A Phase II Trial of Biweekly High Dose Gemcitabine for Patients with Metastatic Pancreatic Adenocarcinoma

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BACKGROUND. Although the novel cytidine analog gemcitabine has shown superior antitumor activity compared with weekly bolus 5-fluorouracil in patients with advanced pancreatic carcinoma, further improvements of therapeutic results are warranted. The current Phase II study was initiated to investigate whether this might be achieved by dose intensification.

METHODS. Between August 1997 and September 1998, 43 consecutive patients with metastatic pancreatic adenocarcinoma were enrolled in this multicenter Phase II trial. Patients received 4 weekly courses of gemcitabine 2200 mg/m^2 given as intravenous infusion during 30 minutes on Days 1 and 15 for a duration of 6 months unless there was prior evidence of progressive disease. The efficacy of treatment was assessed according to standard criteria, i.e., objective response, progression free survival, and overall survival, as well as by analysis of clinical benefit response (defined as $\geq$ 50% reduction in pain intensity, $\geq$ 50% reduction in daily analgesic consumption, and/or $\geq$ 20 point improvement in Karnofsky performance status that was sustained for $\geq$ 4 consecutive weeks).

RESULTS. Of 43 patients evaluable for objective response, 1 achieved complete and 8 partial remissions, for an overall response rate of 21% (95% confidence interval, 10–36%); 18 additional patients (42%) had stable and 16 (37%) progressive disease. The median time to progression was 5.3 months. Median survival was 8.8 months, and the probability of surviving beyond 12 months was 26.3%. Of 36 patients with tumor-related symptoms who were considered evaluable for clinical benefit response, 16 (44%) experienced significant palliation. The median time to achieve a clinical benefit response was 6 weeks, and its median duration was 27 weeks. Chemotherapy was well tolerated, with leukopenia/granulocytopenia representing the most common side effect. Gastrointestinal and other subjective toxicities were infrequent and generally mild.

CONCLUSIONS. Biweekly high dose gemcitabine seems to represent a safe, tolerable, and effective regimen for the palliative treatment of patients with advanced pancreatic carcinoma. ***Cancer* 2000;88:2505–11.**
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Pancreatic adenocarcinoma, which is responsible for approximately 5% of all cancer-related deaths in the Western world,[1] continues to be a major unresolved health care problem. The large majority of patients presents with disease that is beyond the scope of surgical cure, and their clinical course is characterized by debilitating symptoms and an extremely poor prognosis: in case of distant metastases, the median survival duration is generally $<$ 3 months.[2]

In a recently published randomized trial, the novel cytidine an-

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alog gemcitabine was shown to be more effective than 5-fluorouracil (FU), though the latter drug might have been used in a suboptimal way, i.e., a single weekly bolus rather than an infusional schedule with or without leucovorin. The reported objective response rate for gemcitabine was only 5.4%. Similarly, there was only a modest survival advantage (5.65 vs. 4.41 months), and only 1 of 4 patients (23.8%) experienced clinical benefit.[3] Further improvements in the therapeutic management of patients with advanced pancreatic carcinoma are certainly warranted and might be achieved by combining gemcitabine with other active cytotoxic drugs. Encouraging preliminary data in patients with this common and fatal malignancy have been reported for its combination with cisplatin,[4,5] and bolus and continuous FU,[6–8] docetaxel,[9] as well as epirubicin.[10] Another possibility to enhance the antitumor potential of gemcitabine may represent its dose intensification. Preclinical data evaluating the in vitro activity of gemcitabine against human tumor colony-forming units taken directly from patients and growing in soft agar,[11] as well as studies with various established human tumor cell lines including those of pancreatic carcinoma origin,[12–14] have suggested a dose–response relation. Similar observations have been made in the clinical setting, at least in patients with advanced nonsmall cell lung carcinoma (NSCLC); an analysis of European, South African, Japanese, and other international Phase II studies showed that responses were not observed in patients who received < 900 mg/m^2/week as opposed to higher doses.[15–19] Furthermore, in two disease-oriented Phase I trials in chemotherapy-naive patients with NSCLC evaluating dose escalations from 1000 to 3500 mg/m^2/week, an obvious trend of higher responses at higher dose levels (> 2200 mg/m^2/week) was noted.[20,21] Thus, despite a possible threshold of transport saturation with higher doses of gemcitabine when given during a short duration, a certain dose–response relation seems to exist; this might be explained by the multiplicity of the sites of action of this drug.[22] Of note, much higher doses than the usual 1000 mg/m^2 schedule of 30-minute weekly infusions seem to be well tolerated with myelosuppression and reversible transaminase elevation representing the most common dose-limiting toxicity.

