Dose-Escalating Study of Capecitabine Plus Gemcitabine Combination Therapy in Patients With Advanced Cancer

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Purpose: **The goals of this phase I study were to determine the maximum-tolerated doses of capecitabine and gemcitabine in patients with advanced cancer and to describe the dose-limiting toxicities (DLT) and safety profile of this combination.**

Patients and Methods: **Eligible patients had advanced solid tumors that had failed to respond to standard therapy or for which no standard therapy was available, measurable or assessable disease, Karnofsky performance status ≥ 70%, and acceptable organ function. Capecitabine was administered twice daily by mouth each day for 21 consecutive days followed by a 1-week break. Gemcitabine was administered as a 30-minute intravenous infusion weekly for 3 weeks followed by a 1-week break.**

Results: **Forty patients were enrolled onto the study, and 33 are fully assessable for toxicity. The most common toxicities during the first cycle of chemotherapy were neutropenia and mucositis. Only one patient treated at gemcitabine and capecitabine doses of 800 and 2000 mg/m^2, respectively, met protocol-specified DLT criteria; however, at these doses 65% of successive cycles required dose reduction or delay for toxicity. No episodes of DLT were observed at gemcitabine and capecitabine doses of 1,000 and 1,660 mg/m^2, respectively, and 70% of cycles of therapy were delivered without dose reduction or delay. Therefore, these doses are recommended for further study. Tumor responses were observed in patients with metastatic colorectal and pancreatic cancer.**

Conclusion: **Gemcitabine and capecitabine can be combined with acceptable toxicity at nearly full doses. Antitumor activity of the combination merits further investigation in phase II studies.**

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CAPECITABINE IS AN orally administered, tumor-selective fluoropyrimidine that is converted to fluorouracil (5-FU) in tissues by pyrimidine nucleoside phosphorylase (PyNPase).[1] Its tumor selectivity seems to be derived from selective overexpression of PyNPase, a pro-angiogenic molecule, in many tumors compared with normal tissues.[2-5] Capecitabine has demonstrated activity in treatment of patients with breast and colorectal cancer.[6,7]

Gemcitabine is a pyrimidine nucleoside antimetabolite that, once converted to difluorodeoxycytidine triphosphate, inhibits DNA synthesis by inhibition of DNA polymerase and direct incorporation into DNA leading to premature termination of DNA chain elongation.[8] The diphosphate intermediate of gemcitabine also inhibits ribonucleotide reductase and thereby depletes intracellular pools of deoxyuridine monophosphate, resulting in enhanced binding of 5-fluorodeoxyuridine monophosphate, the active metabolite of 5-FU, to thymidylate synthase.[9,10] This biochemical interaction may explain the supra-additive effects of combining gemcitabine and capecitabine in MAXF401 and MX-1 human breast cancer xenograft models. In MX-1 human breast cancer, treatment with gemcitabine also resulted in a dose-dependent 1.5- to 2.7-fold increase in expression of PyNPase and, presumably, an increase in intracellular release of 5-FU from capecitabine (H. Ishitsuka, personal communication, January, 2001). In vitro studies in colon cancer cells have also demonstrated synergy when exposure to 5-FU precedes exposure to gemcitabine.[11]

These preclinical studies provided the basis for a number of phase I clinical trials that examined combinations of 5-FU and gemcitabine administered on several doses and schedules. At the University of Chicago, we conducted a phase I trial of continuous intravenous infusion of 5-FU with weekly 30-minute intravenous infusions of gemcitabine.[12] The recommended phase II doses determined in this study were 5-FU 200 mg/m^2/d for 21 days with gemcitabine 450 mg/m^2 weekly for 3 consecutive weeks or 5-FU 200 mg/m^2/d for 14 days with gemcitabine 1,800 mg/m^2 weekly for 2 consecutive weeks. Dose-limiting toxicities (DLT) were mucositis, bone marrow suppression, and diarrhea. Tumor responses were observed in several tumor types, most notably renal cell carcinoma (RCC).

