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Clinical report

Phase I trial of weekly gemcitabine at 3-h infusion in refractory, heavily pretreated advanced solid tumors

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Gemcitabine (2′,2′-difluorodeoxycytidine) is a nucleoside analog with antitumor activity against a variety of malignancies. The critical enzyme cytidine kinase is saturated at plasma concentrations achieved after a 30-min infusion at conventional doses. Prolonged infusion time may yield higher intracellular dFdCTP concentrations. A phase I study was designed to determine the maximum tolerated dose (MTD) of gemcitabine, given by infusion for 3 h, in heavily pretreated patients. Twenty-seven patients (13 head and neck cancer, seven sarcoma, three esophageal cancer, three non-small-cell lung cancer and one ovarian cancer) were enrolled. Twenty patients were defined as refractory at first- or second-line chemotherapy. Four different entry dose levels (300, 400, 450 and 500 mg/m^2) were evaluated for gemcitabine administered on days 1, 8 and 15 of a 28-day cycle. The MTD was defined as 450 mg/m^2, with granulocytopenia, thrombocytopenia and asthenia being dose limiting. The maximum grade III/IV patient toxicities for hemoglobin, leukocytes, neutrophils and platelets for all doses were 7, 19, 19 and 11%, respectively. Non-hematological toxicities included asthenia, nausea/vomiting and diarrhea. Thus, gemcitabine administered at a fixed 3-h infusion was well tolerated up to 450 mg/m^2 in heavily pretreated patients. Myelosupression and asthenia were dose-limiting toxicities. [© 2001 Lippincott Williams & Wilkins.]

Key words: Gemcitabine, phase I, prolonged infusion, refractory.

Introduction

Gemcitabine is a nucleoside analog with antitumor activity in a wide range of solid tumors. The rate-limiting enzyme for gemcitabine conversion to dFdC 5′-triphosphate is deoxycytidine kinase. *In vitro* studies have suggested that the ability of mononuclear cells to use dFdC for triphosphate formation is saturable. Increased dose intensity could be achieved only by prolonging the duration of the infusion.[1] Phase I studies in untreated patients have established the maximum tolerated dose (MTD) for gemcitabine (at a constant rate of 10 mg/m^2/min) to be the 1500 mg/m^2 dose level.[2] Data from series with previously treated patients suggest that at 6-h infusion MTD is reached at the 300 mg/m^2 dose level.[3] Responses were observed in 14% of patients.

The primary objective of this study was to determine the MTD and dose-limiting toxicity (DLT) for gemcitabine administered as a prolonged 3-h infusion on a weekly (days 1, 8 and 15 every 28 days) schedule. A secondary objective was to document any antitumor activity in a selected previously refractory population of patients.

Patients and methods

Patient selection

Patients with advanced, previously treated, solid tumors who fulfilled all the following criteria were eligible for the study: 18–75 years of age, Eastern Cooperative Oncology Group performance status (PS) of 0–2, estimated life expectancy of >12 weeks, prior treatment with at least one chemotherapy schedule (including 30-min gemcitabine infusion) and no radiotherapy for at least 3 weeks prior to protocol entry. We defined as refractory those patients with progressive disease during or within 6 months of adjuvant therapy or during or within 3 months of chemotherapy in advanced disease. Exclusion criteria included: active infection, prior central nervous system metastases, significant renal, hepatic or bone marrow impairment, active cardiac disease requiring therapy for failure, angina, arrhytmias and/or myocardial infarction in the preceding 6 months. Informed consent was obtained from all patients.

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Study design

Four different dose levels of gemcitabine (300, 400, 450 and 500 mg/m^2) were evaluated in this open-label, non-randomized study. The DLT was defined by the presence of grade 4 thrombocytopenia, grade 4 neutropenia or grade $\geqslant$3 non-hematologic toxicity. The MTD was defined as the dose level below the DLT, during the first cycle. If two patients developed grade 3 non-hematologic toxicity or grade 4 hematological toxicity, five more patients should be accrued. Criteria for termination of treatment were objective or clinical evidence of disease progression, patients request or unacceptable drug toxicity. All patients enrolled in the study were evaluated for toxicity. All patients who completed appropriate imaging studies were assessed for clinical efficacy.

