

Phase I Trial of Gemcitabine Combined with Radiation for the Treatment of Locally Advanced Pancreatic Adenocarcinoma¹

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ABSTRACT

Gemcitabine has modest activity in the treatment of advanced pancreatic cancer and is a potent radiosensitizer. We conducted a Phase I trial to determine the maximum tolerated dose of weekly gemcitabine delivered concurrently with radiation therapy for the treatment of locally advanced adenocarcinoma of the pancreatic head and to assess the treatment-related toxic effects associated with such a regimen. Eighteen patients with pathologically proven, locally advanced adenocarcinoma of the pancreatic head were enrolled in this study. Patients received seven weekly doses of gemcitabine with 3000 cGy of external beam radiation therapy delivered during the first 2 weeks of therapy. Six patients received gemcitabine at 350 mg/m²/week, nine at 400 mg/m²/week, and three at 500 mg/m²/week. Grade 3–4 hematological toxicity was observed in over half the patients treated. Nonhematological toxicities were significant and included fatigue, anorexia, nausea, vomiting, and dehydration. Forty-four % of the patients required admission to the hospital for management of nausea/vomiting and dehydration. The risk of hospitalization appeared to be dose-related; all of the three patients treated at 500 mg/m²/week required hospital admission during treatment. Seventeen patients were evaluated for response, and eight patients (47%) had evidence of a local anticancer effect. Four of these eight patients (24%) had a partial response to therapy. The median survival for the entire group was 6 months. The 1-year survival rate for patients with an objective response to therapy was 66%. The clinical responses observed in this group of patients suggest gemcitabine is a clinically relevant radiosensitizer in patients with pancreatic adenocarcinoma.

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However, the toxic effects are significant, suggesting that until dose and scheduling issues are explored further, concomitant administration of gemcitabine and radiation therapy should still be considered investigational.

INTRODUCTION

Approximately 27,000 new cases of pancreatic adenocarcinoma are diagnosed each year in the United States, and pancreatic cancer is the fifth leading cause of cancer-related death in America (1). Long-term survival is uncommon and likely only after curative surgical resection. Moreover, this cancer is associated with significant morbidity. From a clinical standpoint, patients fall into one of three categories: (a) those with resectable tumors, commonly defined as tumors not involving vascular structures such as the superior mesenteric artery, the portal vein-superior mesenteric vein confluence, or the celiac axis (imaging studies, laparoscopy, or laparotomy should also rule out metastatic disease to the liver, peritoneum, and lung); (b) patients with locally advanced disease who have unresectable tumors based on invasion of surrounding vascular structures but with no evidence of distant metastatic spread; and (c) patients who present with metastatic disease, which typically appears on routine CT³ scans of the abdomen as liver lesions, ascites, or peritoneal implants. Occasionally, chest X-ray or CT of the chest will reveal pulmonary metastases.

For patients undergoing curative resections, single-institution studies report long-term survival rates ranging from 3–20% (2, 3). Five-year survival rates for patients with node-negative disease may be as high as 36% (3). However, only 15–20% of patients diagnosed with adenocarcinoma of the pancreas have potentially resectable disease. This proportion is likely an overestimate of patients with truly resectable tumors because many with potentially resectable tumors have pathologically positive surgical margins after pancreaticoduodenectomy. The survival of these patients is often as poor as that of patients with locally advanced disease (4, 5).

Roughly half of all of the patients present with locally advanced disease (stage II and stage III). Despite its grim prognosis, data suggest a survival advantage to chemoradiation compared with radiation therapy alone for this group of patients. Studies by the GITSG demonstrated that delivery of a split course of radiation combined with bolus injection of 5-FU is superior to radiation therapy alone for locally advanced cancer of the pancreas. A median survival of 10 months was observed in patients undergoing combined modality therapy compared with 5.5 months for patients receiving radiation therapy alone (6). It has been postulated that 5-FU provides radiosensitization

³ The abbreviations used are: CT, computed tomography; GITSG, Gastrointestinal Tumor Study Group; 5-FU, 5-fluorouracil; MTD, maximum tolerated dose; EBRT, external beam radiation therapy.

and possibly some systemic benefit. In this regard, the rate of response to single agent 5-FU for pancreatic cancer ranges from 0 to 28% (7, 8).