A subsequent phase II trial of this combination was conducted in patients with metastatic RCC most of whom

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had already been treated with immunotherapy or chemotherapy.[13] 5-FU was administered by continuous infusion at a dose of 150 mg/m^2/d for 21 days with gemcitabine at 600 mg/m^2 weekly for 3 weeks. Cycles were repeated every 28 days. Toxicities were primarily bone marrow suppression, mucositis, nausea, and fatigue. Partial responses were noted in 7 of 39 assessable patients (17%; 95% confidence interval, 8% to 34%). Median progression-free survival for patients in this study was 28.7 weeks, which was significantly better than that observed in similar patients with RCC treated on other phase II studies at our institution. Because daily oral capecitabine can mimic continuous infusion of 5-FU and because upregulation of PyNPase by gemcitabine can enhance the intracellular activation of capecitabine, we undertook a phase I trial of these drugs in combination with the primary objectives to determine the maximum-tolerated doses (MTD) of capecitabine and gemcitabine in patients with advanced cancer and to describe the DLT and safety profile of this combination.

PATIENTS AND METHODS

Patient Selection

Patients with histologically confirmed advanced solid tumors that had failed to respond to standard therapy or for which no standard therapy was available were eligible to participate in this study. Other eligibility criteria included measurable or assessable disease by computed tomography, magnetic resonance imaging, radiograph, or physical examination; age at least 18 years; Karnofsky performance status of at least 70% (ambulatory and capable of self-care); life expectancy of at least 3 months; and adequate organ function defined as absolute neutrophil count of at least 1,500/μL, platelet count of at least 100,000/μL, hemoglobin at least 9.0 g/dL, serum creatinine level $<$ 1.6 mg/dL, total bilirubin $<$ 2.0 mg/dL, serum albumin $>$ 2.5 g/dL, prothrombin time $<$ 1.5 times control level, AST and ALT levels $<$ 2.5 times the upper limit of normal or $<$ five times the upper limit of normal if liver metastases were present, and serum alkaline phosphatase $<$ 2.5 times the upper limit of normal or $<$ five times the upper limit of normal if liver metastases were present or $<$ 10 times the upper limit of normal if bone metastases were present. Patients must have been off previous anticancer therapy, including radiation therapy, for at least 4 weeks (6 weeks if the previous therapy included a nitrosourea or mitomycin) and must have recovered from the toxic effects of any previous therapy. Patients were excluded from the study if they had any unstable, pre-existing medical condition, prior unanticipated severe reaction to fluoropyrimidine therapy, organ allograft, evidence of CNS metastases, or history of significant gastric or small bowel resection, malabsorption syndrome, or other lack of integrity of the upper gastrointestinal tract that might compromise absorption of capecitabine. Pregnant and lactating women were also excluded from participation, and all patients with reproductive potential were required to use an effective contraceptive method if they were sexually active. All patients gave written informed consent according to federal and institutional guidelines.

Study Design

This was an open-label, single-center, nonrandomized, dose-escalating phase I study. All laboratory tests required to assess eligibility had to be completed within 7 days before start of treatment. Capecitabine was administered twice daily by mouth each day for 21 consecutive days followed by a 1-week break. Gemcitabine was administered as a 30-minute intravenous infusion weekly for 3 weeks followed by a 1-week break. Initially, all patients received capecitabine at a dose of 1,660 mg/m^2/d. Cohorts of at least three patients each received escalating doses of gemcitabine until the MTD was determined or up to a maximum dose of 1,000 mg/m^2. Once the MTD of gemcitabine given with capecitabine at 1,660 mg/m^2/d was established, all subsequent patients enrolled onto the study received a gemcitabine dose at one dose level below the MTD, and cohorts of at least three new patients each received escalating doses of capecitabine until the MTD was established or up to a maximum dose of 2,500 mg/m^2/d. Before entry of patients at a new dose level, all patients at the previous dose level must have been observed for at least 3 weeks. No intrapatient dosage escalation was permitted.

