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A Phase I trial of weekly gemcitabine administered as a prolonged infusion in patients with pancreatic cancer and other solid tumors

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Summary

Purpose: Pharmacological studies of gemcitabine (2′,2′-difluorodeoxycytidine) have shown that increased levels of the active triphosphate metabolite are achieved by prolonging infusion time while holding the dose rate constant. The primary aim of this study was to determine the maximum tolerated dose (MTD) of gemcitabine administered as a fixed rate infusion (10 mg/m^2/min) on a weekly schedule in patients with untreated non-hematologic malignancies.

Patients and methods: Twenty-seven patients (21 pancreatic adenocarcinoma, 3 hepatoma, 1 neuroendocrine tumor, and 2 adenocarcinoma of unknown primary) were enrolled in this open-label, non-randomized study. Three different entry dose levels (1200 mg/m^2, 1500 mg/m^2 and 1800 mg/m^2) were evaluated for gemcitabine administered on days 1, 8, and 15 of a 28-day cycle.

Results: The MTD was defined as 1500 mg/m^2 with granulocytopenia and thrombocytopenia being dose-limiting. There were no non-hematological dose limiting toxicities. The maximum WHO grade 3 or 4 toxicities for hemoglobin, leukocytes, neutrophils, and platelets for all doses of gemcitabine administered were 11.5%, 30.8%, 57.7%, and 26.9%, respectively. Non-hematologic toxicities included nausea, vomiting and fever. Four patients were withdrawn from the study for non-hematological toxicities: pneumonitis, ascites, disabling fatigue, and an acute myocardial infarction. Two of these events were severe (pneumonitis and myocardial infarction) but these may not be related to drug administration.

Conclusion: Gemcitabine administered at a rate of 10 mg/m^2/min was tolerated up to 1500 mg/m^2 in patients with previously untreated non-hematologic malignancies. Myelosuppression seen in this study is more severe than anticipated based on previous reports of bolus administration of similar doses of gemcitabine. This supports earlier studies suggesting that prolonged duration of infusion increases the intracellular accumulation of active metabolites of gemcitabine.

Introduction

Gemcitabine (2′,2′-difluorodeoxycytidine) is a novel nucleoside analog which is structurally similar to cytosine arabinoside. Studies in animal models and cell lines indicated that, unlike cytosine arabinoside, gemcitabine has activity against non-hematologic malignancies [1–2]. This led to Phase I and II clinical studies which demonstrated definite anti-tumor activity by gemcitabine in a wide range of solid tumors including non-small cell cancer of the lung and cancers of the pancreas, bladder, breast, ovary, and head and neck [3–9].

Studies on the mechanism of action of gemcitabine demonstrated that the compound must be converted to the active metabolite by intracellular phosphorylation resulting in the accumulation of the active nucleotide gemcitabine triphosphate [10]. The rate limiting enzyme for this conversion is deoxycytidine kinase, the first enzyme involved in the phosphorylation sequence. Studies have suggested that maximum accumulation of gemcitabine triphosphate in leukemia and mononuclear cells was achieved at a plasma concentration of gemcitabine of 15–20 μM [11, 12]. Grunewald and colleagues [13] showed in leukemic patients that an infusion rate of 10 mg/m^2/min of gem-

citabine produced plasma levels of 26.5 ± 9 μM, which is above the concentration necessary to achieve maximal intracellular accumulation of gemcitabine triphosphate by leukemic cells in plasma. An important observation in this study was that prolonging infusion time (120–240 min) at the rate of 10 mg/m^2/min led to a linear increase in intracellular accumulation of gemcitabine triphosphate. This suggests that simply increasing the dose of gemcitabine may not improve dose intensification. Prolonging the infusion time while holding the dose rate constant may result in increased dose intensification.

Phase I studies of gemcitabine in solid tumors have been performed using an infusion time of 30 minutes [6, 11, 14]. The primary objective of this study was to determine the maximum tolerated dose and the relationship between dose and toxicity for gemcitabine administered as a prolonged infusion on a weekly schedule. A secondary objective of this study was to document any anti-tumor activity by gemcitabine in patients with advanced metastatic cancer, especially pancreatic adenocarcinoma.