The current multicenter Phase II study was initiated to investigate the feasability and therapeutic index of such an escalated dose regimen of gemcitabine in patients with advanced pancreatic adenocarcinoma. The antitumor efficacy was assessed by conventional measures, i.e., objective response, time to progression, and median survival, as well as by clinical benefit response analysis as previously described.[3,23]

PATIENTS AND METHODS

Patient Selection

Patients eligible for the study were required to have histologically or cytologically ascertained metastatic adenocarcinoma of the pancreas. Patients with resectable tumors as well as those with locally advanced, inoperable disease were not included in the study. Further inclusion criteria were bidimensionally measurable disease, age between 19 and 75 years, and an anticipated life expectancy of at least 3 months. Furthermore, patients were required to have a baseline Karnofsky performance status of at least 50% and to have adequate renal (serum creatinine level < 1.5 mg/dL), liver (total bilirubin level < 1.5 mg/dL and transaminase levels less than two times the upper limits of normal) and bone marrow function (leucocyte count $\geq 4000/\mu$L, absolute granulocyte count $\geq 2000/\mu$L, and platelet count $\geq 100{,}000/\mu$L). Patients with other serious or uncontrolled concurrent medical illness or with central nervous system metastases were not eligible for treatment, and neither were those who had undergone any prior palliative chemotherapy. A minimum of 2 weeks was required to have elapsed in case of prior abdominal exploration or palliative surgery. Informed consent was obtained from all patients according to institutional regulations.

Pretreatment and Follow-Up Evaluation

Pretreatment evaluation included a complete medical history, physical examination, electrocardiogram, echocardiography, and routine laboratory studies. The latter consisted of a complete blood count with platelet and leucocyte differential count, and an 18-function biochemical profile. Imaging procedures included chest X-ray and computed tomography of the abdomen. Complete blood counts, differential counts, and liver functional parameters were determined weekly, and complete biochemical profiles were assessed before each treatment cycle. Objective tumor assessments were performed at the end of every two cycles during chemotherapy and every 2–3 months after discontinuation of treatment.

Treatment Protocol

Chemotherapy consisted of gemcitabine (2200 mg/m^2) diluted in 250 mL normal saline administered as a 30-minute intravenous infusion on Days 1 and 15. Treatment courses were repeated every 4 weeks and continued for patients achieving objective response or stable disease until a total of 6 courses. Ondansetron (8 mg) was routinely administered before cytotoxic drug administration.

Toxicity and Dosage Modification Guidelines

Adverse reactions were evaluated according to World Health Organisation (WHO) criteria.[24] Chemotherapeutic drug doses were reduced by 25% in subsequent cycles if the lowest WBC (absolute granulocyte) count was $< 1000/\mu L$ ($500/\mu L$), the lowest platelet count was $< 50{,}000/\mu L$, or if any severe (WHO Grade 3 or higher) nonhematologic toxicity was observed in the previous cycle. Treatment could be delayed for up to 2 weeks if the WBC count was lower than $3000/\mu L$ and/or the platelet count lower than $75{,}000/\mu L$. Any patient who required more than 2 weeks for hematologic recovery was taken off the study.