Dose-Escalation and Definition of Study End Points

The starting dose of gemcitabine was 400 mg/m^2 given in combination with capecitabine at 1,660 mg/m^2/d. The starting doses were based on available clinical information about the tolerable doses of each drug used individually and about the MTD of gemcitabine used in combination with 5-FU. Gemcitabine doses were increased in increments of 200 mg/m^2/wk in cohorts of at least three new patients each until MTD was established or a maximum gemcitabine dose of 1,000 mg/m^2/wk was achieved. At that point, all new patients were treated with gemcitabine at one dose level below the MTD and escalating doses of capecitabine. Capecitabine dose levels studied were 1,660 mg/m^2/d, 2,000 mg/m^2/d, and 2,500 mg/m^2/d.

Capecitabine was supplied by Roche Pharmaceuticals (Nutley, NJ) as Xeloda tablets in two dosage strengths, 150-mg and 500-mg tablets. The total daily dose was taken as two divided doses approximately 12 hours apart within 30 minutes after the ingestion of food. The two doses were divided so as to allow the administration of whole tablets.

Gemcitabine was commercially available as Gemzar (Eli Lilly, Indianapolis, IN) in 20-mg/mL vials, 10- and 50-mL sizes. The drug was prepared for administration according to directions in the package labeling.

For purposes of determining the MTD, only DLTs occurring during the first cycle of therapy were considered. DLTs were defined as any of the following: grade 4 neutropenia lasting at least 3 days or grade 3 or 4 neutropenia associated with fever $\geq$ 38.1°C; grade 4 thrombocytopenia lasting at least 3 days; grade 3 or 4 nonhematologic toxicity except alopecia, gastrointestinal toxicity, and palmar-plantar erythrodysesthesia (hand-foot syndrome); grade 3 or 4 nausea, vomiting, or mucositis not reduced to grade 1 with maximal supportive therapy; grade 3 and 4 diarrhea or a second occurrence of grade 2 diarrhea; grade 2 or 3 hand-foot syndrome not reduced to grade 1 before the start of cycle 2; inability to administer two successive doses of gemcitabine within the first treatment cycle; or delay of $\geq$ 14 days in initiating the second cycle of therapy because of persistent toxicity of grade 2 or higher. If one or more patients at a dose level experienced DLT, then three additional patients were treated at that dose level. The MTD was defined as the dose level at which no more than one of six patients experienced a DLT. Once this dose level was established, six additional patients were enrolled (maximum of 12) to gain additional experience with the combination. Patients who experienced DLT could be contin-

Table 1. Capecitabine Dose-Modification Schedule

Appearance of Toxicity	Schedule Modification According to Toxicity Grade		
	Grade 2	Grade 3	Grade 4
First	Interrupt treatment until resolved to grade 0-1, then continue at same dose	Interrupt treatment until resolved to grade 0-1, then continue at 75% of original dose	Discontinue treatment unless investigator considers it to be in the best interests of the patient to continue at 50% of original dose, once toxicity has resolved to grade 0-1 (after approval by the sponsor)
Second	Interrupt treatment until resolved to grade 0-1, then continue at 75% of original dose	Interrupt treatment until resolved to grade 0-1, then continue at 50% of original dose	
Third	Interrupt treatment until resolved to grade 0-1, then continue at 50% of original dose	Discontinue treatment permanently (off study)	
Fourth	Discontinue treatment permanently (off study)		

ued on treatment at a modified dose at the discretion of the treating physician if they seemed to be benefiting from the therapy.

