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ORIGINAL ARTICLE

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Phase I and pharmacokinetic study of two sequences of gemcitabine and docetaxel administered weekly to patients with advanced cancer

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Abstract *Purpose*: To determine the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), and effect of drug sequence on toxicities and pharmacokinetics of the combination of gemcitabine and docetaxel. *Methods*: A total of 34 patients with advanced cancers were treated with gemcitabine and docetaxel on days 1 and 8 of each 21-day cycle according to the following dose escalation schedule: level 1, 800 and 30 mg/m^2, respectively; level 2, 800 and 40 mg/m^2; level 3, 1000 and 40 mg/m^2; and level 4, 1250 and 40 mg/m^2. At each dose level, at least three patients were assigned to one of the two sequences of drug administration: gemcitabine→docetaxel or docetaxel→gemcitabine. Once the MTD had been reached, six additional patients, who had received no more than one chemotherapy regimen, were enrolled to dose levels 3 and 4 (gemcitabine→docetaxel) to determine the MTD in minimally pretreated patients. *Results*: Neutropenia was the most frequent DLT with an overall incidence of 23.5%. Grade 3/4 neutropenia occurred in 62% of patients (8/13) who had received two or more prior chemotherapy regimens, but not at all (0/15) in patients who had received no more than one prior chemotherapy regimens ($P < 0.001$). Additional DLTs included grade 4 diarrhea and grade 4 stomatitis in one patient each. The MTD was determined to be gemcitabine 800 mg/m^2 and docetaxel 40 mg/m^2 in patients who had received two or more prior chemotherapy regimens. However, minimally pretreated patients (no more than one prior chemotherapy regimen) were able to tolerate higher doses with an MTD of gemcitabine 1250 mg/m^2 and docetaxel 40 mg/m^2. There were no significant differences in toxicities or pharmacokinetics between the two sequences of administration. Partial and minor responses were observed in 23.5% of patients: non-small-cell lung (two of eight), gastric (two of three), head and neck (one of two), bladder (two of four) and hepatocellular cancer (one of one). *Conclusions*: The combination of gemcitabine and docetaxel administered on days 1 and 8 every 21 days was feasible and well tolerated in patients with advanced malignancies. The sequence of administration had no significant effect on the toxicity or pharmacokinetics of either drug. Minimally pretreated patients tolerated higher doses of this combination without significant toxicities. This schedule and combination demonstrated activity in a variety of solid tumors, and merits further evaluation.

Keywords Advanced malignancy · Docetaxel · Gemcitabine · Sequencing · Pharmacokinetics · Phase 1

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Introduction

The combination of gemcitabine and docetaxel is conceptually attractive as the individual agents have activity against a wide range of malignancies, and non-overlapping mechanisms of action and clinical toxicities. Gemcitabine is a novel deoxycytidine analogue that is structurally and metabolically similar to cytarabine. Gemcitabine inhibits DNA synthesis by blocking DNA polymerases and, after incorporation into DNA, leads to termination of DNA chain elongation [1]. In phase II trials, gemcitabine has been shown to have antitumor activity against non-small-cell lung (NSCL) [2], ovarian [3], breast [4], pancreas [5], and bladder [6] cancers.

Gemcitabine has mild hematologic toxicity [1], and is therefore suitable for combining with more myelosuppressive agents. The primary nonhematologic toxicity of gemcitabine is a 'flu-like syndrome consisting of fatigue, weakness, and mild fever with chills seen in up to 60% of patients [7].

Docetaxel is a new semisynthetic taxane, which promotes the assembly of microtubules and stabilizes them, preventing their depolymerization leading to cell death [8, 9]. In phase II trials, docetaxel has been shown to be active against breast [10], NSCL [11], ovarian [12], head and neck [13], gastric [14], and pancreatic [15] cancers. The dose-limiting toxicity (DLT) of docetaxel is myelosuppression, consisting primarily of neutropenia [11]. Nonhematologic toxicities include alopecia, nausea, diarrhea, dermatologic effects such as erythema, pruritus, dry skin, macular eruptions, and desquamation, and hypersensitivity reactions [16]. Fluid retention characterized by peripheral edema, pleural effusions, ascites, and weight gain may be observed above a cumulative dose of 400 mg/m^2. Fluid retention and hypersensitivity reactions are uncommon with steroid premedication [17].