Patients and methods

Patient selection

All patients with a histologic or cytologic diagnosis of advanced or metastatic cancer who were not candidates for treatments of higher priority or efficacy and fulfilled the following criteria were eligible for the study: $\geq$18 years of age; Zubrod performance status of 0 or 1; estimated life expectancy of $\geq$12 weeks; patient compliance and geographic proximity permitting adequate follow up; no prior treatment with gemcitabine; no previous chemotherapy treatments except for 5-fluorouracil given in combination with radiation; and no other forms of therapy such as local radiation or steroids for at least three weeks prior to protocol entry. Patients may have had prior irradiation treatment if the treatment ports did not include extensive pelvic or vertebral areas. Exclusion criteria included: patients with leukemia and/or a second primary cancer (except those patients who have had resected basal cell carcinoma, stage I or less curatively resected cervical carcinoma, or were >5 years disease free from any prior malignancy); active infection; prior central nervous system metastases or patients who had prior brain radiation for central nervous system metastases; creatinine >1.5 mg/dl; total bilirubin >1.5 mg/dl and/or transaminases >3 times normal; calcium >10.5 mg/dl; WBC <3500/mm^3, platelets <100,000/mm^3, hemoglobin <10 gm%, and hematocrit <30%; pregnancy; breastfeeding; active cardiac disease requiring therapy for failure, angina, arrhythmias and/or infarctions in the preceding 6 months; severe pulmonary disease or significant peripheral vascular disorders; or significant neurological or psychiatric disorders. The study protocol was reviewed and approved by the Institutional Review Board. Informed consent was obtained from all patients.

Study design

Three different dose levels of gemcitabine (1200 mg/m^2, 1500 mg/m^2, and 1800 mg/m^2) were evaluated in this open-label, non-randomized study. No concomitant marrow-suppressive radiotherapy, chemotherapy, hormonal therapy or immunotherapy was administered. After determination of the dose-limiting toxicity (DLT), 12 additional patients with pancreatic cancer were treated at a dose level of 1200 mg/m^2 to allow for further toxicity and efficacy determination in patients with pancreatic cancer. The DLT was defined by the presence of $\geq$ grade 3 non-laboratory toxicity, grade 4 leukopenia, or $\geq$ grade 3 thromcobytopenia in 2 patients. The MTD was defined as the dose level before the DLT. Criteria for termination of treatment were objective or clinical evidence of disease progression, patient request, or unacceptable drug toxicity. All patients enrolled in the study were evaluated for toxicity. All patients who completed appropriate imaging studies and laboratory work were assessed for clinical efficacy.

Drug administration

The drug was provided as a hydrochloride salt with doses expressed in milligrams of gemcitabine (base). The drug was reconstituted and/or diluted with normal saline. All gemcitabine doses were administered at a rate of 10 mg/m^2/min. At least three patients were studied at each dose level and evaluated for a minimum of three weeks before starting additional patients at escalated doses. At each dose level, the first patient treated received at least two doses of gemcitabine and was observed for evidence of acute toxicity before the second and third patients began treatment. No individual patient was dose escalated. Three different entry dose levels of gemcitabine were administered during the study: 1200 mg/m^2, 1500 mg/m^2, and 1800 mg/m^2.

A cycle of therapy was defined as three weekly doses of the drug followed by one week of observation.

A patient was considered to receive a cycle of therapy if at least one dose of gemcitabine was administered during the four week period. Dose modifications were based on weekly blood counts and assessment of toxicity. For World Health Organization (WHO) grade 3 leukopenia or WHO grade 1 or 2 thromcobytopenia, doses were reduced to 75%. For WHO grade 4 leukopenia or WHO grade 3 or 4 thrombocytopenia, doses were held for the remainder of a cycle and then decreased by 25% for the next cycle after their marrow had recovered. The last 12 patients enrolled had similar dose adjustments based on absolute granulocytopenia rather than leukopenia. For grade 3 non-hematological toxicities, dose modifications were based on the judgement of the senior investigator and could consist of no change, dose reduction of 50%, or dose held. Patients who experienced grade 4 non-hematologic toxicity were removed from the study. Doses held during a course of therapy were not made up. Prophylactic antiemetics were only used if a patient had experienced nausea with prior doses of gemcitabine.

Clinical assessments

All toxicities were graded in every cycle according to WHO toxicity criteria. Complete blood count, blood chemistries, and urinalysis were obtained at baseline and then weekly. In the event of abnormal laboratory findings, appropriate laboratory testing was obtained until the values resumed pre-study levels or could be explained. An electrocardiogram, history and physical examination, chest X-ray (CXR) and WHO rating scale was obtained on entry. In addition, a computed tomography (CT) scan of the area of known disease involvement was performed during a 3 week period prior to entry into the protocol. For further evaluation of efficacy, the following were repeated at the stated intervals: a limited history and physical examination including tumor measurements, weight, and performance status (prior to each cycle of therapy); CXR; and tests (usually CT scan) demonstrating disease measurements (every other cycle).