It has become common practice to treat patients with locally advanced pancreatic cancer with external beam radiation therapy and radiosensitizing doses of 5-FU. The Eastern Cooperative Oncology Group performed a Phase I study to determine the MTD of prolonged infusional 5-FU when combined with 5940 cGy of external beam radiation in patients with pancreatic or extrahepatic biliary tumors. The MTD was 250 mg/m²/day with gastrointestinal toxicity being the dose-limiting factor (9). A subsequent study demonstrated the feasibility of using low-dose continuous-infusion 5-FU (200 mg/m²/day) over 5.5 weeks combined with a single course of 5040-cGy radiation for patients with locally advanced adenocarcinoma of the pancreas (10). This was followed by weekly 5-FU treatments until disease progression was documented. Eighty-five % of patients completed the chemoradiation. The median survival was 10 months, identical to that reported by the GITSG. Of note, this study reported that only 10% of patients treated in this fashion had an objective response to therapy. Objective response was not a reported end point in the GITSG or Eastern Cooperative Oncology Group trials.

Gemcitabine, a new deoxycytidine analogue approved for the treatment of advanced pancreatic cancer, has shown modest single-agent activity. In one randomized study comparing weekly gemcitabine with weekly 5-FU for advanced disease, gemcitabine demonstrated a small survival advantage (median survival, 5.65 months *versus* 4.41 months), with more patients reporting a clinical benefit with gemcitabine than with 5-FU (7). Gemcitabine also has very potent radiosensitizing properties (11, 12). Studies by Lawrence *et al.* demonstrated radiation enhancement ratios of 1.7–1.8 when pancreatic cancer cell lines are exposed to as little as 10 nM gemcitabine. These authors reported that cells treated with this concentration of gemcitabine alone demonstrated no cytotoxicity (12). This concentration is easily achieved in the plasma of patients receiving weekly doses of gemcitabine (13).

Previous clinical studies of gemcitabine as a radiosensitizing agent in the treatment of non-small cell lung cancer and head and neck tumors have shown promise (14,15). However, these studies also provide insight into the risk of significant toxicity when gemcitabine is combined with radiation. Skin reactions and mucosal toxicity were particularly notable in patients with head and neck cancers treated with a combination of low-dose gemcitabine (300 mg/m² weekly) and external beam radiation therapy (total dose of 70 Gy in 35 fractions; Ref. 14). Fatal radiation fibrosis has been reported in patients receiving gemcitabine and EBRT for non-small cell lung cancer (15).

On the basis of the modest superiority of gemcitabine over 5-FU as a systemic therapy for advanced pancreatic cancer and its radiosensitization in pancreatic cell lines, we conducted a Phase I trial of weekly gemcitabine combined with a fixed dose of radiation in a population with locally advanced pancreatic cancer confined to the head of the pancreas. The design of the protocol was determined by two general goals. The first goal was to design a chemoradiation regimen that might ultimately prove to be superior to 5-FU-based chemoradiation. Second, we sought to develop a gemcitabine-based chemoradiation regimen

for use preoperatively in patients with resectable pancreatic adenocarcinoma that builds on our previous experience in this area (16). Thus, we designed a program whereby the course of treatment was delivered over 7–8 weeks with a view toward using such a regimen preoperatively.

In patients with potentially resectable pancreatic cancer, we have described previously a preoperative chemoradiation approach that combines infusional 5-FU at 300 mg/m²/day with EBRT to a total dose of 30 Gy administered in 10 fractions over 2 weeks (16). At the time of pancreaticoduodenectomy, patients received an additional 10–15 Gy with intra-operative radiation bringing the total dose to 40–45 Gy. This approach has led to lower costs and less toxicity than treatment with infusional 5-FU and EBRT to a dose of 50.4 Gy over 5 weeks (16). The shortened course of infusional 5-FU with 30 Gy of radiation has also achieved a 3-year actuarial survival rate of 23% in patients undergoing curative resection for pancreatic adenocarcinoma (17).

In vitro studies (18) suggested that radiosensitization could be demonstrated with gemcitabine when the drug is delivered as early as 48 h before radiation. Preclinical studies in tumor-bearing animals performed at our institution using a mouse sarcoma model demonstrated that peak radioenhancement occurred when gemcitabine was delivered 24–72 h before a single fraction of radiation and that normal tissues recovered from the effects of gemcitabine more rapidly than malignant tissues (19). Therefore, we explored a schedule of concomitant chemotherapy and radiation whereby the first dose of gemcitabine was administered 3 days before the initiation of radiation therapy.