Gemcitabine is administered using a weekly schedule, while docetaxel is typically administered once every 3 weeks. However, recent studies indicate that docetaxel can be administered weekly with markedly decreased myelosuppression while maintaining the same dose intensity [18]. In this phase I trial, we administered both gemcitabine and docetaxel weekly on days 1 and 8 in order to determine the maximum tolerated dose (MTD) and DLT associated with this regimen. Given that there are limited data with this novel combination, we also studied the effect of drug sequence (gemcitabine followed by docetaxel versus docetaxel followed by gemcitabine) on toxicities and the pharmacokinetic profiles of both drugs.

Patients and methods

Patient eligibility

Patients were required to have a histologically confirmed advanced cancer that was refractory to standard therapy or for which no standard therapy was available, and to have measurable or evaluable disease or an elevated tumor marker. Other eligibility criteria included: age ≥18 years, Eastern Cooperative Oncology Group performance status of 0 to 2; adequate bone marrow (leukocytes ≥3000/mm^3, absolute neutrophil count ≥1500/mm^3 and platelet count ≥100,000/mm^3), hepatic (bilirubin < 1.5 mg/dl, AST and ALT less than 1.5 times the upper limit of normal, and alkaline phosphatase less than 2.5 times the upper limit of normal), and renal function (serum creatinine < 1.5 mg/dl, or creatinine clearance > 60 ml/min); recovery from the toxicities of previous anticancer therapy; and a life expectancy of at least 8 weeks. Women of childbearing age were required to have a negative pregnancy test and use effective means of contraception during study participation. Patients with clinically active brain metastases, uncontrolled seizures or congestive heart failure not adequately controlled with medication were not eligible for treatment. All patients signed an informed consent prior to treatment, and the study was approved by the Georgetown University Institutional Review Board.

Treatment plan

Docetaxel and gemcitabine were administered on days 1 and 8 of each 21-day cycle. The starting doses were 65–80% of the MTDs of both drugs when administered alone using a similar schedule [18, 19, 20]. The following dose escalation scheme was used for gemcitabine and docetaxel, respectively: level 1, 800 and 30 mg/m^2; level 2, 800 and 40 mg/m^2; level 3, 1000 and 40 mg/m^2; and level 4, 1250 and 40 mg/m^2. To evaluate the effects of drug sequence on toxicity, six patients were enrolled at each dose level, three to receive gemcitabine→docetaxel (arm 1) and three to receive docetaxel→gemcitabine (arm 2). Each arm was escalated in parallel. If a DLT occurred at a specific dose level and sequence, three additional patients were treated for a total of six patients at that dose level and sequence. The MTD was defined as the highest dose level which resulted in a DLT in fewer than two of six patients in the first 3 weeks of treatment. Docetaxel was administered as a 1-h infusion and gemcitabine as a 30-min infusion. Patients were premedicated with oral dexamethasone 8 mg twice daily starting 12 h before treatment and continuing for four doses. Growth factors were not administered during the first cycle but were allowed during subsequent cycles at the discretion of the investigator.

Pretreatment and follow-up evaluations

Patients underwent a complete history and physical examination weekly for the first two cycles, and then once every 3 weeks during subsequent treatment cycles. Laboratory tests, including complete blood counts and chemistry survey, were performed weekly, and urinalysis was performed once every 3 weeks throughout study participation. All patients were staged with baseline radiologic studies within 2 weeks of starting the study. Tumor assessments were repeated every two cycles (6 weeks) to evaluate response. Patients were allowed to continue treatment if there was no evidence of disease progression. Dose escalation was not permitted within individual patients.