Drug administration

All gemcitabine doses were administered as a 3-h infusion. At least five patients were studied at each dose level and evaluated for a minimum of 1 month before starting additional patients at escalated doses. No individual patient was dose escalated. A cycle of therapy was defined as three weekly doses of the drug followed by 1 week of observation. A patient was considered to have received a cycle of therapy if at least one dose of gemcitabine was administered during the 4-week period. Dose modifications were based on weekly blood counts and assessment of toxicity. For NCI-CTC grade 3 neutropenia or grade 2 thrombocytopenia toxicity, doses were reduced to 75%. For NCI-CTC grade 4 neutropenia and grade 3 thrombocytopenia, doses were held for the remainder of a cycle and then decreased by 25% in the next cycle after marrow recovered. For grade 3 non-hematological toxicities, doses were held and reduced after recovering to 75%. Patients who experienced grade 4 non-hematological toxicity were removed from the study.

Clinical assessments

All toxicities were graded in every cycle according to NCI-CTC toxicity criteria. Complete blood count and blood chemistries were obtained at baseline and then weekly. An electrocardiogram, history and physical examination, chest X-ray, and a computed tomography scan of the area of known disease involvement was performed during a 4-week period prior to entry into the protocol. For further evaluation of efficacy, the following were repeated at the stated intervals: physical examination including tumor measurements, weight, performance status and toxicity (every week treatment), and chest X-ray or computed tomography scan every two cycles.

Tumor measurements were recorded for the longest diameter and the perpendicular diameter at the widest portion of the tumor. Complete response was defined as the disappearance of all measurable disease for 4 weeks or more. Partial response was defined as 50% or more decrease in the sum of the products of all bi-perpendicular dimensions of measurable lesions. Stable disease was defined as a decrease of less than 25% in the sum of the products of the bi-perpendicular dimensions of the measurable lesions or an increase in tumor mass less than 25% without the development of new lesions. Progressive disease was defined as more than 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. A patient was considered assessable for toxicity if given at least one dose of gemcitabine.

Results

Patients characteristics

The characteristics of the 27 patients (23 males and four females, median age 54 years) enrolled in this study are listed in Table 1. There were 13 patients with head and neck squamous carcinoma, seven patients with sarcoma (four soft-tissue sarcoma, two osteosarcoma and one Ewing sarcoma), three patients with esophageal carcinoma, three patients with non-small cell lung cancer and one patient with ovarian carcinoma. All head and neck squamous carcinoma patients had previously received radiotherapy and platinum–5-fluorouracil or fluorouracil oral prodrug (UFT) combination treatment. Sarcoma patients had previously received adriamycin and ifosfamide therapy. At study entry all patients had demonstrated progressive metastatic disease. Sixteen patients had received one previous chemotherapy regimen, 10 patients had received two and one patient had received three. Best response to previous chemotherapy for advanced disease was progressive disease in 18 patients. Two patients with locally advanced head and neck cancer treated radically with chemo-radiotherapy and with less than a 3-month disease-free interval were also considered as refractory. One patient had not been correctly evaluated, previously, for response.

Treatment

All patients received gemcitabine at a fixed infusion rate of 3 h. Six patients received 300 mg/m^2, five patients 400 mg/m^2, six patients 450 mg/m^2 and 10 patients 500 mg/m^2. Sixty-nine cycles of gemcitabine were administered. Five of six (83%), three of five (60%), five of six (83%) and three of 10 (30%) patients were able to complete their first cycle without dose adjustments or omissions at each level respectively. The median total cumulative dose of gemcitabine, administered weekly during all treatments, was 225 mg/m^2/week at the 300 mg/m^2 dose level, 300 mg/m^2/week at the 400 mg/m^2 dose level, 325 mg/m^2/week at the 450 mg/m^2 dose level and 285 mg/m^2/week at the 500 mg/m^2 dose level. The DLT was determined at a dose level of 500 mg/m^2 due to the occurrence of grade 4 thrombocytopenia in one patient, grade 4 neutropenia in another patient and three cases of grade 3 asthenia which reverted in all cases after 2–3 weeks of treatment discontinuation. Thus, the MTD was determined to be at the dose level of 450 mg/m^2.