PATIENTS AND METHODS

Patient Selection. Pretreatment evaluation included physical examination and routine laboratory evaluation including a complete blood cell count, electrolytes, blood urea nitrogen values, creatinine, glucose levels, and liver function studies. All of the patients underwent 3-mm-thin cut, helical CT of the pancreas and a chest X-ray. All of the patients were required to have histological or cytological proof of adenocarcinoma of the head of the pancreas. Because the toxicity of the combination of gemcitabine and radiation therapy to the abdomen was unknown, patients with tumors in the body or tail of the pancreas that might require treatment with a larger radiation field were excluded.

Patients were required to have locally advanced, unresectable disease, defined as tumor encasement of the celiac axis or superior mesenteric artery or radiographic evidence of occlusion of the superior mesenteric-portal vein confluence. There could be no evidence of distant metastatic disease based on physical examination or radiographic imaging.

All of the patients had no prior chemotherapy or radiation therapy. Patients were required to have a Zubrod performance status of 0–2. Adequate bone marrow reserve, defined as a pretreatment WBC count of >3000/μL, a hemoglobin level of >9.0 g/dl, and a platelet count of >100,000/μL, was necessary to be eligible. Patients were required to have a life expectancy of more than 12 weeks, be 18 years of age or older, and sign an informed consent document meeting institutional and federal regulations.

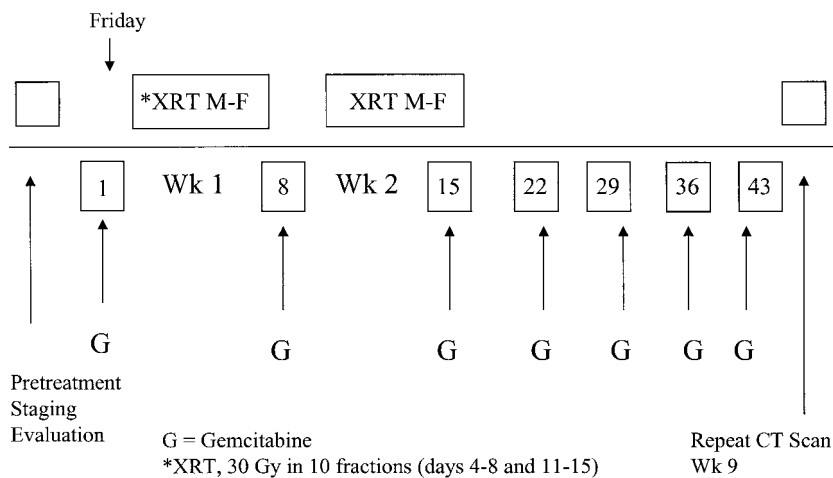


Fig. 1 Treatment schema for the combination of gemcitabine and radiation therapy. Patients received their first dose of gemcitabine on a Friday. The following Monday (72 h later) patients started radiation therapy.

Patients excluded from the study included those whose tumors had neuroendocrine features, pregnant women, and patients with inadequate hepatic or renal function. Inadequate hepatic function was defined as a total bilirubin level >2.0 mg/dl or transaminase levels $>$ five times the upper limit of normal. Renal dysfunction was defined by radiographic evidence of a loss of more than two-thirds of the renal parenchyma or by a serum creatinine level greater than 1.5 mg/dl.

Study Design. The protocol was designed to deliver 30 Gy of fractionated radiation therapy (3 Gy/fraction \times 10 fractions) over 2 weeks in combination with seven weekly injections of gemcitabine (the recommended induction schedule for patients with advanced disease treated with gemcitabine alone). The radiation therapy was delivered during the first 2 weeks of treatment (Fig. 1). The starting dose of gemcitabine was 400 mg/m² weekly for 7 weeks. If the MTD was not reached, the study was designed to evaluate additional patient cohorts at escalated doses of 600, 800, and 1000 mg/m²/week. A modified Fibonacci strategy for gemcitabine dose escalation was used, whereby a minimum of three patients would be treated at each dose level. If dose-limiting toxicity occurred in one of these three patients, a minimum of three additional patients would be studied at the same dose level.

The MTD was defined as that dose of gemcitabine associated with dose-limiting toxic effects (defined as grade 4 hematological toxicity or grade 3 or 4 nonhematological toxicity) occurring in 33% of the patients treated at that dose level.