Pharmacokinetic analysis

Blood samples for pharmacokinetic studies were collected on day 1 of the first cycle. Samples for gemcitabine levels were collected at 0, 15, 30, 35, 45, 60, and 120 min after starting infusion, and for docetaxel were collected at 0, 15, 45 min, and 1.5, 3, 6 and 24 h after starting infusion. Blood samples for gemcitabine levels were collected in tubes containing tetrahydrouridine to inhibit cytidine deaminase activity. Samples were centrifuged at 4°C, and plasma for gemcitabine and docetaxel assays was stored at –20°C.

Gemcitabine and its major metabolite 2′-difluoro-2′,2′-deoxyuridine (2dFdU) were measured in plasma using high-performance liquid chromatography (HPLC), which was adapted from a previously described method [21], and subsequently validated at our institution. The assay was linear for gemcitabine and dFdU over a concentration range 0.2 to 9.6 μg/ml, with an accuracy of ±8% and within- and between-day variation of < 7%. Plasma docetaxel concentrations were measured by HPLC with a quantitation limit of 10 ng/ml [22] (PPD Pharmaco, Richmond, Va.). For gemcitabine, pharmacokinetic analysis was carried our using model-independent (noncompartmental) methods using WinNonlin (Pharsight. Corporation, Mountain View, Calif.) and linear/log trapezoidal rules. Docetaxel pharmacokinetic parameters were estimated by a Bayesian estimation using time-concentration data for each patient and the previously defined population model as prior information [23]. A three-compartmental structure model with first-order elimination was used. Individual pharmacokinetic analysis was performed using the NONMEM program [24].

Toxicity assessment

Toxicities were graded using the National Cancer Institute Common Toxicity Criteria (Version 1.0). For hematologic toxicity, DLT

was defined as grade 4 myelosuppression lasting 1 week or more of the first treatment cycle, or grade 3/4 myelosuppression occurring during the first 7 days of the first treatment cycle. Nonhematologic toxicities grade 3 or more (except hair loss) were considered as DLT if they occurred within the first treatment cycle. If a patient experienced DLT, treatment was stopped until the toxicity resolved to grade 1 or less, and then resumed at 75% of the dose of both drugs.

Response criteria

Patients who had completed at least two cycles of therapy were assessable for response. Responses required confirmation by repeat radiologic assessments at least 4 weeks apart. Complete response was defined as a complete clinical and radiologic disappearance of tumor. Partial response was defined as ≥50% reduction in the size of the measurable lesions as demonstrated by a decrease in the sum of the products of the longest perpendicular lesion measurements. Minor response was defined as 25–50% reduction in the size of the measurable lesions as demonstrated by a decrease in the sum of the products of the longest perpendicular lesion measurements. Stable disease was defined as a decrease in index lesions by $<25\%$ or an increase in index lesions by $<25\%$. Progressive disease was defined as the appearance of new lesions or an increase of ≥25% in the sum of the products of the longest perpendicular measurements of the measurable lesions.

Statistical analysis

The Fisher exact test was used for comparing various types of grade 3/4 toxicities between the two study arms and according to the number of prior chemotherapy regimens (no more than one versus two or more). Pharmacokinetic parameters between the two arms of the study were compared using a two-sample *t*-test or a Mann Whitney rank sum test for nonparametric distributions.

Table 1 Baseline characteristics of 34 enrolled patients

	Number of patients (%)[a]
Age (years)	
Median	58
Range	38–79
ECOG performance status	
0	6 (18%)
1	18 (53%)
2	10 (29%)
Sex	
Male	16 (47%)
Female	18 (53%)
Tumor type	
Non-small-cell lung	8 (23%)
Breast	5 (15%)
Bladder	4 (12%)
Gastric	3 (9%)
Cervix	2 (6%)
Esophagus	2 (6%)
Renal	2 (6%)
Other	8 (23%)
Prior therapy	
Chemotherapy	26 (76%)
Surgery	26 (76%)
Radiation	18 (53%)

[a]Unless otherwise stated

Results

Patient characteristics

A total of 34 patients with an advanced malignancy received a total of 141 cycles of treatment between February 1997 and May 1998. Patient characteristics are listed in Table 1. All patients were evaluable for toxicity, while 26 patients received at least two cycles of treatment and were evaluable for response. Eight patients were not evaluable for response due to DLT or toxicity requiring a treatment delay of >3 weeks (seven patients) and deep vein thrombosis (one patient). The median number of chemotherapy cycles administered was three per patient (range 0.5 to 26 cycles).

