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Clinical study

Phase I trial of gemcitabine (Gemzar®), 24 h infusion 5-fluorouracil and folinic acid in patients with inoperable pancreatic cancer

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Gemcitabine (Gemzar®) has a significant impact upon survival and quality of life for patients with pancreatic cancer, compared with 5-fluorouracil (5-FU). This phase I study was initiated to define the recommended dose of 5-FU delivered as a 24 h infusion in combination with gemcitabine (1000 mg/m^2) and folinic acid (200 mg/m^2) in patients with inoperable pancreatic cancer, treated on an outpatient basis. Drugs were administered weekly for 4 weeks out of 6 weeks. Sixteen chemonaive patients (median age 59 years, range 51–66) were enrolled, 15 had stage IV and one stage III disease. The median Karnofsky performance score (KPS) was 70 (range 60–80). Six patients received 5-FU 750 mg/m^2, eight received 5-FU 1000 mg/m^2 and two received 5-FU 1250 mg/m^2. The maximum tolerated dose of 5-FU was 1000 mg/m^2. Hepatotoxicity was dose limiting. One patient who received 5-FU 1250 mg/m^2 died as a result of hepatorenal failure. There was one partial response, nine patients had stable disease for more than 3 months and 13 patients had improved KPS. The median time to progressive disease was 31 weeks (range 5–50 weeks). A phase II trial is underway to further assess the activity of this combination at the recommended dose of 750 mg/m^2 5-FU. [© **1999 Lippincott Williams & Wilkins.**]

Key words: 5-Fluorouracil, folinic acid, gemcitabine, phase I study, pancreatic cancer.

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Introduction

Pancreas cancer is the fifth leading cause of cancer death in the US.[1] Surgery is the only curative treatment, but greater than 80% of patieints have non-resectable or metastatic tumors at the time of diagnosis and less than 15% will survive 1 year. Responses of pancreatic cancer to conventional radiotherapy or chemotherapy are rare and usually short lived. Phase II studies evaluating the activity of single agents in unresected tumors have failed to identify any agent that has had a major impact on survival. The most extensively studied agent to date is 5-fluorouracil (5-FU). Response rates with 5-FU, with or without modulation by folinic acid, range from 0 to 67%,[2] reflecting the small numbers of patients in the individual study groups, the variable doses and schedules used, differences in patient selection, and variable response criteria. In reality the response rate rarely exceeds 20%, with no consistent effect on disease-related symptoms and survival.[3–5]

Gemcitabine (Gemzar®), a novel nucleoside analog, has shown promising activity in patients with pancreatic cancer.[6–10] In a large, randomized study comparing single-agent gemcitabine with single-agent 5-FU, the median time to progressive disease (PD) for patients treated with gemcitabine was 2.33 months, compared with 0.92 months in patients treated with 5-FU.[8] More importantly, patients treated with gemcitabine had a better clinical benefit response than patients treated with 5-FU. Overall, toxicity was mild

and no cumulative hematological toxicity was noted.

Gemcitabine and 5-FU are both active as single agents in the treatment of pancreatic cancer. The toxicity profile and mechanism of action of 5-FU do not overlap with those of gemcitabine. The present phase I study was initiated to investigate the use of gemcitabine plus 5-FU and folinic acid for the palliative treatment of patients with advanced pancreatic cancer, without incurring unacceptable side effects. The aim was to determine the maximum tolerated dose (MTD) for 5-FU when used in this combination with a fixed dose of gemcitabine and to determine the dose-limiting toxicities and efficacy of the combination. Folinic acid was included as it has been reported to enhance the cytotoxicity of 5-FU *in vitro* and *in vivo*, and to improve response rates, with a trend towards improved survival in patients with colorectal cancer treated with 5-FU.[11]

Materials and methods

Patient selection

Patients with histologically or cytologically confirmed locally advanced (Union Internationale Contre le Cancer [UICC] stage III, T1-4, N1) or metastatic (UICC stage IV, T1-4, N0-1, M1) pancreatic cancer were enrolled into this study. Tumor lesions were required to be bidimensionally measurable, with a minimum size of 1×1 cm. Patients were chemonaive. Other eligibility criteria were: age ≥ 18 years, expected life expectancy ≥ 12 weeks, Karnofsky performance status (KPS) $\geq 60\%$ and adequate bone marrow reserve (white cell count $\geq 3.5 \times 10^9$/l, platelets $\geq 1000 \times 10^9$/l and hemoglobin ≥ 80 g/l). Written informed consent had to be provided by all patients. Patients with endocrine tumors of the pancreas or lymphoma of the pancreas were excluded from this study. Central nervous system metastases and secondary primary malignancies were also criteria for exclusion, as were inadequate liver function, pregnancy, active infection and serious concomitant disorder. This study received approval from the local ethics committee.