Table 1. Patient characteristics

	N	Percentage
Patients entered	27	
assessable for response	22	81
assessable for toxicity	27	100
Dose level (mg/m^2)		
300	6	22
400	5	18
450	6	22
500	10	38
Age		
median	54	
range	(27–74)	
Sex		
male	23	85
female	4	15
Performance status (ECOG)		
0	2	7
1	10	37
2	15	56
Prior chemotherapy regimen		
1	16	63
2	10	33
3	1	4
Prior irradiation	13	48
Tumor types		
squamous head and neck	13	48
sarcoma	7	26
squamous esophageal	3	11
non-small cell lung cancer	3	11
ovarian	1	4
Response to previous chemotherapy		
refractory	20	74
sensitive	6	22
not evaluated	1	4

Toxicity

Twenty-seven patients, six at 300 mg/m^2, five at 450 mg/m^2, six at 450 mg/m^2 and 10 at 500 mg/m^2, were assessable for toxicity (see Tables 2 and 3). One patient with retroperitoneal sarcoma received only one gemcitabine dose at 300 mg/m^2 and dropped out because grade IV diarrhea. She was admitted to the hospital and was found to have a tumor-related intestinal obstruction that led to a rapid clinical deterioration. Another patient with esophageal carcinoma treated at 450 mg/m^2 was considered a protocol violation because gemcitabine dose was omitted instead of reducing it by 25% in the first cycle of therapy. Myelosuppresion appeared to be the most common toxicity accounting for dose adjustments during the study. At 500 mg/m^2, seven of 10 patients (70%) were unable to complete their first cycle. All

Table 2. Hematologic toxicity produced by weekly gemcitabine (number of cycles: 69)

	Dose level (mg/m^2/week)											
	300			400			450			500		
Patients on level (*n*)	6			5			6			10		
Cycles (*n*)	12			16			13			28		
Toxicity (grade)	2	3	4	2	3	4	2	3	4	2	3	4
First course												
anemia	1	1	0	2	0	0	3	0	0	4	1	0
neutropenia	0	0	0	0	0	0	0	0	0	2	4	2
thrombocytopenia	0	0	0	1	0	0	0	0	0	2	1	2
All courses												
anemia	0	0	0	4	0	0	4	0	0	4	0	0
neutropenia	0	0	0	0	0	0	1	0	0	2	1	0
thrombocytopenia	1	0	0	1	0	0	1	0	0	1	3	0

Table 3. Grade 3/4 non-hematologic toxicity

Toxicity	Gemcitabine dose (mg/m^2/week)			
	300	400	450	500
Nausea/vomiting	0	0	1	0
Alopecia (grade 2)	0	0	0	1
Mucositis	0	0	0	0
Diarrhea	1	0	0	0
Flu-like symptoms	0	0	0	0
Peripheral edema	0	0	0	0
Dermatitis	0	0	0	0
Asthenia	0	0	1	3
Hepatotoxicity	0	0	0	0

patients required dose reduction at day 15. In four patients dose was reduced because of grade 3 neutropenia, and in three patients dose was held due to grade 4 thrombocytopenia in two cases and grade 4 neutropenia in another patient. The most common non-hemathological toxicity was grade 3 severe asthenia in three patients at the 500 mg/m^2 dose level. Nausea and vomiting were generally mild (NCI-CTC grade 4 occurred in only one of 69 cycles). Flu-like symptoms were reported in two patients (grade 2 fever and grade 2 dermatitis), but were not responsible for dose reduction or omission.

Response

Twenty-two patients underwent appropriate studies to determine response to therapy. A total of 19 patients completed two cycles of treatment and 18 were assessable for response. Four patients who received one cycle of chemotherapy were felt to be clinically progressing because of rapid deterioration from their underlying malignancies. There were six patients with stable disease from 2 to 7 months, one partial response (a patient with nodal cervical tumor with stable disease to previous carboplatin–UFT therapy) and one complete response in a patient with locally advanced squamous carcinoma of the tongue (T4N0M0), previously treated with cisplatin–5-FU and concomitant radiotherapy. Response rate was two of 19 (10%).