Dose escalation

At least three patients were treated per arm at each dose level as summarized in Table 2. Toxicities for each arm and dose level are shown in Table 3. Each arm was escalated and expanded for DLT in parallel until two of three patients experienced DLT at dose level 3 (arm 2), consisting of grade 4 neutropenia (lasting >3 weeks) and grade 4 stomatitis, respectively. Therefore, the MTD had been exceeded at dose level 3 (arm 2). No

Table 2 Patients enrolled per dose level and arm. Numbers in parenthesis indicate number of patients with DLT

Dose level	Gemcitabine dose (mg/m^2)	Docetaxel dose (mg/m^2)	Arm	No. of patients	No. of prior chemotherapy regimens		Total no. of cycles
					One or none	Two or more	
1	800	30	1	3 (0)	1 (0)	2 (0)	13
			2	6 (1)	4 (1)	2 (0)	44.5
2	800	40	1	10 (2)	4 (1)	6 (1)	24.5
			2	6 (0)	4 (0)	2 (0)	28.5
3	1000	40	1	3 (1)[a]	3 (1)	0 (0)	15
			2	3 (2)	2 (1)	1 (1)	7
4	1250	40	1	3 (0)[a]	3 (0)	0 (0)	8.5
			2	0 (0)	0 (0)	0 (0)	0
Total				34 (6)	21 (4)	13 (2)	141

[a]Additional patients enrolled after study amendment (patients who had received no more than one prior chemotherapy regimen)

Table 3 Adverse events (all cycles) according to dose level and study arm

Toxicity	Arm	Level 1 (arm 1, $n=3$; arm 2, $n=6$)				Level 2 (arm 1, $n=10$; arm 2, $n=6$)				Level 3 (arm 1, $n=3$; arm 2, $n=3$)				Level 4 (arm 1, $n=3$; arm 2, $n=0$)			
		Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	1		1	1			2	3	1		1			2	1		
	2		1		1	2	1	1			2		1				
Thrombocytopenia	1	1				1	3										
	2	2		1			1				1						
Anemia	1			2			2										
	2		2				1	1			2	1					
Fatigue	1		2			4	1			3				1			
	2	2	1				1			3							
Diarrhea	1	3				2			1	2							
	2	2				1											
Stomatitis/mucositis	1	1				2				1							
	2	1											1				
Hyperbilirubinemia	1						1								1		
	2			1													
Skin	1																
	2	1				1						1					
Nausea	1	1	2			3				1	1			1			
	2	2	1			1	1			1							
Edema	1		3														
	2	1															
SGOT/SGPT	1	1				1	1			1		1		1	1		
	2	1	1				1										
Anorexia	1	1								1							
	2	2				1				1							
Hair loss	1									2	1			1			
	2																

patient had started treatment on arm 1 at dose level 3 at this time. Therefore, six additional patients were enrolled at dose level 2 (three per arm). One of these patients (on arm 1) experienced DLT consisting of grade 4 diarrhea. Analysis of clinical data at this time showed no significant differences in clinical toxicities between the two arms of the study (Table 3, *P*-values for comparison of individual toxicities according to grade and study arm ranged from 0.07 to >0.90); therefore data were combined for either sequence of administration. Overall, 2 of 16 patients treated at dose level 2 developed DLT, therefore, dose level 2 (gemcitabine 800 mg/m^2 and docetaxel 40 mg/m^2) was determined to be the MTD.