Chemotherapy and dose escalation

Gemcitabine (Gemzar®; Eli Lilly and Co, Indianapolis, IN; 1000 mg/m^2) was administered as a 30 min infusion, followed by 200 mg/m^2 folinic acid (Rescuvolin®; Medac, Hamburg, Germany) administered over 2 h on days 1, 8, 15 and 22 of a 42-day schedule. A portable battery-driven pump (Walkmed 300) was used to administer 5-FU as 24 h continuous infusion on days 1, 8, 15 and 22 of a 42-day schedule. This deviation from the more usual 28-day schedule for gemcitabine was an attempt to increase the level of exposure to the drug and also to improve quality of life, by allowing the patients 3 weeks (days 23-42) without therapy. To determine the MTD of the combination, the 5-FU dose was to be escalated by 250 mg/m^2, from a starting dose of 1000 mg/m^2, until dose-limiting toxicity occurred. Dosage regimens are shown in Table 1, with dose level 0 corresponding to 750 mg/m^2 5-FU, dose level I corresponding to 1000 mg/m^2 5-FU and dose level II corresponding to 1250 mg/m^2 5-FU. The MTD was conservatively determined as the dose at which any WHO grade III or IV non-hematological toxicity (other than nausea and vomiting or alopecia) or any grade IV hematological toxicity was noted. Prophylactic antiemetics were allowed and growth factors could be used if required.

Patient assessment

Prior to study entry, all patients had a full blood count and prothrombin time measurements. Blood chemistries were measured and urine analysis performed. Prior to treatment, the disease state of each patient was assessed. Tumor measurement was carried out by magnetic resonance imaging (MRI).

Efficacy was assessed throughout the treatment as follows: limited physical examination, weekly weight measurement and performance status elevation. Patients who had received at least one dose each of gemcitabine, 5-FU and folinic acid were considered evaluable for safety. A full blood count was taken on each day of treatment and blood chemistries at the start of each cycle. Patients were discontinued from therapy when treatment was associated with unacceptable toxicity, or at patient or investigator request. MRI was used to define partial responses and measurement was performed every 6-8 weeks after initial assessment. Responses were defined according to WHO criteria. Karnofsky performance measure-

Table 1. Dose escalation

Level	GEM mg/m^2 (30 min)	FA mg/m^2 (2 h)	5-FU[a] mg/m^2 (24 h)
0	1000	200	750
I	1000	200	1000
II	1000	200	1250

[a]Each dose escalation step=250 mg/m^2.
GEM, gemcitabine; FA, folinic acid.

ments were used as a measure of patient well-being in this study. However, because KPS is subjective, measurements at the onset of the study and during treatment were performed by two different people unconnected to the study with the intention of minimizing observer bias. If there was any doubt over performance status, the lower value was always taken.

Results

Sixteen patients were enrolled into the study: six at dose level 0, eight at dose level I and two at dose level II. All study drugs were administered on an outpatient basis. One patient had UICC stage III disease, the others had UICC stage IV disease. The median age was 59 years (range 51-66) and the median KPS was 70 (range 60-80). No patient had received radiotherapy. Patient characteristics at study entry are summarized in Table 2. All 16 patients were evaluable for toxicity, efficacy and time to PD evaluation.

The median number of treatment cycles administered was 3 (range 1-6). These are summarized per dose level in Table 3. Three patients were entered into the study at dose level I. There were no dose-limiting toxicities in any of these patients and the 5-FU dose was escalated to level II for the next two patients enrolled into the study. The first patient received five cycles of treatment and then developed DLT with grade III mucositis and grade III hepatotoxicity. The second patient received three drug administrations in the first treatment cycle. The 5-FU dose was reduced to 75% during one administration due to grade III leukopenia. After the third dose, grade III thrombocytopenia and grade IV leukopenia occurred. This patient died as a result of acute hepato-renal failure, which was probably related to the combination of 5-FU and gemcitabine. As a consequence, the subsequent five patients were enrolled at level I. One patient experienced WHO grade III leukopenia and had grade IV glutamate-pyruvate transferase (GPT) and glutamate oxalacetate transferase (GOT), and grade III alkaline phosphatase elevation. A second patient had grade III elevations of GPT and GOT. Elevated liver enzyme levels could not be linked to liver metastases or PD levels in either patient. Further treatment therefore was continued at dose level 0 (5-FU 750 mg/m^2), in order to avoid any risk of hepatotoxicity. A further six patients were enrolled at dose level 0. Three patients had grade III leukopenia, one of whom also had grade III thrombocytopenia. No hepatotoxicity was seen at this dose level. Thus, the MTD was defined as dose level I and the dose-limiting toxicity was hepatotoxicity.