Radiation Therapy. The primary tumor was encompassed in the radiation field with a margin of 3–5 cm. The pancreaticoduodenal, porta hepatis, and celiac axis nodes were included in the fields. Field size ranged from 10 cm \times 10 cm up to 15 cm \times 15 cm. The total dose prescribed to the isocenter was 30 Gy delivered in 10 fractions over 2 weeks using 18-mV photons. Anterior-posterior, posterior-anterior, and lateral fields were used. Radiation therapy was initiated on Monday (day 4) and completed on the second Friday (day 15; Fig. 1).

Chemotherapy. Gemcitabine was administered i.v. in 50–100 ml of normal saline over 30 min. All of the patients were premedicated with 10–20 mg of i.v. ondansetron. The starting gemcitabine dose was 400 mg/m²/week for 7 weeks

with planned dose escalations of 200 mg/m² to reach a final dose of 1000 mg/m². On the basis of the theoretical considerations outlined above, the first dose was administered on Friday with the first fraction of radiation delivered the following Monday. The treatment schema is outlined in Fig. 1. No additional doses were given beyond week 7, if doses during the treatment course were withheld.

Evaluation During Therapy. Routine laboratory tests (complete blood count with differential, electrolytes, glucose, renal function, and hepatic function studies) were monitored weekly during therapy. Patients were assessed clinically each week by medical oncology and a clinical research nurse in a multidisciplinary clinic setting. Decisions to reduce dose, withhold therapy, or proceed on schedule were made after the patient's clinical status and laboratory studies were reviewed.

Post-treatment Evaluation and Follow-up. Three to 4 weeks after completing therapy, patients were restaged with a physical examination, routine laboratory studies, a chest X-ray, and CT of the abdomen and pelvis. These procedures were repeated every 8–12 weeks thereafter. Patients were followed for evidence of continued toxicity, response to therapy, disease progression, and survival. Response to therapy was not a primary end point of this study. However, patients were defined as having had a complete response to therapy if restaging imaging demonstrated no radiographic evidence of tumor within the pancreatic head and no evidence of metastatic disease. A partial response was defined as a 50% or greater reduction in the total volume of the tumor in the head of the pancreas with no evidence of extrapancreatic spread of disease. A minor response was defined as a reduction in the total volume of the tumor of more than 25% but less than 50%. Stable disease was defined as a reduction of less than or equal to 25% or a less than 25% increase in the volume of the tumor with no evidence of extrapancreatic spread of disease. Progressive disease was defined as clinical or radiographic evidence of disease progression based on a post-treatment increase of 25% or more in the size of the primary tumor or the development of malignant ascites, liver lesions suspicious for metastatic foci, or other abnormalities suggesting metastatic disease.

Table 1 Patient characteristics

Characteristic	No. of patients	Percentage
Sex		
Male	10	56
Female	8	44
Race or ethnicity		
White	14	78
Black	2	11
Hispanic	2	11
Age (median, 62.5 yr)		
41–50 yr	3	17
51–60 yr	5	28
61–70 yr	8	44
71–79 yr	2	11
Zubrod performance status		
0	1	6
1	17	94

RESULTS

Patient Characteristics. From December 1996 through May 1998, 18 patients were enrolled and treated. The median age of the participants was 62.5 years (range, 41–79 years). The group consisted of 10 men and 8 women. Table 1 summarizes the patients' characteristics. All of the patients had a Zubrod performance status of 0 or 1 at the initiation of treatment.

Acute Toxicities. All of the 18 patients received the radiation therapy component of the protocol and were evaluated for toxicity. The significant toxic effects encountered in this protocol included fatigue, nausea, vomiting, anorexia, and myelosuppression. Table 2 outlines the doses of gemcitabine studied. We initially planned to increase the gemcitabine dose in increments of 200 mg/m²/cohort. However, of the first three patients treated at 400 mg/m²/week, one developed grade 3/4 nonhematological toxicity with diabetic ketoacidosis and upper gastrointestinal tract bleeding and required hospital admission. Therefore, an additional three patients were treated at this dose level. Similarly, one of these three patients was hospitalized with grade 3/4 nausea, vomiting, and dehydration and grade 3 neutropenia. On the basis of the concern that the 400 mg/m²/week dose was at or very close to the MTD, three patients were treated with a minor, unplanned dose escalation to 500 mg/m²/week. All three of these patients required hospitalization with reversible grade 3/4 nausea, vomiting, and dehydration. This dose (500 mg/m²/week) was therefore considered above the MTD for the combination of gemcitabine with radiation therapy.