Tumor measurements were recorded for the longest diameter and the perpendicular diameter at the widest portion of the tumor. All responses to gemcitabine therapy were defined by the following criteria. Complete response was defined as the disappearance of all measurable disease for $\geq$4 weeks. Partial response was defined as $\geq$50% decrease in the sum of the products of all bi-perpendicular dimensions of measurable lesions. Minor response was defined as a 25–50% decrease in the sum of the products of all bi-perpendicular dimensions of measurable lesions. To qualify for a partial or minor response, the reductions in tumor size had to last $\geq$4 weeks with no simultaneous increase in the size of any lesion or appearance of new lesions. Stable disease was defined as a decrease of <25% in the sum of the products of the bi-perpendicular dimensions of the measurable lesions, or an increase in tumor mass <25% without the development of new lesions. Progressive disease was defined as >25% increase in the sum of the products of the bi-perpendicular dimensions of the measurable lesions or the appearance of any new lesions while the patient was on therapy. Patients with obvious clinical deterioration and no objective evidence of progressing disease were considered to have progression. In these cases, treatment was terminated at the discretion of the senior investigator. A patient was considered evaluable for toxicity if they were given at least one dose of gemcitabine.

Results

Patient characteristics

The characteristics of the 27 patients (20 males, 7 females, median age 62 years) enrolled in this study are listed in Table 1. There were 21 patients with pancreatic cancer, 3 patients with hepatoma, 2 patients with adenocarcinoma of unknown primary and one patient with a neuroendocrine tumor. At the time of study entry all non-pancreatic cancers had evidence of distant metastatic disease. Extent of disease for patients with adenocarcinoma of the pancreas at study entry was as follows: 2 patients with local disease (equivalent to Stage II), 4 patients with local disease and regional lymph node involvement (equivalent to Stage III), and 15 patients with distant metastatic disease (equivalent to Stage IV). One patient had prior radiation treatment with concurrent 5-fluorouracil as neoadjuvant therapy.

Treatment

All patients received gemcitabine at a fixed dose rate of 10 mg/m^2/min. Patients given higher doses received these over a corresponding longer duration of infusion. Eight patients were initially treated at 1200 mg/m^2, 5 patients at 1500 mg/m^2 and 2 patients at 1800 mg/m^2. After determination of the MTD, 12 additional patients

Table 1. Patient characteristics and treatment summary

	Age	Sex	Diagnosis	Extent of disease at entry	Prior therapy	Number of cycles	Response	Time to progression (months)	survival (months)	Reason for study termination
1200 mg/m^2	64	M	Pancreas	Liver, Lung METS	None	2	Prog	2	4	Prog
Dose level	60	M	Pancreas	Liver METS	LAP	4	Stable	4	7	PROG
	76	M	AUP	Liver METS	None	1	NE	NE	4	PT Request
	68	M	Pancreas	Local & REG LN	INC RES	1	NE	NE	0.5	Died (MI)
	57	F	Pancreas	Local	None	1	Stable	NE	5	Toxicity (fatigue)
	67	M	Hepatoma	Lung METS	None	3	Stable	3	5	PROG
	58	F	NEUROEND	Liver	None	2	PROG	2	51+	PROG
	62	M	Pancreas	Liver	None	1	PROG	1	3	PROG
1500 mg/m^2	66	M	AUP	Liver METS	None	1	PROG	1	4	PROG
Dose level	70	M	Hepatoma	Lung METS	None	2	PROG	2	2	Died (disease)
	67	M	Pancreas	Liver METS	None	2	PROG	2	2	PROG
	61	M	Hepatoma	Lung METS	None	1	PROG	1	2	PROG
1800 mg/m^2	47	M	Pancreas	Liver METS	None	2	PROG	2	3	PROG
Dose level	37	M	Pancreas	Liver METS	LAP	2	PROG	2	3	PROG
Additional patients*	70	M	Pancreas	Local	Bypass	25	Stable	NE	46++	Completed treatment

Table 1. Continued.

Age	Sex	Diagnosis	Extent of disease at entry	Prior therapy	Number of cycles	Response	Time to progression (months)	Survival (months)	Reason for study termination
67	F	Pancreas	Local & REG LN	LAP	13	Partial	15	17	PROG
46	M	Pancreas	Liver METS	None	1	PROG	0.5	0.5	Died (disease)
62	F	Pancreas	Liver METS	None	1	PROG	1	1	PROG
59	M	Pancreas	Peritoneal METS	Bypass	2	PROG	2	4	PROG
68	M	Pancreas	Peritoneal METS	LAP	2	Minor	NE	10	Toxicity (respiratory)
49	F	Pancreas	Local & REG LN	LAP	21	Stable	20	20	PROG
63	F	Pancreas	Local & REG LN	Bypass	20	Minor	NE	32	Toxicity (Ascites)
45	M	Pancreas	Liver METS	Bypass	4	Stable	4	5	PROG
66	M	Pancreas	Liver METS	None	2	PROG	2	4	PROG
61	M	Pancreas	Liver METS	RAD, LAP	1	PROG	1	1	Died (disease)
67	M	Pancreas	Liver METS	None	1	NE	NE	2	PT request
52	F	Pancreas	Liver METS	Bypass	9	Stable	9	10	PROG

