dose between our MTD and that of Santini et al. is small. Both regimens were tolerated well. Therefore, both regimens appear appropriate for phase II evaluation.

Among 27 patients evaluable for response, we noted four with a PR and 12 with SD. The median duration of PR was 5.5 months. The median duration of SD was 4.1 months. Based on these preliminary efficacy results, our regimen may deserve further evaluation in advanced esophageal, biliary, renal cell, bladder, rectal, pancreatic and anal carcinomas. Advanced breast carcinoma may also be appropriate for phase II evaluation with our regimen given

Table 3 Maximal severity of toxicities per patient and type over all cycles regardless of attribution to study drugs reported by ≥10% patients

Toxicity[a]	Gemcitabine dose level (infused at 10 mg/m^2/min)																Total (n = 30)			
	400 mg/m^2 (n = 9)				600 mg/m^2 (n = 6)				800 mg/m^2 (n = 7)				1,000 mg/m^2 (n = 8)							
	Grade				Grade				Grade				Grade				Grade			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Rash	1	3	1		2	1			1	4				4			4	12	1	
Fatigue	3	2			1	1			6				4				14	3		
Pain	4				3	1			2	1	1		1	2	2		10	4	3	
Neutropenia			3			1	2	2		1	2	1			2	1		2	9	4
Leukopenia		1				2	2			2	2	1		1	2	1		6	6	2
Nausea	3				1				6				4				14			
Thrombocytopenia						2	1			3	1				1	1		5	3	1
Anemia	1					1	1			2				2			1	5	1	
Anorexia	2				1				2				2				7			
Constipation	2				1	1			1				2				6	1		
Mucositis	2				1	1			1	1			1				5	2		
Diarrhea	2	1			1				2								5	1		
Dyspnea		1			2							1	2				4	1		1
Vomiting	1	2			1				1	1							3	3		
Headache	2								1				2				5			
Fever without neutropenia									2				1	1			3	1		
Infection without neutropenia		1				1								1	1			3	1	
Peripheral neuropathy	1				1				1	1							3	1		
Pruritus	1				1								2				4			
Anxiety					1				2								3			
Cough	2								1								3			
Edema	1				1	1											2	1		
Epistaxis					2								1				3			
Hand–foot syndrome					1	1			1								2	1		
Lightheadedness									1	1			1				2	1		

n Number

[a] National Cancer Institute Common Toxicity Criteria version 3.0

the activity of bolus gemcitabine with capecitabine in this setting [2]. The preliminary results of two small ongoing phase II studies of FDR gemcitabine with capecitabine using the regimen recommended in the Santini phase I study [17] have been reported thus far only in abstract form. First, in 21 chemotherapy-naive patients with advanced biliary carcinoma, the response rate (RR) was 30% (including 1 patient with CR and 5 with PRs) and median overall survival (OS) was 15 months [16]. Second, Santini et al. reported a RR of 24% (including 1 patient with a CR and 4 with PRs) and median OS of eight months in 25 chemotherapy-naive patients with advanced pancreatic carcinoma [15].

A limitation in the interpretation of our findings is that 57% (17/30) of patients had a PS of 1 and only two patients (6.7%) had a PS of 2. Additionally, 85% (17/20) of patients in the Santini phase I study had a PS of 0 and no patient had a PS of 2 [17]. Therefore, these safety and tolerability results may not generalize well to patients with a PS >1.

We conclude that capecitabine at 500 mg/m^2 PO BID days 1–14 with FDR gemcitabine at 800 mg/m^2 infused at 10 mg/m^2 per min days 1 and 8 on a 21-day cycle is a safe and tolerable regimen for patients with advanced solid malignancies. Advanced gastrointestinal and genitourinary carcinomas may be appropriate for further evaluation of this regimen.

Acknowledgments We thank our patients and their families for their participation in this study. We thank the nurses and research specialists of the University of Wisconsin Phase I Program for their devotion to these patients and this study. The study was partially supported by Roche. We acknowledge support from National Institutes of Health grant T32 CA009614 Physician Scientist Training in Cancer Medicine (Dr. Attia).

Disclosures None.