To clarify whether 400 mg/m²/week was at or above the MTD, this dose level was expanded, and an additional three patients (a total of nine patients at this dose level) were treated. Two of these patients were hospitalized with nausea, vomiting, and dehydration. During hospitalization, one patient died suddenly and was found on postmortem examination to have had an acute thrombosis of the right coronary artery. Thus, at 400 mg/m²/week, a total of four of nine patients experienced dose-limiting toxic effects. It was concluded that this dose was above the MTD for the combination of gemcitabine with radiation therapy. Subsequently, the dose of gemcitabine was reduced to 350 mg/m²/week, and six patients were evaluated. In this cohort, only a single patient was hospitalized with reversible grade 3 neutropenia, nausea, vomiting, diarrhea, and dehydration, estab-

Table 2 Gemcitabine doses administered in Phase I trial of patients with pancreatic cancer

Dose level	Weekly dose	No. of patients
–1	350 mg/m ²	6
0 ^a	400 mg/m ²	9
+1	500 mg/m ²	3

^a Starting dose.

lishing the MTD for concomitant gemcitabine and radiation using this schedule.

Table 3 shows the incidence of grades 2–4 hematological toxic effects at each dose level. Leukopenia was common and developed in over 75% of the patients. Neutropenia also developed in a substantial proportion of patients, but febrile neutropenia occurred in only one patient. The significant nonhematological toxic effects (grades 2–4) are summarized in Table 4. A substantial percentage of the patients treated on this study experienced gastrointestinal toxicity characterized by anorexia (72%) and nausea and vomiting (61%). Seventy-two % of patients required i.v. hydration for support during or shortly after completing therapy. The risk of grade 3–4 nausea/vomiting, anorexia, and fatigue appeared to be dose-related. One-third of patients experienced grade 2 or 3 abdominal pain, which was thought to be the result of injury to the mucosa of the stomach and small intestine. The pathogenesis of this pain syndrome was suggested through the upper gastrointestinal endoscopic evaluation of two patients who experienced continuous epigastric abdominal pain. Both patients had gastritis and duodenitis within the radiation field. Another patient had hematemesis on presentation to the emergency department during therapy, but nasogastric lavage rapidly cleared the bleeding, and endoscopy was not performed. Two patients underwent unplanned CT of the abdomen during the treatment to evaluate abdominal pain and distention. Both were found to have ascites and were taken off the study with progressive disease after having received treatment for only 3 weeks of the planned 7-week course.

The results suggest that the risk of hospitalization was dose-related. Hospitalization rates were 16%, 44%, and 100% for the 350 mg/m², 400 mg/m², and 500 mg/m² doses, respectively. Fig. 2 demonstrates the time course of gemcitabine dose reductions and deletions. Fig. 2 shows that although the intended dose of gemcitabine could be maintained during the first 2 weeks, subsequent intended doses of gemcitabine had to be reduced or eliminated altogether. None of the patients assigned to the 500-mg/m²/week dose were able to receive gemcitabine during week 5 of treatment. In general, hematological toxicity occurred near the end of the radiation therapy requiring dose reductions by 25%. As therapy continued, unacceptable nonhematological toxicity led to dose deletions during weeks 4 through 7 (Fig. 3). The frequency of dose deletions increased dramatically during week 4 and peaked during week 5 of therapy, with 87% of the hospitalizations occurring during that interval.

Response to Therapy. Of the 18 patients enrolled on the protocol, one died before being evaluated for response. Two patients demonstrated rapid progression of disease before completion of the 7-week program. Eight (47%) of 17 evaluated

Table 3 Hematological toxic effects

Dose (mg/m ²)	Anemia			Leukopenia			Neutropenia			Thrombocytopenia		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
350	11%	11%	0%	0%	50%	16%	33%	33%	0%	0%	0%	0%
400	66%	11%	0%	22%	44%	22%	33%	22%	11%	11%	0%	0%
500	66%	0%	0%	0%	66%	0%	66%	0%	0%	66%	0%	0%
Total		61%			78%			67%			22%	