Overall, eight patients received a total of 21 5-FU dose level I cycles (84 dose administrations). Of these, 10 gemcitabine doses and 13 5-FU doses were reduced by 25%, and one gemcitabine dose and four 5-FU doses were reduced by 50%. There were four dose omissions involving both drugs. Nine patients received 37 cycles (148 dose administrations) at 5-FU dose level 0. Three of these patients had previously been treated at 5-FU

Table 2. Summary of patient baseline characteristics at study entry

	n
No. entered	16
No. evaluable	16
Mean age (range)	59 (51–66)
Male	10
Female	6
Karnofsky median performance status (range)	70 (60–80)
Disease stage UICC	
III	1
IV	15

Table 3. Summary of treatment cycles administered at each dose level

	Dose level		
	0	I	II
Total no. of patients	6[a]	8	2
Total no. of cycles	37	21	6

[a]An additional three patients, originally enrolled into dose level I, subsequently received treatment at dose level 0.

Table 4. Summary of cycles with WHO grade III and IV toxicities

Dose levels	Total no. of cycles	No. of cycles with WHO grade III/IV toxicity				
		Leukopenia	Thrombocytopenia	Liver	Oral	Nausea/vomiting
0	37	4/0	1/0	0/0	0/0	0/0
I	21	1/0	0/0	2/1	0/0	2/0
II	6	0/1	1/0	1/1	1/0	0/0

dose level I. Six gemcitabine doses and three 5-FU doses were reduced by 25% at dose level 0, and eight 5-FU doses were reduced by 50%. There were 14 gemcitabine dose omissions and 20 5-FU dose omissions. These were mainly due to myelosuppression.

Efficacy

Of the 16 patients treated with the three different 5-FU dose levels, one patient who was initially treated at 5-FU dose level I and then treated after two cycles at dose level 0 had a partial response (PR). Nine patients had stable disease (SD) lasting more than 3 months, five had PD and there was one early death (Table 5). Four patients with SD were treated at dose level 0. Two patients with SD were initially treated at 5-FU dose level I for four cycles and then treated at dose level 0. The remaining patients with SD were treated at dose level I.

Karnofsky performance score improved during the treatment of 13 patients, remained stable in one, decreased in one and there was one early death. Two patients, both of whom had stable disease, showed an improvement from an initial KPS of 60 to KPS 100 within 4 weeks of treatment, lasting 18 weeks. Five patients with initial KPS of 70 had improvements once on study of greater than 10 points and which lasted more than two cycles. In the other six patients with stable disease the KPS increased greater than 10 points for at least 4 weeks. Four patients who progressed following gemcitabine, 5-FU and folinic acid treatment were subsequently treated with taxol and another received 5-FU monotherapy.

Table 5. Summary of responses

Response	No. patients
Partial response	1
Stable disease	9
>3 months	3
>6 months	4
>9 months	2
Progressive disease	5
Early death	1

Time to PD

The median time to PD across all dose levels was 31 weeks (range 5–50 weeks). Two patients are still alive and without PD, one at 40 weeks. The other progressed after 41 weeks, then began treatment with taxol and is still alive at 84 weeks. The Kaplan-Meier time to progression curve for all patients is shown in Figure 1.

Discussion

Gemcitabine has been shown to be useful in the treatment of patients with pancreatic cancer, for whom other treatment options are limited. There is, however, room for improvement in response rates and increased survival rates. When used in combination with other agents active in pancreatic cancer, gemcitabine may have a greater impact on response and survival in this disease. Gemcitabine has already been used in combination with cisplatin in the treatment of