Abbreviations: AUP = adenocarcinoma of unknown primary; INC RES = incomplete resection; LAP = exploratory laparotomy; LN = lympho adenopathy; METS = metastasis; NE = not evaluable; NEUROEND = neuroendocrine tumor; PROG = progression of disease; RAD = radiation; REG = regional

* First patient treated at a dose level of 1500 mg/m^2, remaining patients treated at a dose level of 1200 mg/m^2.

were treated at a dose level of 1200 mg/m^2 (Table 1). Including these 12 extra patients, 127 cycles of gemcitabine were initiated during the study with most patients receiving 1 or 2 cycles (10 and 9 patients, respectively) (Table 1). Six of 20 patients (30%), 2 of 5 patients (40%), and 0 of 2 patients (0%) treated at 1200 mg/m^2, 1500 mg/m^2, and 1800 mg/m^2 respectively, were able to complete their first cycle without dose adjustments or omissions. The mean total cumulative dose of gemcitabine administered during the first cycle was 2953 mg/m^2 at the 1200 mg/m^2 dose level, 3746 mg/m^2 at the 1500 mg/m^2 level and 3371 mg/m^2 at the 1800 mg/m^2 dose level.

Dose reduction over time

The main reasons for dose adjustment in the 7 patients who were treated with gemcitabine for at least 4 or more cycles were neutropenia and thrombocytopenia. Two of the three patients treated for more than 20 cycles required late, after cycle 6, dose adjustments for thrombocytopenia.

Toxicity

The DLT was determined at a dose level of 1800 mg/m^2 due to the occurrence of grade 3 thrombocytopenia in one patient and grade 3 nausea and fevers in the second patient. Thus, the MTD was determined to be at a dose level of 1500 mg/m^2.

Twenty-six patients, 19 at 1200 mg/m^2, 5 at 1500 mg/m^2, and 2 at 1800 mg/m^2, were evaluable for toxicity (Tables 2 and 3). One patient received just one dose of gemcitabine and then refused further participation in the study. He did not appear to have any apparent toxicity; however, follow-up laboratory work could not be obtained. Myelosuppression appeared to be the most common toxicity accounting for dose adjustments during the study. At 1800 mg/m^2, both patients experienced grade 3 granulocytopenia and 1 patient had grade 3 thrombocytopenia during their first cycle. Grade 3 or 4 leukopenia, granulocytopenia, and/or thrombocytopenia occurred in 13 of 30 (43%) cycles at the entry dose of 1200 mg/m^2, and 2 of 11 (18%) cycles at the entry dose of 1500 mg/m^2. Hematologic toxicities also occurred in cycles in which gemcitabine was administered at a reduced dose with 1 of 2 cycles at 1350 mg/m^2 (1800 mg/m^2 entry level) and 17 of 82 (21%) cycles at doses <1000 mg/m^2 (1500 and 1200 mg/m^2 entry levels) having grade 3 or 4 leukopenia, granulocytopenia, and/or thrombocytopenia.

Table 2. Laboratory toxicities

		Worst WHO grade attained				
Toxicity	Dose level	0	1	2	3	4
Hemoglobin	**1200**	**1**	**4**	**3**	**0**	**0**
	1500	**2**	**2**	**1**	**0**	**0**
	1800	**2**	**0**	**0**	**0**	**0**
	1200	2	5	1	3	0
Platelet	**1200**	**5**	**0**	**2**	**1**	**0**
	1500	**2**	**1**	**1**	**1**	**0**
	1800	**1**	**0**	**0**	**1**	**0**
	1200	6	1	0	4	0
WBC	**1200**	**2**	**1**	**2**	**2**	**1**
	1500	**1**	**0**	**3**	**1**	**0**
	1800	**0**	**1**	**1**	**0**	**0**
	1200	1	2	3	4	1
Neutrophils	**1200**	**2**	**0**	**1**	**2**	**3**
	1500	**1**	**1**	**2**	**1**	**0**
	1800	**0**	**0**	**0**	**2**	**0**
	1200	2	2	0	4	3
Bilirubin	**1200**	**6**	**2**	**0**	**0**	**0**
	1500	**3**	**1**	**1**	**0**	**0**
	1800	**1**	**1**	**0**	**0**	**0**
	1200	6	0	3	2	0
AST	**1200**	**0**	**3**	**2**	**3**	**0**
	1500	**0**	**3**	**0**	**1**	**1**
	1800	**1**	**0**	**0**	**1**	**0**
	1200	1	4	3	2	1
Alkaline	**1200**	**1**	**2**	**3**	**2**	**0**
phosphatase	**1500**	**0**	**2**	**3**	**0**	**0**
	1800	**0**	**0**	**2**	**0**	**0**
	1200	0	3	5	3	0
Creatinine	**1200**	**8**	**0**	**0**	**0**	**0**
	1500	**5**	**0**	**0**	**0**	**0**
	1800	**2**	**0**	**0**	**0**	**0**
	1200	9	1	0	1	0
Proteinuria	**1200**	**0**	**8**	**0**	**0**	**0**
	1500	**0**	**4**	**1**	**0**	**0**
	1800	**0**	**2**	**0**	**0**	**0**
	1200*	1	3	5	1	0
Hematuria	**1200**	**7**	**1**	**0**	**0**	**0**
	1500	**2**	**2**	**0**	**1**	**0**
	1800	**1**	**1**	**0**	**0**	**0**
	1200*	2	4	3	1	0

