

# A Phase I Study of Gemcitabine and Docetaxel in Patients with Metastatic Solid Tumors

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**BACKGROUND.** A Phase I study was initiated to determine the maximum tolerated dose of weekly gemcitabine combined with monthly, fixed-dose docetaxel.

**METHODS.** Patients with metastatic solid tumors were treated with docetaxel, 60 mg/m<sup>2</sup>, on Day 1 every 28 days. Gemcitabine was administered on Days 1, 8, and 15 and underwent dose adjustment in cohorts of 3–6 patients. At the maximum tolerated dose, 11 additional patients were enrolled.

**RESULTS.** Twenty-six patients received 85 cycles of therapy. At the first dose level, the planned gemcitabine dose on Days 1, 8, and 15 was 800 mg/m<sup>2</sup>. Two of the 6 patients treated at this dose level experienced dose-limiting toxicities (DLTs) requiring the reduction of gemcitabine to 600 mg/m<sup>2</sup> per dose and the administration of ciprofloxacin, 500 mg orally twice daily, on Days 8–18. At the second dose level the first 3 patients experienced no DLTs and the dose of gemcitabine was increased to 700 mg/m<sup>2</sup>. Two of the 6 patients treated at the 700 mg/m<sup>2</sup> dose level experienced DLTs. Eleven additional patients were enrolled at the recommended Phase II dose of gemcitabine (600 mg/m<sup>2</sup>). At this dose level, Grade 3/4 (according to the National Cancer Institute's common toxicity criteria) neutropenia and thrombocytopenia occurred in 12.5% and 2.1% of cycles, respectively. Grade 3 and 4 nonhematologic toxicities were uncommon. Three of seven evaluable patients with pancreatic carcinoma had evidence of significant antineoplastic activity (three partial responses). In addition, two complete responses (one patient with gastric carcinoma and one patient with ovarian carcinoma) and one partial response (patient with hepatocellular carcinoma) were noted in patients with other solid tumors.

**CONCLUSIONS.** The regimen comprised of docetaxel, 60 mg/m<sup>2</sup>, on Day 1 and gemcitabine, 600 mg/m<sup>2</sup>, on Days 1, 8, and 15 with ciprofloxacin on Days 8–18 every 28 days is safe, well tolerated, and active. *Cancer* 2000;88:180–5.

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Gemcitabine (difluorodeoxycytidine) is a pyrimidine analogue that results in the accumulation of active triphosphate metabolites and subsequent depletion of intracellular deoxycytidine triphosphate pools.<sup>1</sup> As a single agent, gemcitabine has a broad range of antitumor activity including pancreatic carcinoma, nonsmall cell lung carcinoma, bladder carcinoma, and ovarian carcinoma. Docetaxel is a semisynthetic taxane that enhances microtubule assembly and inhibits the depolymerization of tubulin.<sup>2</sup> It also has a broad range of antitumor activity in solid tumors; preliminary reports have documented activity in pancreatic carcinoma.<sup>3–5</sup>

Given the distinct mechanisms of action and single agent activities, the combination of gemcitabine and docetaxel appears to be an

important regimen to study in a wide range of tumors. This Phase I trial was developed to determine the maximum tolerated dose (MTD) of gemcitabine given weekly and docetaxel given monthly. All patients with metastatic solid tumors were eligible for the study.

## MATERIALS AND METHODS

### Patient Selection

Eligible patients were those who had metastatic disease who had received no more than three prior chemotherapy regimens. Patients were required to have adequate bone marrow, hepatic, and renal functions as defined by an absolute neutrophil count (ANC)  $\geq 1500/\mu\text{L}$ , a platelet count  $\geq 100,000/\mu\text{L}$ , total bilirubin within normal limits, aspartate aminotransferase  $\leq 2.5$  times the upper limit of normal, alkaline phosphatase  $\leq 4$  times the upper limit of normal, and creatinine  $\leq 1.5$  mg/dL, respectively. All patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status  $\leq 2$ . All patients were informed of the investigational nature of this study and provided written informed consent. This Phase I trial was approved by the Institutional Review Board of Dana-Farber/Partners CancerCare.