Pretreatment and Follow-Up Studies

Before initiation of therapy, all patients had a history and physical examination, assessment of Karnofsky performance status, chest radiograph, 12-lead electrocardiogram, determination of tumor measurements, dipstick urinalysis, and routine laboratory studies that included a complete blood count with differential WBC count, electrolytes, urea, creatinine, glucose, total protein, albumin, calcium, phosphate, uric acid, alkaline phosphatase, total and direct bilirubin, and ALT and AST levels. History, physical examination, and laboratory tests were repeated on day 1 of each cycle of therapy. Assessment of toxicity and hematology tests were performed weekly during each cycle of therapy. Tumor assessments were performed after every two cycles of therapy, and response was assessed using World Health Organization criteria. A complete response was defined as disappearance of all clinically detectable disease determined by two observations at least 4 weeks apart. Partial response was defined as $\geq$ 50% decrease in total tumor size of all measured lesions lasting at least 4 weeks, no new lesions, and no progression of any lesion. Progressive disease was defined as a 25% or more increase of one or more measurable lesions or the appearance of new lesions. Time to progression was defined as the time from first day of treatment until documentation of disease progression.

Dose Modifications

The capecitabine dose was interrupted or modified based on observed toxicity according to the guidelines listed in Table 1. Patients were permitted to begin a new treatment cycle when the absolute neutrophil count exceeded 1,000/μL and the platelet count was $\geq$ 100,000/μL and other treatment-related toxicities had resolved to grade 0 to 1. Gemcitabine dosing was interrupted whenever capecitabine was held because of toxicity. Doses of gemcitabine were not otherwise modified during the study.

RESULTS

The characteristics of the 40 patients enrolled onto this study are listed in Table 2. The median age was 65 years (range, 41 to 83 years) and the median Karnofsky performance status was 80% (range, 70% to 100%). All but two patients had previously received chemotherapy.

Seven patients did not complete the first cycle of therapy and are, therefore, not assessable for toxicity. Three patients were noncompliant with the treatment protocol; one patient had rapid tumor progression and was withdrawn from the study, one patient developed sepsis from a pre-existing indwelling central venous catheter shortly after beginning treatment, one patient developed arm pain within 2 days of

Table 2. Patient Characteristics

Characteristic		No. of Patients
Patients enrolled		40
Men		18
Women		22
Age, years		
Median	65	
Range	41-83	
Karnofsky performance status		
100		6
90		11
80		21
70		2
Prior therapy		
Chemotherapy only		26
Chemotherapy and radiation		12
None		2
Diagnosis		
Colorectal		21
Pancreatic		3
Ovarian		3
Prostate		2
Breast		2
Mesothelioma		1
Melanoma		1
Sarcoma		1
Other		6

Table 3. Dose Levels

No. of Patients	Capecitabine (mg/m^2/d)	Gemcitabine (mg/m^2)	No. of Cycles
5	1,660	400	17
3	1,660	600	10
7	1,660	800	25
12	1,660	1,000	44
6	2,000	800	23

initiating chemotherapy and withdrew from the study to undergo a cardiac evaluation, and one patient was determined to be ineligible because of a prior bone marrow transplant. The dose levels evaluated in the 33 fully assessable patients are listed in Table 3.