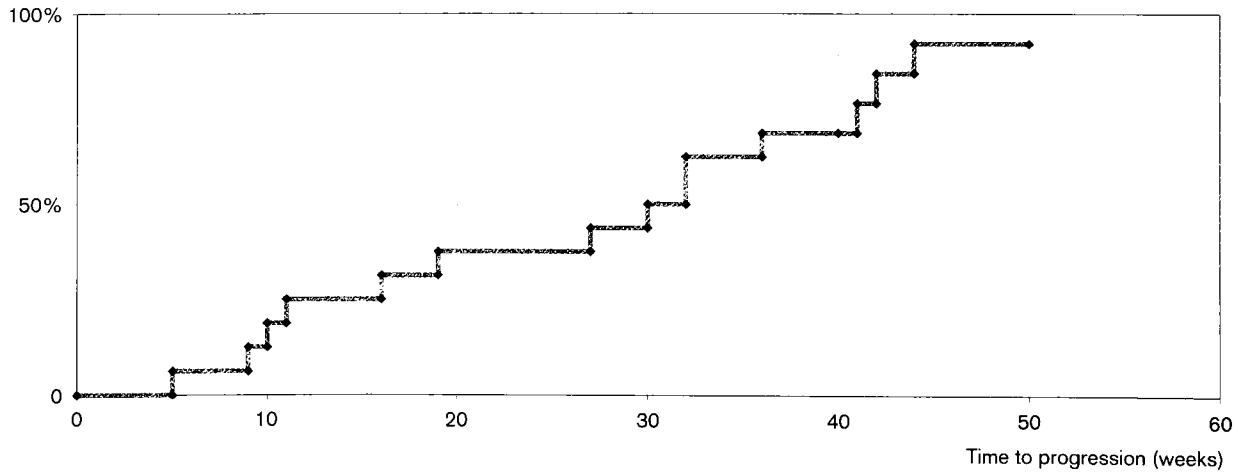

Figure 1. Kaplan-Meier curve for time to PD in all patients.

poor prognosis patients with advanced and metastatic pancreatic cancer,[12] and initial results have been promising. The combination of 5-FU and folinic acid has also been used to treat patients with advanced pancreatic cancer and resulted in partial responses and extended survival.[13]

The present study was designed to determine the MTD, dose-limiting toxicities and efficacy of 5-FU in combination with folinic acid and gemcitabine delivered with palliative intent to patients with inoperable pancreatic cancer, without affecting patient quality of life. The MTD of 5-FU in this combination was defined as 1000 mg/m^2 5-FU and hepatotoxicity was dose limiting. The combination of gemcitabine plus 5-FU and folinic acid was well tolerated by this group of patients with extremely poor prognoses who were not carefully selected from a large patient population. One partial response was seen and nine patients had stable disease. The high proportion of patients with stable disease is very encouraging, given that these patients had a poor prognosis in the absence of treatment. The median time to PD for all patients treated with gemcitabine, 5-FU and folinic acid was 31 weeks (7.7 months), which compares favorably with the median time to PD of 6.2 months in patients treated with high-dose folinic acid and 5-FU.[13] Median time to PD reported in studies of single-agent gemcitabine in pancreatic cancer were 2.33 months[8] and 2.5 months in patients with a poor performance status who had progressed despite 5-FU treatment.[10] Therefore this combination appears to be associated with increased time to PD, even in patients with stage IV disease.

It is important to note that the increase in time to PD observed in the present study was not achieved at the expense of toxicity to patients, as palliation of symptoms and patient quality of life are especially important in patients with advanced incurable disease. Although quality of life instruments were not administered in this study, patients' well-being was measured by determination of their performance status. The majority (13 of 16) of patients in this study had improved KPS, with sustained (lasting longer than two cycles) improvements from an initial performance score of 60–100 (two patients), sustained improvements from 70 to 100 (five patients) and less marked, but significant improvements in a further six patients. This is particularly important, as one of the study aims was to investigate the efficacy of the combination of gemcitabine, 5-FU and folinic acid, without affecting patient quality of life.

Grade III and IV hematological toxicities had no clinical consequences in patients treated with the lower doses of 5-FU (750 and 1000 mg/m^2). Platelet transfusions were not necessary. Non-hematological toxicities were also uncommon at these dose levels. There was only one incidence of grade III nausea, and vomiting and alopecia was rare, with only one report of grade I hair loss.

Hepatotoxicity was the dose limiting toxicity in this patient population. However, it should be stressed that 15 out of 16 patients in this study had liver metastases at study entry, making this patient population more susceptible to drug-induced hepatotoxicity than others. Both patients at dose level II and two out of five patients at dose level I showed significant elevations of hepatic enzymes which could not be correlated with disease progression. One patient even died due to hepato-renal syndrome, indicating that 5-FU doses in excess of 750 mg/m^2 should be avoided.

Several other phase I and II studies of gemcitabine and 5-FU, with or without folinic acid, are currently underway in pancreatic cancer.[14–18] Complete and partial responses have been reported, as well as median survival rates in the range 7–13 months. The combination of gemcitabine and 5-FU was generally well tolerated, with minimal myelosuppression and symptomatic toxicity, supporting the observations of the present study. In the study for which most details are available, 5-FU was given by continuous infusion, using an ambulatory infusion pump, throughout the duration of the study.[16] This is less convenient for patients than the 24 h continuous infusion used in the present study, which can be easily administered on an outpatient basis.

The promising results seen in this phase I palliative study, in which all but one patient had stage IV disease, have led to the initiation of a phase II study of gemcitabine 1000 mg/m^2, 5-FU 750 mg/m^2 and folinic acid 200 mg/m^2 once weekly for 4 weeks out of every 6 weeks.

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