N = 26; initial experience (bold print); toxicity for BUN is not shown, as there was no grade 2, 3 or 4 toxicity at any dose level. *One patient did not have a follow-up urinalysis obtained.

Table 3. Clinical toxicities

		Worst WHO grade attained				
Toxicity	Dose level	0	1	2	3	4
Nausea &	**1200**	**0**	**5**	**3**	**0**	**0**
vomiting	**1500**	**0**	**1**	**3**	**1**	**0**
	1800	**0**	**0**	**1**	**0**	**0**
	1200	0	3	4	4	0
Diarrhea	**1200**	**5**	**3**	**0**	**0**	**0**
	1500	**3**	**2**	**0**	**0**	**0**
	1800	**2**	**0**	**0**	**0**	**0**
	1200	6	1	3	1	0
Pulmonary	**1200**	**6**	**0**	**2**	**0**	**0**
	1500	**1**	**3**	**1**	**0**	**0**
	1800	**1**	**0**	**1**	**0**	**0**
	1200	8	1	0	0	2
Fever	**1200**	**3**	**4**	**1**	**0**	**0**
	1500	**0**	**2**	**3**	**0**	**0**
	1800	**0**	**0**	**1**	**1**	**0**
	1200	2	4	5	0	0
Infection	**1200**	**7**	**0**	**1**	**0**	**0**
	1500	**3**	**0**	**2**	**0**	**0**
	1800	**2**	**0**	**0**	**0**	**0**
	1200	5	4	1	1	0
Cardiac	**1200**	**6**	**1**	**0**	**0**	**1**
rhythm	**1500**	**1**	**3**	**1**	**0**	**0**
	1800	**1**	**1**	**0**	**0**	**0**
	1200	11	0	0	0	0
Cardiac	**1200**	**7**	**0**	**0**	**0**	**1**
function	**1500**	**4**	**1**	**0**	**0**	**0**
	1800	**1**	**1**	**0**	**0**	**0**
	1200	11	0	0	0	0
Constiptation	**1200**	**4**	**2**	**1**	**1**	**0**
	1500	**1**	**3**	**1**	**0**	**0**
	1800	**0**	**1**	**1**	**0**	**0**
	1200	5	3	1	0	0

N = 26; initial experience (bold print). The following toxicities are not shown as there was no grade 3 or 4 toxicity at any dose level: hemorrhage, oral, allergic, cutaneous, alopecia, pericarditis, state of consciousness and peripheral neurotoxicity.

Nineteen of 27 patients were unable to complete the first cycle without a dose adjustment or omission. Thirteen of these 19 (68%) dose modifications were due to hematologic toxicity. Only two of the 19 patients (11%) required dose omissions or adjustments due to non-hematologic toxicity (acute myocardial infarction and severe peripheral edema). Gemcitabine was felt to be responsible for the peripheral edema since it resolved with the discontinuation of the drug. Two of the remaining four patients voluntarily removed themselves from the study, one patient seeking treatment in an alternate care facility and the other patient refusing to return to our medical center after receiving one dose of gemcitabine. The other two patients had rapid progression of their malignancy leading to their death.

Liver enzyme abnormalities were difficult to interpret in this patient population since many patients had abnormalities at baseline or progressing liver metastases. The remaining symptomatic toxicities did not appear to be dose-related. The most common non-hematologic toxicity was nausea and vomiting which affected all patients at least once during their course of treatment, although grade 4 toxicity was not seen and grade 3 toxicity was experienced in only 6 patients. Fevers were also quite common with 42% of the patients experiencing grade 2 fevers at least once during their course of treatment. This toxicity only contributed to a change in therapy (dose omission) in one patient with grade 3 fevers. Other common toxicities which were typically mild (< WHO grade 2) included constipation, cutaneous, hair loss, paresthesia, diarrhea, proteinuria and hematuria. One patient requested termination of gemcitabine after one cycle due to disabling fatigue, which resolved within two weeks of cessation of gemcitabine. Treatment was stopped after 20 cycles in one patient because of concerns over progression of her disease with new onset ascites. Following discontinuation of gemcitabine, her ascites resolved and a follow-up CT scan showed no progression of her disease. In retrospect, it was felt that her ascites was related to toxicity from gemcitabine.