### Toxicity

Toxicities were assessed weekly and graded according to the National Cancer Institute common toxicity criteria. Dose limiting toxicities (DLTs) were defined as Grade 4 neutropenia (ANC  $< 500/\mu\text{L}$ ) lasting for  $\geq 3$  days, febrile neutropenia (fever  $\geq 38.1^\circ\text{C}$  and ANC  $< 500/\mu\text{L}$ ), Grade 4 thrombocytopenia (platelet count  $< 25,000/\mu\text{L}$ ), and any Grade 3 or 4 nonhematologic toxicity excluding nausea, emesis, alopecia, and hypersensitivity reactions. Patients with Grade 4 neutropenia on Days 8 or 15 were required to have a repeat complete blood count within 4 days demonstrating resolution of the Grade 4 neutropenia.

### Treatment Plan

Docetaxel,  $60\text{ mg}/\text{m}^2$ , was administered as a 1-hour infusion on Day 1 of each 28-day cycle. Premedication with dexamethasone, 8 mg orally twice daily, for 5 days began on the day prior to docetaxel according to the recommended guidelines. Gemcitabine was administered as a 30-minute infusion on Days 1, 8, and 15 of each 28-day cycle. Dose levels are listed in Table 1. The first dose level of gemcitabine was  $800\text{ mg}/\text{m}^2$ . After the first dose level, the dose of gemcitabine was reduced to  $600\text{ mg}/\text{m}^2$ . Ciprofloxacin, 500 mg orally, twice daily was given between Days 8–18 for patients treated on the second and third dose levels but not for patients treated on the first dose level. The use of hematopoietic growth factors was not allowed.

TABLE 1  
Dose Levels

Dose level	Docetaxel on Day 1	Gemcitabine on Days 1, 8, and 15	Patients
1	$60\text{ mg}/\text{m}^2$	$800\text{ mg}/\text{m}^2$	6
2 <sup>a</sup>	$60\text{ mg}/\text{m}^2$	$600\text{ mg}/\text{m}^2$	14
3 <sup>a</sup>	$60\text{ mg}/\text{m}^2$	$700\text{ mg}/\text{m}^2$	6

<sup>a</sup> Ciprofloxacin, 500 mg orally twice daily, on Days 8–18.

The dose of gemcitabine was reduced by 25% on Days 8 and 15 of each cycle for an ANC of  $500\text{--}900/\mu\text{L}$  or a platelet count of  $50,000\text{--}99,000/\mu\text{L}$ , and the treatment with gemcitabine was withheld for an ANC  $< 500/\mu\text{L}$  or a platelet count  $< 50,000/\mu\text{L}$ . Docetaxel was not dose adjusted.

### Dose Escalation Design

On registration, patients were enrolled and received therapy at a specified dose level. Cohorts of three patients were treated at each dose level. If all 3 patients treated at a dose level were observed for  $\geq 21$  days on the first cycle without a DLT, then a cohort of 3 patients received the next dose level. If one of three patients experienced a DLT, then three more patients were added to the cohort. If two or more patients in a cohort developed a DLT, then the previous dose level was considered the MTD. An additional 11 patients were enrolled at the MTD.

### Patient Evaluation

Prior to each cycle of therapy, patients were required to have a physical examination, complete blood count, and serum chemistries. A physical examination and complete blood count with an ANC were required on Days 8 and 15 of each cycle. Measurable disease was evaluated prior to the initiation of therapy and after every two cycles. Complete response was defined as the disappearance of all measurable disease, signs, symptoms, and biochemical changes related to the tumor for  $\geq 28$  days, during which time no new lesions could appear. Partial response was defined as a reduction of  $\geq 50\%$  in the sum of the products of the perpendicular dimensions of all measurable lesions lasting for  $\geq 28$  days, during which time no new lesions could appear. Patients were allowed to remain on study in the absence of progressive disease. Continuation of chemotherapy beyond the sixth cycle for patients with stable or responding disease was left to the discretion of the treating physician.