A review of the hematologic toxicities revealed that all grade 3 and 4 neutropenia had occurred in patients who had received two or more prior chemotherapy regimens (Table 4). Since neutropenia had been the DLT in most cases, we sought to determine if doses could be escalated further in minimally pretreated patients. Therefore, the protocol was amended to limit enrollment to patients who had received no more than one prior chemotherapy regimen, and all patients were enrolled to arm 1 of the study. Three patients each were enrolled at dose level 3 ($n=3$) and dose level 4 ($n=3$). One patient at dose level 3 experienced transient grade 3 transaminitis (lasting 7 days) during cycle 3 of treatment, while the remaining five patients tolerated treatment well without DLT. Therefore, in patients who had received no more than one prior chemotherapy regimen, dose level 4 (gemcitabine 1250 mg/m^2 and docetaxel 40 mg/m^2) was determined to be the MTD. Further dose escalations were not planned since the individual MTDs of both drugs had been reached.

Hematologic toxicity

Neutropenia was the principal DLT. Grade 3/4 neutropenia was encountered at dose levels 1 (2/9), 2 (5/16) and 3 (1/6), and occurred only in patients who had received two or more prior chemotherapy regimens (8/13 or 61.5%, Table 4). The overall incidence of grade 3/4 neutropenia was 23.5% (8/34). The onset of neutropenia typically occurred between days 7 and 18 of cycle 1, and lasted 2–12 days. Growth factor support for neutropenia was required in 2/34 patients (5.8%), and there was no incidence of febrile neutropenia. Anemia and thrombocytopenia were typically mild and were not dose-limiting. One patient at dose level 1 developed grade 3 thrombocytopenia on day 18 of cycle 1. This patient had previously undergone bone marrow transplantation for metastatic breast cancer, and did not have a recurrence of thrombocytopenia after dose reduction. Overall, treatment was delayed in 5 of 141 cycles (3.5%) and the dose was reduced in 4 of 34 patients (11%) due to hematologic toxicities.

Table 4 Toxicity according to number of prior chemotherapy regimens ($n=34$)

Type of toxicity (grade 3/4)	Number of prior chemotherapy regimens		*P*-value
	One or none	Two or more	
Neutropenia	0/21	8/13	<0.001
Thrombocytopenia	0/21	1/13	0.38
Anemia	1/21	2/13	0.54
Diarrhea	1/21	0/13	>0.90
Stomatitis/mucositis	1/21	0/13	>0.90
Hyperbilirubinemia	1/21	0/13	>0.90
SGOT/SGPT	1/21	0/13	>0.90

Nonhematologic toxicities

Nonhematologic toxicities included diarrhea, stomatitis, hepatotoxicity, skin toxicity and nausea. Diarrhea was encountered in 11 patients (32%) and was grade 1 in all except one patient who experienced grade 4 diarrhea that constituted a DLT. Six patients (17%) experienced stomatitis or mucositis, of whom one developed grade 4 stomatitis that constituted a DLT. The grade 4 stomatitis occurred after the first cycle of treatment in a patient who had previously received neck irradiation for head and neck cancer. Hepatotoxicity consisted of mild (grade 1–2) elevations of SGOT/SGPT in nine patients (26%). One patient at dose level 3 experienced transient grade 3 transaminitis during cycle 3, but was able to continue treatment at a reduced dose (dose level 2) for a total of six cycles without recurrence of hepatotoxicity. Hyperbilirubinemia was observed in three patients (9%), including one patient who experienced grade 3 hyperbilirubinemia during the first cycle of treatment. Skin toxicity was seen in three patients (8%), and consisted of hand-foot syndrome ($n=2$) or a generalized maculopapular rash (grade 3, $n=1$). Grade 1–2 nausea was encountered in 15 (44%) patients. Other nonhematologic toxicities consisted of grade 1–2 fatigue (53%), anorexia (17%) and hair loss (11%). The median cumulative dose of docetaxel was 190 mg/m^2 (range 30–1560 mg/m^2), and eight patients (23%) received a cumulative dose of $\geq$400 mg/m^2. However, with the use of steroid premedication, fluid retention (grade 1–2 edema) was seen in only four patients (11%). No neuromuscular toxicity was observed in this study.