Two patients had severe cardiorespiratory complications which were possibly related to gemcitabine. One patient was not continued on gemcitabine due to concern that a hospitalization at the end of his second cycle for ARDS was gemcitabine induced, despite a follow-up CT scan showing that the mass in the head of the pancreas had decreased by 33% in size and there was resolution of changes consistent with infiltration of the peripancreatic fat. The other patient presented with substernal chest pain several days after receiving his second dose of gemcitabine. An EKG showed changes consistent with an acute anterior wall MI. He developed increasing cardiopulmonary compromise and died within 6 days of admission. Autopsy was refused by the family. There was no conclusive evidence to support a relationship to gemcitabine treatment.

One patient had a reversible grade 4 pulmonary event felt to be related to over-sedation from morphine. Two patients had grade 3 hematuria and one of these patients also had grade 3 proteinuria. These events were self-limiting, and did not require or cause any modifications in their course of treatment.

Study termination

The reasons for termination from the study for all the patients are included in Table 1. Treatment with gemcitabine was terminated in 17 patients due to progression of their disease. Four patients died while still actively participating in the study.

Response

Twenty patients underwent appropriate studies to determine response to therapy (Table 1). A total of 17 patients completed 2 cycles of treatment and were evaluable for response. An additional 4 patients who received one cycle of chemotherapy could also be evaluated for response. Also, two patients who died during their first cycle were felt clinically to have died secondary to rapid deterioration from their underlying malignancies. One patient had stabilization of disease by CT scan performed after one cycle but was withdrawn from the study at that time due to non-hematologic toxicity. The patient with the neuroendocrine tumor progressed on gemcitabine and remains alive at 4 years following conventional chemotherapy. One patient had a partial response and two patients had minor responses.

Survival

Survival from the start of the study is shown in Table 1. Figure 1 shows the Kaplan-Meier survival curve for the 21 patients with adenocarcinoma of the pancreas. The patients with pancreatic adenocarcinoma had a median survival of 4 months and survival rates of 20% at 1 year, 10% at 2 years and 5% at 4 years.

Discussion

Few studies have evaluated the toxicity of gemcitabine in non-hematologic malignancies when given as a prolonged infusion. As the potential clinical uses of gemcitabine are defined in non-hematologic malignancies, it is important to explore different methods of dose intensification. Grunewald et al. [13] has shown in leukemic patients that prolonging infusion time caused a linear increase in intracellular gemcitabine. In their study, doses of up to 6400 mg/m^2 administered over 480 minutes, were given weekly for 3 weeks followed by 1 week of observation. Only 3 of 22 patients received a second course of gemcitabine. Two early phase I studies investigated frequent administration of gemcitabine but both resulted in unacceptable toxicities: flu-like symptoms (fever, malaise, headache) and idiosyncratic episodes of severe hypotension in the 30-minute infusion daily $\times$ 5 schedule (MTD 10 mg/m^2) [15]; and flu-like effects with dose-limiting thrombocytopenia in the twice-a-week schedule (MTD 65 mg/m^2) [16]. In one phase I study in which gemcitabine was administered every other week over 30 minutes, myelosuppression was dose-limiting (MTD 4560 mg/m^2) [17] and pharmacological studies suggested that more frequent administration of less drug would be required. Most studies with gemcitabine have been performed with a 30-minute infusion administered on days 1, 8, and 15 of a 28 day cycle; dose limiting toxicity is myelosuppression (thrombocytopenia and granulocytopenia), and the MTD has been defined as 790 mg/m^2 in a group of heavily pretreated patients [12] and as 2800 mg/m^2 in a chemotherapy-naive population [18].

Our study was designed to define the toxicity profile of gemcitabine when administered at a rate of 10 mg/m^2/min. It is important to recognize that we took a very conservative approach in reporting and interpreting our results. Toxicity was recorded as the worst WHO grade achieved by a patient at anytime during their participation in the study. Responses were also graded quite conservatively with any disease progression documented by radiological studies or clinical deterioration felt to be attributable to their tumor constituting progression regardless of the number of cycles or doses of gemcitabine received. To provide for more toxicity and efficacy determinations in patients with pancreatic cancer, we chose arbitrarily to study additional patients at the dose level of 1200 mg/m^2.