References

1. Abbruzzese JL, Grunewald R, Weeks EA, Gravel D, Adams T, Nowak B, Mineishi S, Tarassoff P, Satterlee W, Raber MN et al (1991) A phase I clinical, plasma, and cellular pharmacology study of gemcitabine. J Clin Oncol 9:491–498
2. Benekli M, Yildiz R, Uner A, Er O, Yamac D, Alkis N, Coskun U, Camci C, Buyukberber S (2007) Gemcitabine plus capecitabine combination in metastatic breast cancer patients previously treated with anthracyclines and taxanes. Oncology 72:308–313
3. Boeck S, Hoehler T, Seipelt G, Mahlberg R, Wein A, Hochhaus A, Boeck HP, Schmid B, Kettner E, Stauch M, Lordick F, Ko Y, Geissler M, Schoppmeyer K, Kojouharoff G, Golf A, Neugebauer S, Heinemann V (2008) Capecitabine plus oxaliplatin (CapOx) versus capecitabine plus gemcitabine (CapGem) versus gemcitabine plus oxaliplatin (mGemOx): final results of a multicenter randomized phase II trial in advanced pancreatic cancer. Ann Oncol 19:340–347
4. Grunewald R, Kantarjian H, Du M, Faucher K, Tarassoff P, Plunkett W (1992) Gemcitabine in leukemia: a phase I clinical, plasma, and cellular pharmacology study. J Clin Oncol 10:406–413
5. Herrmann R, Bodoky G, Ruhstaller T, Glimelius B, Bajetta E, Schuller J, Saletti P, Bauer J, Figer A, Pestalozzi B, Kohne CH, Mingrone W, Stemmer SM, Tamas K, Kornek GV, Koeberle D, Cina S, Bernhard J, Dietrich D, Scheithauer W (2007) Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. J Clin Oncol 25:2212–2217
6. Hess V, Salzberg M, Borner M, Morant R, Roth AD, Ludwig C, Herrmann R (2003) Combining capecitabine and gemcitabine in patients with advanced pancreatic carcinoma: a phase I/II trial. J Clin Oncol 21:66–68
7. Knox JJ, Hedley D, Oza A, Feld R, Siu LL, Chen E, Nematollahi M, Pond GR, Zhang J, Moore MJ (2005) Combining gemcitabine and capecitabine in patients with advanced biliary cancer: a phase II trial. J Clin Oncol 23:2332–2338
8. Mackean M, Planting A, Twelves C, Schellens J, Allman D, Osterwalder B, Reigner B, Griffin T, Kaye S, Verweij J (1998) Phase I and pharmacologic study of intermittent twice-daily oral therapy with capecitabine in patients with advanced and/or metastatic cancer. J Clin Oncol 16:2977–2985
9. Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, Shimma N, Umeda I, Ishitsuka H (1998) Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer 34:1274–1281
10. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649–655
11. Park BB, Park JO, Lee HR, Lee J, Choi DW, Choi SH, Heo JS, Lee JK, Lee KT, Lim do H, Park YS, Lim HY, Kang WK, Park K (2007) A phase II trial of gemcitabine plus capecitabine for patients with advanced pancreatic adenocarcinoma. Cancer Chemother Pharmacol 60:489–494
12. Poplin E, Levy D, Berlin J, Rothenberg M, Cella D, Mitchell E, Alberts S, Benson A (2006) Phase III trial of gemcitabine (30-minute infusion) versus gemcitabine (fixed-dose-rate infusion[FDR]) versus gemcitabine + oxaliplatin(GEMOX) in patients with advanced pancreatic cancer (E6201). Proc Am Soc Clin Oncol 24:4004
13. Riechelmann RP, Townsley CA, Chin SN, Pond GR, Knox JJ (2007) Expanded phase II trial of gemcitabine and capecitabine for advanced biliary cancer. Cancer 110:1307–1312
14. Rini BI, Weinberg V, Small EJ (2005) A phase I trial of fixed dose rate gemcitabine and capecitabine in metastatic renal cell carcinoma. Cancer 103:553–558
15. Santini D, Vincenzi B, Masi G, Catalano V, Virzi V, Fontana A, Vasile E, Intagliata S, Catalano G, Falcone A, Tonini G (2008) Phase II capecitabine and gemcitabine fixed dose rate (FDR) in patients with advanced pancreatic cancer. J Clin Oncol 26, May 20 Suppl, Abstract 15596
16. Santini D, Vincenzi B, Masi G, Catalano V, Virzi V, Vasile E, Intagliata S, Catalano G, Falcone A, Tonini G (2008) Fixed dose rate (FDR) gemcitabine (G) and capecitabine (C) in patients with metastatic biliary tract cancer (BTC): phase II trial. 2008 Gastrointestinal Cancers Symposium, Abstract No. 223
17. Santini D, Virzi V, Vincenzi B, Rocci L, Leoni V, Tonini G (2007) A phase I trial of fixed dose rate gemcitabine plus capecitabine in metastatic cancer patients. Ann Oncol 18:576–580
18. Schilsky RL, Bertucci D, Vogelzang NJ, Kindler HL, Ratain MJ (2002) Dose-escalating study of capecitabine plus gemcitabine combination therapy in patients with advanced cancer. J Clin Oncol 20:582–587
19. Schuller J, Cassidy J, Dumont E, Roos B, Durston S, Banken L, Utoh M, Mori K, Weidekamm E, Reigner B (2000) Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. Cancer Chemother Pharmacol 45:291–297
20. Schulz L SA, Wilmanns W et al (1998) Synergistic interaction of gemcitabine and 5-fluorouracil in colon cancer cells. Proc Am Soc Clin Oncol 17:965
21. Simon R, Freidlin B, Rubinstein L, Arbuck SG, Collins J, Christian MC (1997) Accelerated titration designs for phase I clinical trials in oncology. J Natl Cancer Inst 89:1138–1147
22. Stadler WM, Halabi S, Rini B, Ernstoff MS, Davila E, Picus J, Barrier R, Small EJ (2006) A phase II study of gemcitabine and capecitabine in metastatic renal cancer: a report of Cancer and Leukemia Group B protocol 90008. Cancer 107:1273–1279
23. Storer BE (1989) Design and analysis of phase I clinical trials. Biometrics 45:925–937
24. Tempero M, Plunkett W, Ruiz Van Haperen V, Hainsworth J, Hochster H, Lenzi R, Abbruzzese J (2003) Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol 21:3402–3408
25. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
26. Waters JS, Moss C, Pyle L, James M, Hackett S, A'Hern R, Gore M, Eisen T (2004) Phase II clinical trial of capecitabine and gemcitabine chemotherapy in patients with metastatic renal carcinoma. Br J Cancer 91:1763–1768