**TABLE 2**  
**Patient Characteristics**

Patients	26
Men/women	17/9
ECOG performance status $\leq 1$	25
Mean age (yrs)	61
No prior chemotherapy	13
One prior chemotherapy regimen	6
Liver metastases	13
Tumor types	No. (previously untreated)
Pancreas	9 (7)
Nonsmall cell lung	3 (0)
Gastric	2 (1)
Ovarian	2 (0)
Colorectal	2 (0)
Hepatocellular	2 (2)
Mesothelioma	2 (2)
Esophageal	1 (0)
Prostate	1 (0)
Head and neck	1 (0)
Unknown primary	1 (1)

ECOG: Eastern Cooperative Oncology Group.

## RESULTS

### Dose Escalation and DLTs

Patient characteristics are listed in Table 2. The majority of patients had an ECOG performance status of 0 or 1, and 50% of patients had not received prior chemotherapy. At the first dose level, two of six patients experienced fever, Grade 4 neutropenia, and pulmonary infiltrates requiring admission to the hospital for intravenous antibiotics. Another patient at this dose level experienced Grade 4 neutropenia lasting for 3 days and Grade 3 asthenia. This led to a dose reduction of gemcitabine for the second cohort of patients. The first three patients at the second dose level experienced no DLTs. At the third dose level, one patient experienced fever, Grade 4 neutropenia, and a pulmonary infiltrate requiring administration of intravenous antibiotics. Another patient experienced a Grade 3 foot drop after the first cycle of therapy. The second dose level was considered to be the recommended Phase II dose and 11 additional patients were enrolled on this dose level. One patient at the second dose level had a severe hypersensitivity reaction immediately after the initiation of docetaxel and was not included in the toxicity analysis. Of the remaining 13 patients at the second dose level, 48 cycles of chemotherapy were delivered at the second dose level for a mean of 3.8 cycles delivered to each patient (range, 1–6 cycles).

### Toxicity and Dose Intensity

Neutropenia and thrombocytopenia were the most frequent toxicities encountered, as outlined in Tables

3 and 4. Grade 4 neutropenia was uncommon. At the first dose level, 12% and 0% of the cycles had Grade 4 neutropenia on Day 8 and Day 15, respectively. At the second dose level, 0% and 4% of cycles had Grade 4 neutropenia on Day 8 and Day 15, respectively. One patient at the second dose level died on Day 19 of Cycle 3 after 2 days of Grade 4 neutropenia followed by the development of lactobacillus sepsis. No other cycle in the second dose level was complicated by febrile neutropenia. At the third dose level, 5% and 5% of cycles had Grade 4 neutropenia on Day 8 and Day 15, respectively. Grade 3 thrombocytopenia occurred in 1 of 48 cycles delivered at the second dose level. No bleeding complications secondary to thrombocytopenia occurred on the study. Grade 3 or 4 nonhematologic toxicities are listed in Table 5.

Gemcitabine dose delivery is outlined in Tables 6 and 7. The dose of docetaxel was fixed in all patients at 60 mg/m<sup>2</sup>. In the 85 cycles of chemotherapy administered in all 3 dose levels, neutropenia was the reason for dose reduction or omission in 25% of cycles. Thrombocytopenia was the reason for dose reduction or omission in 27% of cycles. Only 8.2% of cycles were reduced or omitted due to both neutropenia and thrombocytopenia in the same cycle.

### Response Evaluation

Among the 26 patients entered onto the study, 4 patients experienced a DLT during the first cycle of therapy and 1 patient experienced a spinal cord compression during the first cycle of therapy. Twenty-one patients received at least 1 cycle of therapy and were evaluable for response. Seven of nine patients with pancreatic carcinoma received this regimen as initial therapy for their disease and seven patients were evaluable for response. One patient treated at the third dose level had complete resolution of a mass of the pancreatic head and near-complete resolution of liver metastases as noted by computed tomography (CT) scan. A patient with pancreatic carcinoma treated at the second dose level had a partial response that was maintained through six cycles of therapy. Another patient with pancreatic carcinoma treated at the second dose level had complete resolution by positron emission tomography scan of a pancreatic mass, complete resolution of paraaortic lymphadenopathy as measured by CT scan, and reduction of CA 19-9 from 3520 U/mL to 48 U/mL after 6 cycles of therapy. Persistence of subcentimeter pulmonary nodules that did not change with therapy and an ill-defined pancreatic mass on CT scan also was noted in this patient. All responding patients with pancreatic carcinoma received this regimen as initial therapy for their disease.