Discussion

In vitro studies[1] have demonstrated that optimal levels of dFdCTP (15–20 μM) are achieved with low doses of gemcitabine (350 mg/m^2 at a 30-min infusion). In nude mice with colorectal tumors, continuous infusion of gemcitabine at 2 mg/kg for either 3–7 days or for 24 h at 15 mg/kg infusion was more active than 120 mg/kg infusion given over 30 min. Plasma concentrations were below the limit of the assay (0.05 μM).[4] Phase I studies have evaluated the feasibility of more prolonged infusions, the MTD 300 mg/m^2 (days 1, 8 and 15 every 28 days) at 6-h infusion[3,5] and 100–150 mg/m^2 (days 1, 8 and 15 every 28 days) at 24 h infusion.[6] These long continuous infusion schedules waste important clinical resources and are uncomfortable for patients due to the need for a central venous catheter. Shorter infusions at constant rate 10 mg/m^2/min have shown that the MTD dose, in untreated patients, is 1500 mg/m^2 (days 1, 8 and 15 every 28 days).[2] Hematological toxicity was dose limiting. This novel 150-min schedule (1500 mg/m^2) has been compared in a formal phase II study in advanced pancreatic carcinoma with 2200 mg/m^2 at 30-min classical infusion (Tempero *et al.*, personal communication) with a better response rate (16 versus 3%) and survival at 1 year (22 versus 0%). Plasma levels obtained at 150-min infusion were 336 μM, greater than 114 μM at 30-min infusion. These levels are close to dCMP deaminase inhibiting levels (400 μM). We have determined that the MTD with a 180-min fixed continuous infusion schedule in heavily pretreated patients is 450 mg/m^2 with dose-limiting asthenia and grade 4 hematological toxicity. Therefore the MTD in second-line therapy results in half of the dose administered in second-line 30-min infusion (875 mg/m^2) and less than a third of the dose at first line on a 150-min schedule (1500 mg/m^2). Continuous infusion gemcitabine has been tested in pretreated patients in two phase II trials. In breast cancer, Schimid *et al.*[8] demonstrated 25% responses in a 6-h infusion schedule. The MTD was 250 mg/m^2 at days 1, 8 and 15 every 28 days, and liver toxicity was dose limiting. The same authors have described a response rate of 20% in 10 patients with soft tissue sarcoma previously treated with anthracyclines (Späth-Schwalbe *et al.*, personal comunication). This compares favourably with the 10% (three of 30) response rate in soft tissue sarcoma patients treated with a 30-min infusion schedule (Patel *et al.*, personal comunication). We obtained a 3-month stable disease with the 3-h gemcitabine schedule at a 500 mg/m^2 dose level, in one osteosarcoma patient refractory to cisplatin, anthracycline and high-dose ifosfamide. At the Spanish Group of Sarcoma Treatment (GEIS) we have iniciated a phase I–II trial in untreated soft tissue sarcoma patients with adriamycin 60 mg/m^2 on day 1, and gemcitabine 10 mg/m^2/min on days 1 and 8 every 21 days with escalating doses of gemcitabine. In unresectable pancreatic carcinoma, an interesting report has demonstrated the feasibility of 24-h continuous infusion gemcitabine, at doses of 100 mg/m^2, with

concomitant radiotherapy (Kudrimoti *et al*., personal comunication). Nine of 12 (75%) patients with pancreatic and other gastrointestinal malignancies responded to chemoradiotherapy, although the constant infusion gemcitabine rate was extremely low (below 0.1 mg/m^2/min). This trial compares favorably with the 20% response rate with twice-weekly 40 mg/m^2 gemcitabine as a 30-min infusion and concomitant radiotherapy in a recent phase I trial in pancreatic cancer.[9]

Gemcitabine at a dose level of 450 mg/m^2 on days 1, 8 and 15 every 28 days retained antitumor activity when given as a 3-h prolonged infusion (constant infusion rate 2.5 mg/m^2/min) even in refractory heavily pretreated patients. More prolonged infusion trials are needed with or without concomitant radiotherapy before an optimal infusion gemcitabine schedule can be established.

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