Table 4 Nonhematological toxic effects

Dose (mg/m ²)	Nausea/vomiting			Anorexia			Abdominal pain			Fatigue		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
350	0%	33%	16%	50%	16%	0%	50%	0%	0%	50%	0%	0%
400	0%	22%	44%	44%	22%	0%	22%	11%	0%	22%	55%	0%
500	0%	0%	100%	0%	100%	0%	0%	0%	0%	33%	66%	0%
Total		61%			72%		33%			72%		

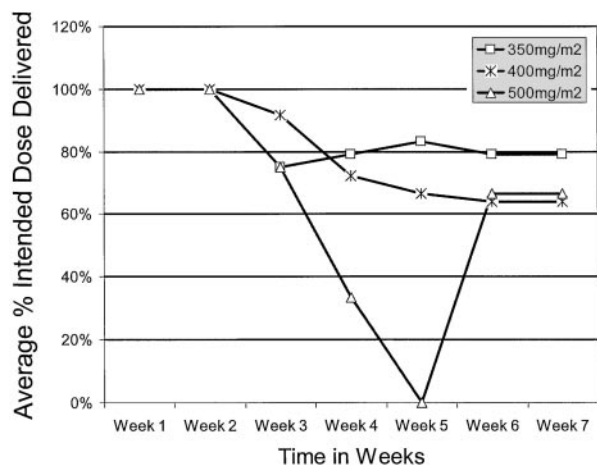


Fig. 2 Proportion of intended dose actually delivered/week. The X axis shows each week of scheduled gemcitabine. The Y axis is the average dose delivered that week divided by the intended dose. All of the patients were able to receive gemcitabine and radiation during the first 2 weeks. Thereafter, many patients required a dose reduction or had to have the gemcitabine dose withheld. This was most dramatic for those receiving 500 mg/m².

patients had a radiographically documented response to therapy assessed by CT after completion of treatment: four (24%) had minor responses, and four (24%) had partial responses. Two patients were felt to have had sufficient improvement in the relationship between the pancreatic tumor and the superior mesenteric vasculature to justify surgical exploration with intent to resect the primary tumor. At surgery, one patient was found to have omental metastases that were not appreciated on preoperative radiographs, and one patient underwent pancreaticoduodenectomy with curative intent. This patient had a marked change in the radiographic appearance of the mass in the head of the pancreas after treatment (Fig. 4), and although viable tumor cells were present, significant fibrosis and marked desmoplastic changes were evident within the excised tumor specimen (20).

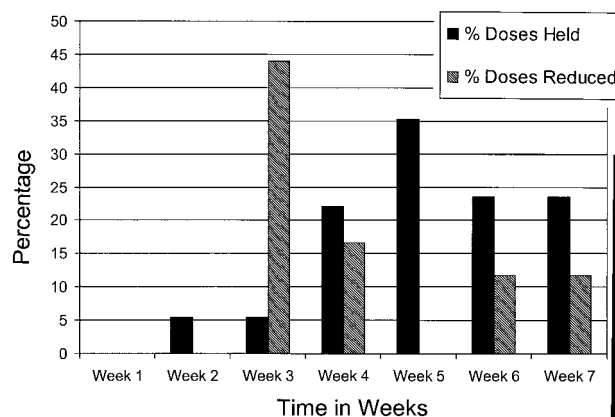


Fig. 3 Time course of dose reductions and dose deletions of gemcitabine. Although hematological toxicity led to 25% dose reductions during week 3, dose elimination became more common during weeks 4 through 7 with a peak at week 5. Hospitalization was most frequent during weeks 4 and 5.

Of the eight responding patients, the initial restaging CT done at 2–4 weeks after the completion of therapy did not demonstrate maximal tumor reduction, and the majority of these patients had their best response documented 10–12 weeks after completion of all of the therapy. In addition, the patient who was found in retrospect to have peritoneal metastases had a nodule that was clearly present on the pretreatment imaging and was noted to have regressed significantly after therapy was completed (Fig. 5).

The median survival for the entire group was 6 months. However, the 1-year survival rate for patients who had any objective response to therapy was 66%, and it was 75% for the four patients who had a partial response.