Since our study allowed for dose adjustments with grade 3 leukopenia or grade 1 or 2 thrombocytopenia while defining the DLT as the finding of $\geq$ grade 3 thrombocytopenia, grade 4 leukopenia or $\geq$ grade 3 non-hematologic toxicity, the DLT was determined to be 1800 mg/m^2. The two patients treated at 1800 mg/m^2 were only able to tolerate a total of 3 doses at the entry dose level. One patient was able to receive two full doses but his third dose was held and subsequent doses reduced because of grade 3 thrombocytopenia,

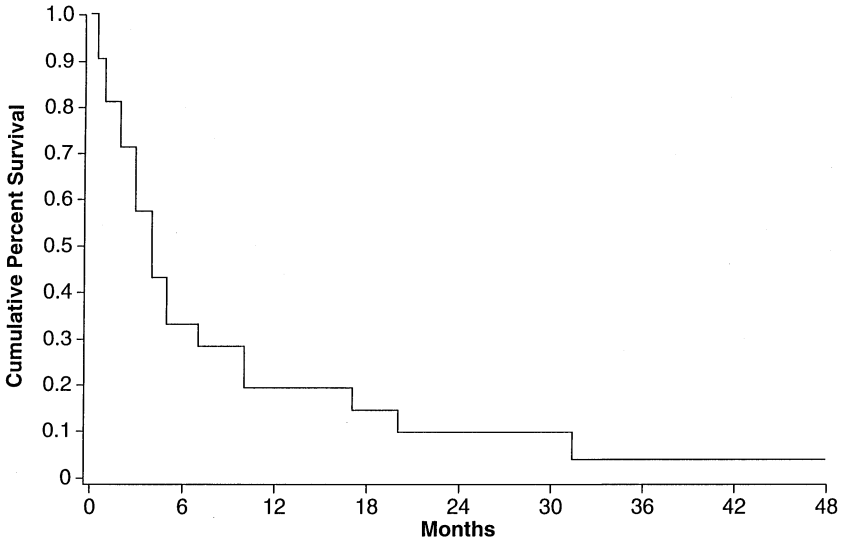

Figure 1. Kaplan-Meier survival curve for the 21 patients with adenocarcinoma of the pancreas. Median survival – 4 months. Survival at 12 months – 20%. Survival at 24 months – 10%. Survival at 48 months – 5%. One patient is alive and progression-free at 48 months.

and the other patient required dose reduction for the second dose in the first cycle because of grade 3 fevers accompanied by constitutional symptoms. This event prompted a hospitalization; however, no infectious etiology or other cause for fever could be identified. Early hematopoietic toxicity and severe malaise was also experienced by both patients treated at 1800 mg/m^2. By determining the DLT to be 1800 mg/m^2, the MTD was defined at 1500 mg/m^2.

The additional patients studied cast some doubts on whether the MTD should be defined at a dose of 1500 mg/m^2 due to the inability to complete many cycles of treatment at a dose level of 1200 mg/m^2. Only 8 of the 27 patients were able to complete the first cycle of treatment without dose adjustment or omission. There were similar rates of dose modifications for patients treated at 1200 mg/m^2 and 1500 mg/m^2 (30% vs. 40% respectively). Even if the four patients who had omission of their dose at the 1200 mg/m^2 level due to death (2 patients) or termination of the study at their request (2 patients) during the first cycle were excluded, <40% of patients (6 of 16) were able to complete the first cycle without dose modification. Approximately 70% of dose adjustments or omissions during the first cycle were for uncomplicated myelosuppression. However, the finding that patients treated at 1500 mg/m^2 received the most gemcitabine during the first cycle with an average total cumulative dose of 3746 mg/m^2 as compared to 2953 mg/m^2 at 1200 mg/m^2 without any obvious differences in toxicity profile, may support defining the MTD at 1500 mg/m^2. In addition, it is our preference to initiate treatment at a higher dose level and de-escalate as long as there is no serious sequela; thereby, allowing for the maximum tolerated dose to be delivered at the first opportunity.

In those patients treated with gemcitabine over an extended period of time, only two dose reductions were prompted by non-hematologic toxicity. In both cases doses were reduced for nausea without vomiting. Although there were several instances when doses were omitted due to non-hematologic toxicities, the majority of dose reductions were related to myelosuppression.