The most common toxicities observed during the first cycle of chemotherapy are listed in Tables 4 and 5. The severity of neutropenia and mucositis increased with increasing doses of chemotherapy, although only one patient, treated at gemcitabine/capecitabine doses of 800/2,000 mg/m^2, respectively, met protocol-specified criteria for DLT (grade 3 mucositis). Although no episodes of DLT were observed at gemcitabine/capecitabine doses of 1,000/1,660 mg/m^2, respectively, further escalation of the gemcitabine dose above the standard dose of 1,000 mg/m^2 was prohibited by the protocol. Furthermore, our ability to administer successive cycles of chemotherapy without dose modification necessitated by toxicity became increasingly difficult at higher dosage levels. Table 6 lists the number of cycles of chemotherapy at each dosage level requiring protocol-specified dose reduction or delay because of severe or unresolved toxicity. At the gemcitabine/capecitabine dose level of 800/2,000 mg/m^2, respectively, 15 (65%) of 23 cycles of therapy (cycle 2 or higher) required dose reduction or delay for toxicity. In 10 of the 15 dose-modified cycles, dose reduction or delay was required because of grade 2 to 3 neutropenia or thrombocytopenia that had occurred during the prior cycle of therapy. Despite the 3-week duration of dosing, few patients experienced clinically significant hand-foot syndrome (grade 2 or higher), and no patients experienced febrile neutropenia or required platelet transfusion. Based on the absence of DLT in cycle 1 and the ability to deliver 70% of successive cycles without dose modification or delay, we recommend doses of gemcitabine and capecitabine of 1,000 mg/m^2 and 1,660 mg/m^2, respectively, for further evaluation in phase II studies.

Table 4. Hematologic Toxicity During Cycle 1

Dose Level of Gem/Cape (mg/m^2)	Total No. of Patients	No. of Patients With Grade of Toxicity									
		ANC			Platelets			Anemia			
		2	3	4	2	3	4	2	3	4	DLT
400/1,660	5	1			1			1			
600/1,660	3	1									
800/1,660	7	4	2			1		2			
1,000/1,660	12	3	3		2			4			
800/2,000	6	1	3					1	1		

Abbreviations: Gem, gemcitabine; Cape, capecitabine; ANC, absolute neutrophil count.

Table 5. Nonhematologic Toxicity During Cycle 1

Dose Level of Gem/Cape (mg/m^2)	No. of Patients	No. of Patients With Grade of Toxicity												
		Mucositis			Diarrhea			Fatigue			HFS			
		2	3	4	2	3	4	2	3	4	2	3	4	DLT
400/1,660	5				1			2						
600/1,660	3				1			2						
800/1,660	7													
1,000/1,660	12							1						
800/2,000	6	2	1								1			1

Abbreviation: HFS, hand-foot syndrome.

Although assessment of tumor response was not a primary objective of this study, patients were evaluated for tumor response after every two cycles of treatment. Partial or significant minor responses occurred in four patients whose characteristics are listed in Table 7. The time to progression for these patients ranged from 24 to 32 weeks. The responses in the colon cancer patients are of particular note in that all had previously received fluoropyrimidine-based therapy. The median time to progression for all 33 assessable patients was 12 weeks ranging from 4 to 32 weeks and 16 patients had a time to progression of 16 weeks or longer.

DISCUSSION

A number of phase I and II trials have now been completed that evaluated various ways of combining 5-FU and gemcitabine.[12-19] In most studies, DLTs of the combination have included mucositis, fatigue, thrombocytopenia, and neutropenia. 5-FU has often been administered as a continuous intravenous infusion for 14 to 21 days, requiring that patients have central venous catheters and infusion pumps. Activity of the combination has been reported in patients with pancreatic cancer and RCC.[13,16,19] At the University of Chicago, we have conducted phase I and II trials of infusional 5-FU and gemcitabine. In patients with RCC, partial responses were observed in seven of 39 assessable patients (17%, 95% confidence interval, 8% to 34%). Toxicities were primarily neutropenia, mucositis, and fatigue, and infectious complications included an episode of *Staphylococcus aureus* endocarditis and a central line infection.[13]

Therefore, we sought to develop a combination of gemcitabine with capecitabine that would mimic the continuous

Table 6. Cycles Requiring Dose Reduction or Delay

Dose Level of Gem/Cape (mg/m^2)	Total No. of Cycles	Cycles With Dose Reduction or Delay	
		No.	%
400/1,660	17	0	–
600/1,660	10	0	–
800/1,660	25	8	32*
1,000/1,660	44	12	31†
800/2,000	23	15	65‡

*In five of eight cycles, dose reduced for grade 3 ANC or platelets in prior cycle.