Assessment of Objective and Clinical Benefit Response

The primary study end point was objective response rate. A complete response (CR) was defined as the disappearance of all clinical evidence of tumor for a minimum of 4 weeks during which time the patient was free of all symptoms related to cancer. Partial response (PR) was defined as a $> 50\%$ decrease in the sum of the products of the longest perpendicular diameters of all measurable disease with no new lesions appearing and none progressing for at least 4 consecutive weeks. Patients were rated progressive (PD) if any new lesion appeared, or tumor size increased by 25% higher than pretreatment measurements, or in case of a deterioration in clinical status that was consistent with disease progression. Patients who failed to meet the criteria of CR, PR, or PD and who remained on study for at least 2 months were classified as having stable disease. In case of PR or CR, a second assessment 4 weeks later was required for confirmation of response; all tumor measurements in patients who responded were reviewed and confirmed by a reference radiologist. Secondary study end points included the duration of response (measured from the onset of the best response to the date of disease progression), time to progression (TTP; calculated from the date of initiation of therapy to the date when progressive disease first was observed), and overall survival.

In addition to these objective study end points, clinical benefit was evaluated in symptomatic patients as previously described.[3,23] Pain (computed as the mean of the pain intensity scores recorded daily by the patient on a 100-mm visual analog scale (VAS), plus analgesic consumption, expressed as morphine equivalent mg/day and computed as the mean of the daily use indicated in a diary) and Karnofsky performance status (assessed weekly by two independent observers with selection of the lower value if the scores differed) composed the primary measures of clinical benefit and were assessed weekly. Weight change, also recorded weekly (and excluding patients who developed third-space fluid or required parenteral nutrition at any time during the study) was considered as a secondary measure. To achieve an overall rating of positive clinical benefit response, patients had to benefit for at least one parameter (pain: a $\geq 50\%$ improvement in pain intensity and/or a $\geq 50\%$ decrease in analgesic consumption compared with baseline; Karnofsky performance status: a $\geq$ 20-point improvement above baseline; weight: increase by $\geq 7\%$ above baseline) without worsening of any other parameter (i.e., deterioration in pain intensity measurements and/or increase in analgesic consumption by any degree; worsening in performance status by ≥ 20 points above baseline). This improvement had to last for at least 4 weeks. The primary measures of pain and performance status were evaluated first; a patient who was rated stable on these primary measures (i.e., neither categorized as positive or as negative) could be classified as having achieved an overall clinical benefit response only if weight was positive. All other patients were classified as not having achieved clinical benefit response.

The duration of clinical benefit response was defined as the duration of the positive classification in case of a single component. If multiple components were positive, the duration of clinical benefit response was defined as the largest number of consecutive weeks during which there was a positive change for at least one of the components.

Statistical Methods

Using standard statistical methods, we used a two-stage design in the protocol.[25] If no CR or PR were noted in the first cohort of 14 patients, a response rate of $> 20\%$ could be excluded with 95% confidence and accrual would stop. If at least one CR or PR was observed, > 30 patients were to be entered in the study to determine the response rate more accurately. For the response rates, 95% confidence intervals were calculated as previously described.[26] The distribution of TTP and time to death from the date of study entry were estimated using the Kaplan–Meier product-limit method.[27]

RESULTS

Patient Population

Between August 1997 and September 1998, a total of 43 patients (27 men and 16 women, with a median age of 65 years) were entered onto this trial from 4 different institutions. All patients were considered evaluable for response and toxicity assessment. The demographic data, prior surgical procedures, histologic grade, and sites of metastatic tumor are listed in Table