A previously untreated patient with gastric carci-

**TABLE 3**  
Grade 3 or 4 Hematologic Toxicity (Per Cycle)

Dose level	Total cycles	Day 8 neutropenia no. (%)	Day 8 thrombocytopenia no. (%)	Day 15 neutropenia no. (%)	Day 15 thrombocytopenia no. (%)
1	17	3 (17.6)	0 (0)	3 (17.6)	1 (5.9)
2	48	4 (8.3)	0 (0)	6 (12.5)	1 (2.1)
3	20	1 (5.0)	0 (0)	4 (20.0)	1 (5.0)

**TABLE 4**  
Grade 3 or 4 Hematologic Toxicity (Per Patient)

Dose level	Patients	Neutropenia (no.)	Thrombocytopenia (no.)
1	6	3	1
2	14	6	1
3	6	2	1

**TABLE 5**  
Grade 3 or 4 Nonhematologic Toxicity

Dose level	Toxicity (no. of patients)
1	Pneumonitis (2) Asthenia (2) Diarrhea (1) Mucositis (1)
2	Lactobacillus sepsis (1) <sup>a</sup> Asthenia (1) Diarrhea (1) Deep venous thrombosis (1) Hypersensitivity reaction (1)
3	Pneumonitis (1) Asthenia (1) Motor neuropathy (1)

<sup>a</sup> Patient died.

noma was treated at the second dose level and had a complete response through five cycles of therapy. A patient with ovarian carcinoma whose disease was resistant to paclitaxel had a complete response of intraabdominal disease and normalization of CA 125 after six cycles of therapy. A patient with hepatocellular carcinoma had resolution of paraaortic lymphadenopathy but persistence of ill-defined, previously alcohol-ablated liver lesions through six cycles of therapy.

## DISCUSSION

Gemcitabine and docetaxel are antineoplastic agents that are active in a wide range of tumors. Although preclinical data showing synergy are lacking, the combination is particularly attractive for those tumors in

which the drugs are active as single agents. The DLT of gemcitabine invariably is hematologic and the MTD differs according to schedule. The weekly dose schedule in which gemcitabine is administered 3 of 4 weeks has gained popularity and the MTD for previously treated patients is 790–1370 mg/m<sup>2</sup>/week.<sup>6,7</sup> In chemotherapy-naïve patients, the MTD for the weekly schedule is 2200 mg/m<sup>2</sup>.<sup>8</sup> However, for prolonged therapy, the standard weekly dose is 1000 mg/m<sup>2</sup>.

The DLT of docetaxel also is hematologic. As a single agent, the recommended dose of docetaxel is 100 mg/m<sup>2</sup> every 3 weeks. At this dose, approximately 74% of patients will have Grade 4 neutropenia and 14% will experience febrile neutropenia.<sup>2</sup> A recent report of 31 heavily pretreated patients with breast carcinoma who received docetaxel, 100 mg/m<sup>2</sup>, every 3 weeks noted that 61% of patients required dose reductions due to toxicity.<sup>9</sup> Toxicity is enhanced in the setting of liver dysfunction in which patients have diminished docetaxel clearance.<sup>10</sup> However, patients with liver metastases and normal liver function tests do not appear to have significantly abnormal docetaxel clearance compared with patients without liver metastases.<sup>11–13</sup> We fixed the dose of docetaxel at 60 mg/m<sup>2</sup>, which to our knowledge is the lowest dose at which activity has been demonstrated consistently.<sup>14–18</sup>

Our recommended Phase II doses for the combination of gemcitabine and docetaxel are approximately 60% of the recommended single agent dose of each drug. Several reasons may explain this discrepancy. First, there may be a pharmacokinetic interaction between gemcitabine and docetaxel that needs to be elucidated. It is interesting to note that gemcitabine can cause a mild, transient elevation in liver function tests that may interfere with docetaxel clearance.<sup>19,20</sup> Second, all patients in this study who experienced a DLT either had prior chemotherapy or liver metastases.