Pharmacokinetics

Pharmacokinetic data for gemcitabine were available in 20 patients and for docetaxel in 12 patients. The C_{max}, AUC and $t_{1/2}$ were estimated for gemcitabine and its metabolite, dFdU, while CL and V_{ss} could be estimated only for gemcitabine. Pharmacokinetic analysis for docetaxel was focused on estimating the CL and AUC since the limited plasma sampling did not permit a reliable estimation of other parameters. As shown in Table 5, the sequence of drug administration was not

Table 5 Pharmacokinetic parameters for gemcitabine (arm 1, $n=8$; arm 2, $n=12$) and docetaxel ($n=6$ per arm) (C_{max} peak concentration, AUC area under the concentration-time curve, $t_{1/2}$ half-life, CL clearance, V_{ss} volume of distribution at steady-state)

	Parameter	Arm 1 (G→D)	Arm 2 (D→G)	*P*-value
Gemcitabine	C_{max} (μg/ml)	18.1 ± 12.0	15.5 ± 3.9	0.75
	AUC (mg/l/h)	11.4 ± 6.5	10.2 ± 2.7	0.79
	t1/2 (h)	22.3 ± 9.8	18.8 ± 8.1	0.39
	CL (l/h/m^2)	85.4 ± 33.0	87.4 ± 22.6	0.87
	V_{ss} (l)	80.0 ± 46.0	64.9 ± 23	0.41
DFdU	C_{max} (μg/ml)	23.6 ± 4.8	24.2 ± 3.6	0.60
	AUC (mg/l/h)	73.7 ± 16.9	92.6 ± 50.0	0.97
	t1/2 (min)	2.2 ± 0.6	2.6 ± 1.3	0.38
Docetaxel	AUC (μg/ml/h)	2.47 ± 0.67	2.24 ± 0.78	0.59
	CL (l/h/m^2)	16.24 ± 3.04	16.58 ± 3.37	0.85

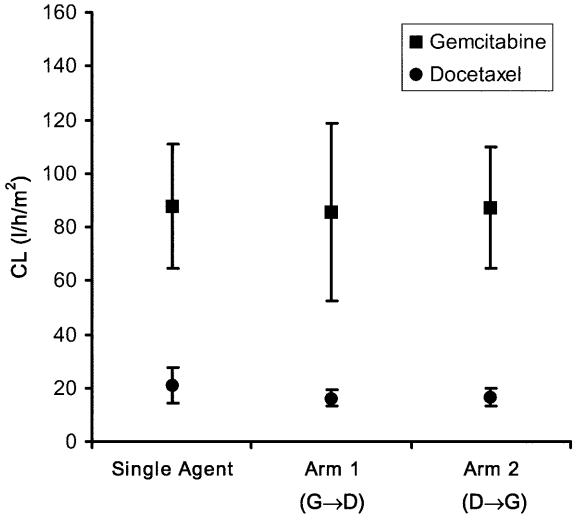

Fig. 1 Comparison of clearance of gemcitabine and docetaxel in the two arms of the study with values reported in the literature (reference 19 for gemcitabine, reference 26 for docetaxel)

associated with significant differences in the disposition of gemcitabine or docetaxel. Results obtained from our study were compared with those reported in the literature for gemcitabine or docetaxel administered alone at comparable doses (Fig. 1). For gemcitabine, our results showed the greatest similarity to those reported by Storniolo et al. [19]. While the C_{max} and AUC of gemcitabine from our study were similar to those reported by Abruzzese et al. [25], the mean $t_{1/2}$ (7.1 ± 2.5 vs 20.1 ± 8.7 min in our study, $P<0.01$) was significantly different, and CL (321 ± 359 vs 86 ± 26 l/h per m^2 in our study, $P=0.1$) missed statistical significance due the wide variability in their study. The pharmacokinetic parameters for docetaxel from our study are in agreement with those reported in the literature [26, 27, 28]. However, when compared with population pharmacokinetic estimates for docetaxel, the mean CL estimate from our study was approximately 23% lower than the clearance estimated from 640 patients (20.9 ± 6.6 vs 16 ± 3.1 l/h per m^2, $P<0.01$).