TABLE 1
Pretreatment Characteristics

Characteristic	No. of patients (%)
Number of patients entered/eligible	43/43
Gender	
Male	27 (63)
Female	16 (37)
Median age in years (range)	65 (46–75)
Karnofsky performance status (%)	
90–100	9 (21)
70–80	23 (53)
50–60	11 (26)
Prior surgery	
None	14 (32)
Explorative laparotomy	3 (7)
Palliative bypass/stent	20 (47)
Whipple	6 (14)
Histologic grade	
G1	2 (5)
G2	32 (74)
G3	9 (21)
Sites of metastases	
Liver	25 (58)
Abdominopelvic mass	23 (53)
Lung	11 (26)
Extraabdominal lymph nodes/soft tissue	3 (7)
Bone	4 (9)
Adrenals	1 (2)
Spleen	2 (5)

1. Six patients had undergone prior potential curative surgery with disease recurrence after a median of 13 months (range, 4–57). Nine patients had undergone palliative surgery for biliary and/or gastric decompression, and 11 patients had received endoscopic stents for relieving obstructive jaundice before study entry. The large majority of patients had multiple intraabdominal sites of metastases, and all except 7 patients were suffering from disease-related symptoms: 30 of the 36 symptomatic patients (83%) had pain at study entry, 16 of whom (53%) had a baseline pain intensity score $>$ 20 points, and 27 (90%) required more than 10 morphine-equivalent mg/day for control of pain. Similarly, most patients had an impaired performance status at study entry (79%), and 25 (58%) had experienced weight loss, ranging from 4–42% of premorbid body weight.

Treatment Summary

A total of 182 cycles were administered with a median of 6 cycles per patient (range, 1–6). The median duration of treatment was 140 days, with a range of 28–186 days. Treatment was withdrawn early for only one patient, who warranted discontinuation for personal reasons; in all other patients therapy was withdrawn after 6 months according to the protocol, or because of progression, including 3 cases with tumor complications while still receiving chemotherapy, who required palliative endoscopic or surgical intervention (1 biliary and 2 intestinal obstructions). There were no major protocol violations.

TABLE 2
Summary of Treatment Results (n = 43)

Therapeutic outcome	No. of patients (%)
Complete response	1 (2)
Partial response	8 (19)
Stable disease	18 (42)
Progression	16 (37)
Overall response rate	9/43 (21)
95% confidence interval	10–36%
Time to progression (mos)	
Median	5.3
Range	1.0–18.0
Overall survival (mos)	
Median	8.8
Range	1.2–21.0+
1-year survival rate	26.3%

Objective Response and Survival

Response, time to progression, and survival data are summarized in Table 2. The overall response rate was 21% (95% confidence interval, 10–36%), including one CR and 8 PR. The median time to response was 3 months (range, 2.0–3.8), and the median duration of response was 6.5 months (range, 3–15). An additional 18 patients (42%) showed disease stabilization lasting for a median of 6 months (range, 3.5–15), and 16 (37%) patients progressed during treatment.

At the time of this analysis all patients had experienced PD. Thirty-two patients (74%) have died, and the median follow-up duration of the 11 patients still alive is 12 months (range, 9–21+). The median time to progression was 5.3 months (range, 1–18). Median survival was 8.8 months (range, 1.2–21+), and the probability of surviving beyond 12 months was 26.3%.

Clinical Benefit Response

Clinical benefit response data are summarized in Table 3. Thirty-six patients with tumor-related symptoms (pain and/or impaired performance status with or without weight loss) were considered evaluable for clinical benefit response. In 9 of 30 patients suffering from pain at study entry, pain intensity and/or analgesic consumption was reduced as compared with baseline values, and 21 were classified as stable in this category (including 10 of 13 patients without pain at entry, but $\geq$ 1 other specific cancer-related symptom).