Using the same schedule, Spiridonidis et al. recommended a Phase II dose of gemcitabine, 800 mg/m<sup>2</sup>, on Days 1, 8, and 15 and docetaxel, 100 mg/m<sup>2</sup>, on Day 1.<sup>21</sup> With that dosing schedule, the mean dose of gemcitabine delivered per injection at the recommended Phase II dose was 656 mg/m<sup>2</sup>. On Days 8 and

**TABLE 6**  
Mean Dose of Gemcitabine

Dose level	Cycles	Day 1 (mg/m <sup>2</sup> )	Day 8 (mg/m <sup>2</sup> )	Day 15 (mg/m <sup>2</sup> )	Per injection (mg/m <sup>2</sup> )
1 (800 mg/m <sup>2</sup> )	17	753 ± 87	612 ± 262	675 ± 304	675 ± 156
2 (600 mg/m <sup>2</sup> )	48	600 ± 0	563 ± 100	516 ± 169	559 ± 68
3 (700 mg/m <sup>2</sup> )	20	700 ± 0	645 ± 162	543 ± 247	629 ± 118

**TABLE 7**  
Percentage of Cycles with Full Dose of Gemcitabine

Dose level	Day 1 (%)	Day 8 (%)	Day 15 (%)
1	76	65	59
2	100	81	69
3	100	55	50

15, the dose was omitted in 28% and 12% of patients, respectively. In our study, the mean gemcitabine dose per injection was 559 mg/m<sup>2</sup> at the recommended Phase II dose, and only 2% and 8% of cycles had the dose omitted on Days 8 and 15, respectively. The clinical relevance of omitting a dose of gemcitabine on Day 8 or 15 versus achieving a higher dose on Day 1 is unknown.

Activation of gemcitabine by deoxycytidine kinase to difluorodeoxycytidine-triphosphate is saturated in leukemic blasts at infusion rates of 10 mg/m<sup>2</sup>/minute.<sup>22,23</sup> Many Phase II studies have shown similar response rates between 800–1250 mg/m<sup>2</sup>.<sup>24</sup> To our knowledge there is no clear evidence that dose escalation with the 30-minute infusion schedule of gemcitabine improves efficacy within this range, possibly due to the saturation of deoxycytidine kinase in solid tumors. Therefore, it may be more important to deliver a lower dose of gemcitabine consistently than to achieve a higher dose intensity by maximizing the Day 1 dose.

The dose intensity of this combination may be increased with the use of growth factors. Georgoulas et al. administered gemcitabine, 900 mg/m<sup>2</sup>, on Days 1 and 8 and docetaxel, 100 mg/m<sup>2</sup>, on Day 8 every 21 days with granulocyte-colony stimulating factor (G-CSF) support on Days 9–15 to 51 chemotherapy-naïve patients with nonsmall cell lung carcinoma.<sup>25</sup> Approximately 8% of the patients experienced febrile neutropenia. Nevertheless, due to both the cost of colony-stimulating factors and the lack of data showing efficacy of dose intensity in solid tumors, we prohibited the use of G-CSF in the patients in the current study.

Promising activity in patients with pancreatic car-

cinoma has been reported in the administration of docetaxel, 100 mg/m<sup>2</sup>, every 3 weeks.<sup>3-5</sup> Alternatively, a preliminary report from Japan has shown no activity for a dose of docetaxel at 60 mg/m<sup>2</sup> in 16 patients with pancreatic carcinoma.<sup>26</sup> Further studies are needed to clarify the safety profile and efficacy of this regimen using various schedules.

Gemcitabine, 600 mg/m<sup>2</sup>, on Days 1, 8, and 15 and docetaxel, 60 mg/m<sup>2</sup>, on Day 1 of each 28-day cycle is a very well tolerated regimen. Despite our relatively low doses of both gemcitabine and docetaxel, we observed significant responses in three of seven evaluable patients with pancreatic carcinoma. Based on this result, a Phase II study of this regimen in pancreatic carcinoma is being undertaken by our group. Future studies also should explore gemcitabine combinations using an infusion rate of 10 mg/m<sup>2</sup>/minute rather than escalating the dose during the standard 30-minute infusion.

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