Responses

Combination therapy with docetaxel and gemcitabine was associated with tumor responses at all dose levels. There were four partial and four minor responses for a response rate of 23.5% in all 34 patients and 25% in the subset of 8 patients with NSCLC. One patient, with untreated NSCLC, had resolution of chest wall pain and shortness of breath, and a partial response that persisted for 26 cycles of therapy. The second patient, who had progressive NSCLC after vinorelbine and cisplatin, had a partial response that lasted for two cycles before she developed progressive disease.

Two of the three patients with gastric cancer had responses. One patient, who had received two prior chemotherapy regimens, had a partial response that was maintained for six cycles. The second patient had a minor response that was maintained for eight cycles. Additionally, one of two patients with head and neck cancer, who had received three prior chemotherapy regimens, experienced a partial response that was maintained for five cycles. Two of four patients with bladder cancer had minor responses including one patient with untreated bladder cancer who had 40% tumor reduction that was maintained for seven cycles. Finally, one patient with untreated hepatocellular cancer had 33% tumor reduction and 90% decrease in AFP that was maintained for eight cycles.

Discussion

The regimen of weekly docetaxel with gemcitabine was developed to combine two active chemotherapeutic agents at the maximum possible dose intensity without growth factor support. We sought to take advantage of the weekly schedule of docetaxel, which allows increased dose intensity with markedly reduced myelosuppression when compared with the once every 3-week schedule [18]. The rationale for combining these two agents was further strengthened by reports of in vitro synergy in lung cancer cell lines [29]. In this phase I study, the combination of docetaxel and gemcitabine was well tolerated by a heterogeneous group of patients with advanced cancers. The majority of patients on this study (76%) had been pretreated with chemotherapy. Although these patient characteristics would predict increased bone marrow toxicity, only 23.5% of patients encountered grade 3 or 4 neutropenia, which was limited to patients who had received two or more prior chemotherapy regimens. Neutropenic episodes were typically brief, and there were no episodes of febrile neutropenia. Growth factor support was used in only 5.8% of patients. Overall, treatment delays (3.5% of cycles) and dose reductions (11% of patients) were infrequent. Expected nonhematologic toxicities, such as 'flu-like symptoms, fatigue, and diarrhea, were generally mild and were manageable by dose reduction or symptomatic treatment. Treatment-related fluid retention was

typically mild with steroid premedication. Peripheral neuropathy, which may be seen with docetaxel alone [30, 31] or in combination with cisplatin [32], was not observed with this regimen.

Six studies utilizing concomitant weekly administration of gemcitabine and docetaxel are ongoing or have been completed, and in two of these a dosing schedule similar to ours was utilized [33, 34]. Although in both studies MTDs of gemcitabine 1000 mg/m^2 and docetaxel 40 mg/m^2 were found, Frasci et al. reported a 37% incidence of grade 3–4 neutropenia, while Jacobs et al. did not report any grade 3–4 neutropenia. A schedule of gemcitabine and docetaxel on days 1, 8 and 15 every 28 days was utilized in three other studies, which showed a 21–46% incidence of grade 3–4 neutropenia with MTDs in the ranges gemcitabine 750–800 mg/m^2 and docetaxel 30–40 mg/m^2 [35, 36, 37]. In one of these studies [36], in which patients who had received no more than two prior chemotherapies were enrolled, escalation of the dose of docetaxel to 50 mg/m^2 was possible. In the final study, by Lueck et al. [38], a unique schedule of weekly docetaxel and gemcitabine for 12 courses with 3-week intervals after the sixth and ninth course was utilized, and MTDs of gemcitabine 1000 mg/m^2 and docetaxel 35 mg/m^2 were found with an 8% incidence of grade 3–4 neutropenia. The reports of none of these studies describes the pharmacokinetics of gemcitabine or docetaxel.