TABLE 3
Results of Clinical Benefit Response Analysis (n = 36)

Symptomatic response	No. of patients (%)
Pain	
Positive	9 (25)
Negative	6 (17)
Stable	21 (58)
Karnofsky performance status	
Positive	11 (31)
Negative	12 (33)
Stable	13 (36)
Weight	
Positive	5 (14)
Nonpositive	31 (86)
Responder	16 (44)
Nonresponder	20 (56)

Improvement in pain without worsening of the performance status occurred in four patients, whereas both pain and performance status improved in five. An additional six patients had an improvement in performance status while being rated stable in the pain category. Therefore, a total of 15 patients was classified as clinical benefit responders by primary measures. With regard to weight gain, the secondary measure of clinical benefit, 5 patients had a positive change (> 7% increase from baseline). Four of these patients already had improved in one of the primary measures, and one was considered stable in pain and performance status. Accordingly, the total number of primarily symptomatic patients experiencing a clinical benefit response with high dose gemcitabine increased to 16 (44.4%). The median duration to achieve a clinical benefit response was 6 weeks (range, 4–14), and the median duration of clinical benefit was 27 weeks (range, 12–38).

Toxicity

All 43 patients, who received a total of 182 cycles were evaluable for toxicity. Side effects associated with treatment are listed in Table 4. The most frequently encountered toxicity was myelosuppression. Leukopenia occurred in 32 patients (74%), and was Grade 3 in 5 patients (12%). The median nadir leukocyte count was 3400/μL (range, 1200–9200/μL). The time to WBC count recovery to more than 3000/μL was short, i.e., 95% of episodes of leukopenia resolved within 7 days. The variations in granulocyte counts paralleled those of WBCs, and the median nadir count was 1600/μL (range, 660–6050/μL). Thrombocytopenia was noted in a total of 11 patients (26%); none of those was rated severe, and there were no episodes of bleeding. The median nadir platelet count was 118,000/μL (range, 53,000–240,000/μL) with no evidence of a cumulative nature of this side effect. Only one patient developed Grade 3 anemia, whereas mild anemia was recorded in 27 patients (63%). The median nadir of hemoglobin was 10.2 g/d: (range, 8.0–13.4 g/dL). Six patients developed documented infection, but none of them required hospitalization.

TABLE 4
Summary of Maximum Treatment Associated Toxicities (n = 43)

	Number of patients/WHO toxicity grade (%)			
Toxicity	1 (%)	2 (%)	3 (%)	4 (%)
Hematologic and other laboratory-based toxicity				
Leukopenia	11 (26)	16 (37)	5 (12)	—
Granulocytopenia	8 (19)	12 (28)	10 (23)	—
Thrombocytopenia	7 (17)	4 (9)	—	—
Anaemia	14 (33)	13 (30)	1 (2)	—
Bilirubin	2 (5)	1 (2)	—	—
Alkaline phosphatase	9 (21)	3 (7)	1 (2)	—
Serum transaminases	10 (23)	4 (9)	—	—
Symptomatic toxicity				
Nausea/vomiting	10 (23)	3 (7)	—	—
Stomatitis	4 (9)	2 (5)	—	—
Diarrhea	5 (12)	4 (9)	—	—
Constipation	1 (2)	2 (5)	—	—
Infection	3 (7)	3 (7)	—	—
Fever	5 (12)	2 (5)	—	—
Alopecia	8 (19)	1 (2)	2 (5)	—
Cutaneous	5 (12)	1 (2)	—	—
Phlebitis	1 (2)	—	—	—
Fatigue	9 (21)	1 (2)	—	—

WHO: World Health Organization.

Minor treatment-related elevations in liver functional parameters were noted in less than one-third of the patients and did not result in any dose modifications or discontinuation from treatment. Apart from hair loss in 26% (total alopecia 5%), and fatigue in 23%, gastrointestinal toxicities were among the most frequently encountered nonhematologic side effects: nausea/vomiting occurred in 30%, though symptoms were generally mild, confined to the day of drug administration, and responsive to standard antiemetic therapy. Stomatitis was recorded in six patients, and diarrhea or constipation occurred in seven and three patients, respectively. Uncommon nonmyelosuppressive toxicities included minor (Grade 1 or 2) skin rash (12%) that was treated symptomatically with topical corticosteroids and/or systemic antihistamines, fever in the absence of infection (12%), and chemically induced phlebitis (2%).