There appears to be an increased rate of myelosuppression in this study when compared to data from studies in which gemcitabine was administered over a fixed 30 minute infusion. Abratt et al. [4] showed low rates of hematologic toxicity in their study of gemcitabine in non-small-cell lung cancer. Patients were treated with doses of 1000 mg/m^2 and 1250 mg/m^2 of gemcitabine administered over 30 minutes with some dose escalations of up to 1850 mg/m^2 depending on the patient's course. Rates in their study of WHO grade 3 or 4 toxicities were 10.8% for leukopenia and 30% for neutropenia with toxicity being reported as worst case per patient, not per dose or cycle. Serious thrombocytopenia occurred but the severity was not reported. Similarly, Pollera et al. [14] in a study of gemcitabine in patients with advanced or metastatic solid tumors at doses ranging from 300 mg/m^2 to 1370 mg/m^2 given

over 30 minutes showed no grade 4 hematologic toxicities. Thirteen percent of their patients attained grade 3 leukopenia and 10% of their patients had grade 3 thrombocytopenia. Data pooled together from over 700 patients in Phase II studies in which gemcitabine was administered over a fixed 30-minute infusion at doses ranging from 800–1250 mg/m^2 showed that 6.4%, 8.1%, 18.7%, and 3.7% had a maximum WHO grade 3 toxicity and 0.9%, 0.5%, 5.7% and 1.0% had a maximum WHO grade 4 toxicity for hemoglobin, leukocytes, segmented neutrophils, and platelets, respectively [19]. This contrasts with the present study in which the maximum WHO grade 3 or 4 toxicities at the entry level of 1200 mg/m^2 were 15.8% and 0%, 26.3% and 10.5%, 31.6% and 31.6%, and 26.3% and 0% for hemoglobin, leukocytes, segmented neutrophils, and platelets, respectively. For all patients in our study, the maximum WHO grade 3 and 4 toxicities were 11.5% and 0%, 23.1% and 7.7%, 34.6% and 23.1%, and 26.9% and 0% for hemoglobin, leukocytes, segmented neutrophils, and platelets, respectively.

Although there were no instances of significant morbidity or any mortality related to these episodes of myelosuppression, the higher rate of myelosuppression seen in this study suggests that prolonging the infusion rate does increase the intracellular phosphorylation of gemcitabine. Additionally, there appeared to be a cumulative dose effect on myelosuppression with 2 out of 3 patients treated for more than 20 cycles requiring adjustment in their gemcitabine dose for thrombocytopenia.

There were no non-hematological dose limiting toxicities. There did not appear to be any pronounced differences in the occurrence of WHO non-hematologic toxicities in our study when compared to studies using a fixed 30-minute infusion rate. There were four patients with apparent toxicity from gemcitabine which required withdrawal from the study and/or possibly contributed to their death. It was felt that the complications of ascites and debilitating fatigue were likely to be related to gemcitabine treatment. It is not clear whether gemcitabine contributed to or caused pneumonitis/ARDS or an acute myocardial infarction in two patients.

Determination of antitumor activity was not the primary objective of this study. However, the data does suggest some benefit for patients with pancreatic cancer. Among 21 patients treated for pancreatic adenocarcinoma, there were three patients with prolonged survival of >18 months, one of whom is still alive without disease progression at the time of manuscript submission (10% and 5% survival rate at 2 and 4 years, respectively). Although these observations are anecdotal, it is unusual to observe such a long progression-free survival in patients who were unresectable at the time of diagnosis. Both patients with survival >2 years underwent exploratory laparotomy and had surgical biopsies confirming the diagnosis of adenocarcinoma of the pancreas.

Several recent studies have demonstrated some clinical efficacy of gemcitabine in the treatment of pancreatic cancer. Casper and colleagues [5] performed a Phase II trial of gemcitabine in pancreatic cancer. Their trial showed that 5 out of 44 patients (11%) had a partial response for a median duration of 13 months with treatment of gemcitabine at 800 mg/m^2 over 30 minutes. These investigators also noted some improvement in quality of life during treatment. Moore et al. [20] demonstrated that gemcitabine treatment resulted in a significant ($p = 0.0025$) survival benefit as well as a significant clinical benefit ($p = 0.0022$) defined as positive effect on pain, Karnofsky performance status, and lean body mass in a multicenter study which compared gemcitabine administered weekly at a dose of 1000 mg/m^2 over 30 minutes and 5-FU weekly at 600 mg/m^2 over 30 minutes as initial treatment of pancreatic cancer. In the studies by Moore et al. [20] and Casper et al. [5] one year survival rates were approximately 20%.

Findings from this study suggest that it is worthwhile to proceed with Phase II and III studies of prolonged infusion of gemcitabine. It appears that gemcitabine can be safely administrated by prolonged infusion at a rate of 10 mg/m^2 for doses up to 1500 mg/m^2. Further experience with prolonged infusion of gemcitabine by studying additional patients with pancreatic cancer suggest that myelosuppression is more severe than anticipated based on previous reports of similar doses of gemcitabine administered at a fixed 30-minute infusion. Additionally, there is some suggestion of clinical benefit for selected patients with pancreatic cancer. Future Phase II and III studies evaluating prolonged infusion of gemcitabine should include patients with pancreatic adenocarcinoma and may consider starting at lower dose levels to determine if a dose could be identified in which the majority of patients completed their cycles of therapy without dose adjustment or omission.

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