Preclinical studies indicate a sequence- and schedule-dependent synergy between gemcitabine and docetaxel based upon their action on different phases of the cell cycle [29]. It has been demonstrated that maximal synergy occurs when docetaxel is administered prior to gemcitabine, with a 48-h washout period between the two drugs. This interaction is being evaluated in two ongoing clinical trials in which an increased incidence of myelosuppression (62% and 66%) with a 24–48-h washout between docetaxel and gemcitabine has been found [39, 40]. These studies suggest that the toxicities of the gemcitabine and docetaxel combination may be modulated by the schedule of administration. Our study did not include a washout period between the two drugs, which may be the reason why we did not observe any difference in toxicity between the two schedules. As shown in Table 2, there were no significant differences between the incidence of DLT among the two arms of our study (3/19 in arm 1 versus 3/15 in arm 2, $P > 0.90$), even when stratified according to prior chemotherapy (1/11 in arm 1 versus 2/10 in arm 2 with no more than one prior chemotherapy regimens, $P = 0.58$; 1/8 in arm 1 versus 1/5 in arm 2 with two or more prior chemotherapy regimens, $P > 0.90$).

This trial was also designed to study any pharmacokinetic interaction between gemcitabine and docetaxel when administered using this schedule. Overall, the sequence of administration had no effect on the pharmacokinetic parameters of gemcitabine. While most pharmacokinetic parameters for gemcitabine from our study were comparable to those previously reported [19], the mean $t_{1/2}$ of gemcitabine estimated from our study was about 64% longer than that reported by Abbruzzese et al. [25] for comparable doses of gemcitabine. Also, the AUC and $t_{1/2}$ of the metabolite, dFdU, from our study were significantly lower than those reported by Abbruzzese et al. (AUC 83.1 ± 13.3 vs 250.4 ± 277.4 mg/l per h, and $t_{1/2}$ 2.4 ± 0.28 vs 12.3 ± 8.6 h, respectively; $P < 0.05$ for both). Some of these differences may have been due to differences in patient populations in the two studies. It is known that the pharmacokinetics of gemcitabine are influenced by age, gender and body surface area [41]. In men, the clearance decreases from 92.2 to 41.9 l/h per m^2 as age increases from 29 to 78 years, and the clearance for age-matched women is 25% lower than for men, and decreases from 69.4 to 31.5 l/h per m^2 as age increases from 29 to 78 years. Because of these confounding effects, no definite conclusions can be made regarding the effect of docetaxel on the pharmacokinetic parameters of gemcitabine and dFdU, although the results are in general agreement with some of the previously reported values for single-agent gemcitabine.

Similarly, the sequence of administration was not associated with any differences in the pharmacokinetic parameters of docetaxel. Nonetheless, the mean clearance in our study (16 l/h per m^2) was approximately 23% lower than that in a previous population study of 640 patients who received docetaxel as a single agent [26]. This difference was not considered to be significant because of the small number of patients in our study, and because the disposition of docetaxel can be affected by variables such as hepatic dysfunction, α_1-acid glycoprotein (AAG) concentrations, and CYP3A4 activity [26]. Patients in our study were required to have normal hepatic function, but neither AAG nor CYP3A4 activity was measured.

Although the majority of patients on this study had been pretreated and had an ECOG performance status of 1–2, the combination of docetaxel and gemcitabine administered on a schedule of days 1 and 8 every 21 days, was active in a variety of solid tumors including NSCL, gastric, head and neck, bladder, and hepatocellular cancers with an overall response rate (minor and partial) of 23.5%.

In conclusion, the combination of gemcitabine and docetaxel administered together weekly on days 1 and 8 every 21 days is a well-tolerated regimen with a favorable myelosuppression profile and manageable nonhematologic toxicities. The sequence of administration did not have any significant effect on the toxicity or pharmacokinetics of this regimen. In patients who had received two or more prior chemotherapy regimens, the MTDs were gemcitabine 800 mg/m^2 and docetaxel 40 mg/m^2, while minimally pretreated patients (no more than one prior chemotherapy regimen) tolerated a higher dose of gemcitabine with MTDs of gemcitabine 1250 mg/m^2 and docetaxel 40 mg/m^2. This combination demonstrated significant antitumor activity, and may represent an attractive alternative to cisplatin-based

combination therapy in a variety of solid tumors, particularly NSCLC. The combination of docetaxel and gemcitabine merits further evaluation, and phase II studies of patients with NSCL, breast, and bladder cancer are under way at our institution.

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