Seven patients had at least one treatment delay of 1 week at some time during therapy, and the total of delayed courses was 10 (5.5%). The reasons for delayed courses were hematologic in 3 and nonhemato-

logic in 4, including intercurrent infection and personal reasons in 2 patients each. None of our patients required a dose reduction of cytotoxic drugs during treatment according to the study protocol, and there were no toxic deaths.

DISCUSSION

Although in a randomized trial the novel cytidine analog gemcitabine was shown to be more effective than FU in advanced pancreatic carcinoma, the reported objective response rate was only 5.4%, there was only a modest survival advantage (5.65 vs.4.41 months), and only 1 of 4 patients (23.8%) experienced clinical benefit.[3] Further improvements are certainly warranted and might be achieved by dose intensification and/or by combining gemcitabine with other active cytotoxic drugs. The objective of the current study was to evaluate the former option and was based on preclinical and clinical evidence that such a dose–response relation might exist.[12–14,20,21] The dose regimen of gemcitabine was chosen according to the recommended Phase II starting dose reported by Fossella et al. in a Phase I study in chemotherapy-naive patients with advanced NSCLC.[21] Treatment thus originally was planned to be given weekly for 3 consecutive weeks followed by a 1-week rest period; in a pilot series, however, 4 of 6 patients were unable to receive all 3 weekly gemcitabine infusions during the first or second cycle due to neutropenia and/or hepatotoxicity (unpublished data). Therefore, we decided to omit Day 8 and perform this study by using a biweekly high dose gemcitabine administration schedule.

In this study, we obtained a 21% overall remission rate (95% CI, 10–36%) in 43 evaluable patients, and a median response duration of 6.5 months. With an additional 42% of patients experiencing stable disease (for a median duration of 6 months), chemotherapy with biweekly high dose gemcitabine resulted in abrogation of progression of this aggressive tumor in 63%. These objective response data are even more noteworthy considering the finding that all of our patients had metastatic disease, as opposed to most other studies of pancreatic carcinoma that also have included patients with advanced locoregional disease, who are known to have a much better prognosis.[28,29] Keeping this in mind, the most striking results of our study are the median time of progression free (5.3 months) and overall survival (8.8 months), as well as the frequent palliative effects obtained: clinically significant and sustained improvements in pain, analgesic consumption, and/or Karnofsky performance score were observed in 44% of symptomatic patients. The onset of clinical benefit (6 weeks) was rapid, and its median duration was 27 weeks. It seems noteworthy that the clinical beneficial effects of biweekly high dose gemcitabine were not negated by frequent or severe clinically relevant treatment-related toxicities. Although neutropenia and thrombocytopenia were commonly observed, nadir values rarely exceeded WHO Grade 3. The low rate of gastrointestinal toxicities (30% in the current trial) might be explained by routine concomitant administration of a serotonin antagonist.

In conclusion, the described biweekly high dose gemcitabine regimen seems to be an effective palliative therapy for nonpretreated advanced pancreatic carcinoma accompanied by a favorable toxicity profile. Although objective and clinical benefit response as well as survival data suggest a possible advantage over conventional gemcitabine monotherapy, reproducibility of our encouraging data remains to be confirmed in a randomized trial. Further dose intensification by increasing the biweekly gemcitabine dose.[30] and/or by prolonging the length of infusion[31] might be achieved. In a patient population affected by an aggressive tumor such as metastatic pancreatic carcinoma, in which patients frequently present in poor general condition due to significant pain, weight loss, and/or other symptoms, however, there is a certain risk that such an attempt will result in an increase of toxicity to an extent that therapy interferes rather than beneficially influences the individuals' quality of life.

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