†In nine of 12 cycles, dose reduced for grade 3 ANC in prior cycle.

‡In 10 of 15 cycles, dose reduced for grade 2 to 3 ANC or platelets in prior cycle.

intravenous infusion of 5-FU used in our prior studies without the complications related to indwelling venous catheters. Indeed, the 21-day regimen described here allows administration of gemcitabine at standard doses (1,000 mg/m^2/wk) with capecitabine at doses that provide similar dose-intensity to the standard dose and schedule for this agent and the same total dose per cycle, ie, 1,660 mg/m^2/d for 21 days is equivalent to 2,500 mg/m^2/d for 14 days. This regimen is generally well tolerated, with the major toxicity being neutropenia and anemia at the recommended phase II dose. Remarkably, little clinically significant hand-foot syndrome was observed despite the 21-day schedule of capecitabine administration. Repetitive cycles could be administered without dose reduction or delay in 70% of cycles, and dose delays, when necessary, rarely required interruption of therapy for longer than 1 week. Indeed, 15 of the 33 fully assessable patients received four or more cycles of therapy, with two patients receiving eight cycles. At the recommended gemcitabine and capecitabine doses of 1,000 mg/m^2 and 1,660 mg/m^2, respectively, seven of 12 patients received four or more cycles of treatment, with four of these seven patients receiving all cycles of chemotherapy without dose reduction or delay.

We were encouraged to observe significant antitumor activity in this heavily pretreated patient population. Four patients had minor or partial responses with progression-free survival of 24 to 32 weeks. Disease stabilization was also observed in 12 patients who, therefore, received multiple cycles of treatment. Phase II studies are now being planned for patients with pancreatic cancer and RCC to further define the antitumor activity and tolerability of this regimen.

Pharmacologic studies were not performed as part of this clinical trial, but it is unlikely that such studies would have contributed much information at this point in the development of this regimen. Gemcitabine is metabolized by deoxycytidine kinase to inactive compounds that are then eliminated primarily by renal excretion. Capecitabine undergoes a complex metabolic activation, but the final cytotoxic derivative, 5-FU, is then rapidly degraded by dihydropyrimidine dehydrogenase to biologically inactive compounds.[1] Given the substrate specificity of these metabolic pathways, it is unlikely that a pharmacokinetic interaction would occur between gemcitabine and capecitabine. Overexpression of PyNPase in tumor cells may be an important, although not the sole determinant of tumor response to fluoropyrimidines, particularly capecitabine. Cellular levels of thymidylate synthase and dihydropyrimidine dehydrogenase are likely to be important determinants of outcome as well.[20] Because tumor response was not a primary end point of our study, we did not evaluate tumor blocks for expression of these enzymes. Such studies are likely to be more informative if performed in the context of phase II and III clinical trials where a more homogeneous population of patients is treated with uniform doses of chemotherapy with the goal of assessing antitumor activity and determining the characteristics of those tumors most likely to respond to therapy with this regimen.

Table 7. Characteristics of Responding Patients

Dose Level of Gem/Cape (mg/m^2)	Response	Time to Progression (weeks)	Diagnosis	Karnofsky Performance Status	Prior Therapy
800/1,660	PR*	32	Pancreatic	100	5-FU plus radiation
1,000/1,660	MR†	24	Colon	90	5-FU/LV, Fudr, CPT-11, CVI 5-FU, RF ablation
1,000/1,660	PR	32	Colon	90	5-FU/LV, CPT-11
800/2,000	PR	32	Colon	80	5-FU/LV, radiation, flavopiridol, CPT-11

Abbreviations: PR, partial response; MR, minor response; Fudr, fluorodeoxyuridine; RF, radiofrequency; CPT-11, irinotecan; LV, leucovorin; CVI, continuous venous infusion.

*71% reduction but confirmatory scan 4 weeks later not performed.

†46% reduction from baseline.

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