DISCUSSION

A number of studies (21) have demonstrated the potent radiosensitizing properties of nucleoside analogues, but the

Fig. 4 CT scans for a 53-year-old white woman with locally advanced disease. This patient underwent exploratory laparotomy at another institution, and the tumor was found to be invading the portal vein. The *left panel* demonstrates a postoperative CT scan of the heterogeneous mass abutting the portal vein. The *right panel* demonstrates marked reduction in the mass 12 weeks after therapy. The patient subsequently underwent pancreaticoduodenectomy with curative intent.

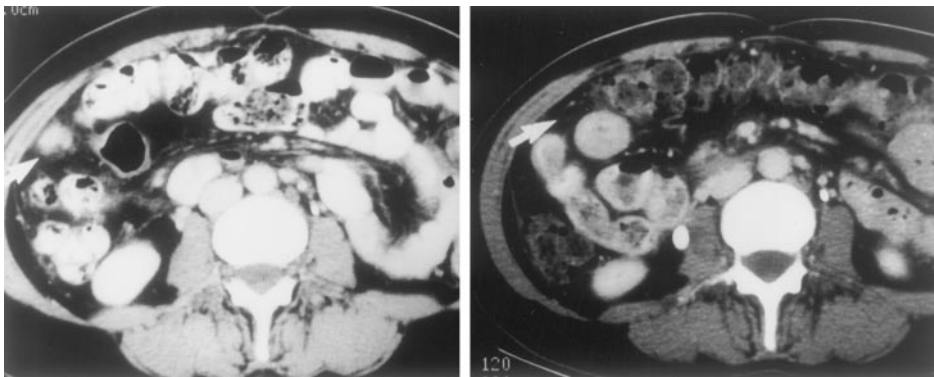
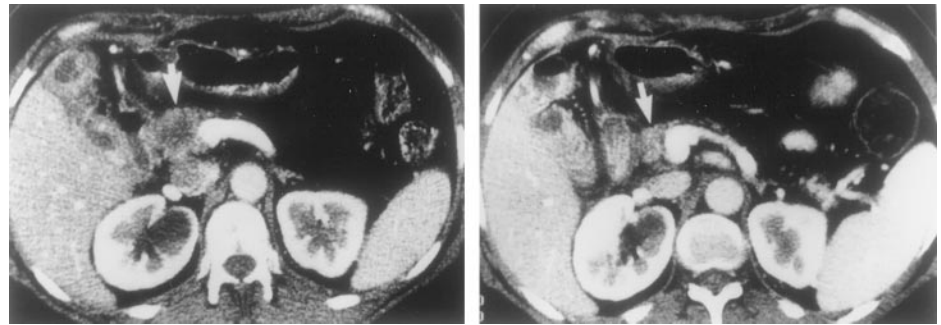


Fig. 5 Pretreatment and post-treatment CT scans of a 42-year-old white woman initially diagnosed with locally advanced disease. The image on the *left* identifies a peritoneal implant (*arrow*), which was thought to represent an unopacified loop of bowel on the pretreatment scan. The image on the *right* shows the disappearance of the implant 4 weeks after completion of the treatment.

mechanisms through which radiosensitization is achieved have not been fully elucidated. Radiosensitization may occur through several distinct mechanisms. First, chemotherapy may cause sufficient apoptosis within a tumor to reoxygenate relatively hypoxic regions, thereby leading to enhanced radiation injury to those areas. Alternatively, agents that inhibit DNA synthesis may slow tumor clonogenic regrowth between fractions of radiation therapy and allow for improved local control with continued radiation. Finally, the inhibition of DNA repair pathways may be a very important mechanism for enhancing radiation-induced cell death.

Although *in vitro* studies (14, 15) have demonstrated that gemcitabine is a potent radiosensitizer, it can also lead to severe injury to normal tissue *in vivo*. However, recent experiments (19) have demonstrated that the radioenhancing effects of gemcitabine may occur at different times in tumor cells and in normal tissues such as bone marrow, skin, and gut and formed the basis for the sequencing of gemcitabine and radiation used in this trial. These early studies were based on experimental protocols using single doses of radiation. Subsequent study of the timing of gemcitabine and fractionated radiation performed by Mason *et al.* (22) suggested that once-weekly gemcitabine delivered at least 24 h before radiation optimized radiosensitization of tumor cells while minimizing normal tissue injury, specifically to the jejunum.

In the current study, the combination of weekly gemcitabine with a short, intensive course of radiation therapy was found to be clinically rigorous, leading to both gastrointestinal and hematological toxicities. Although patients were able to com-

plete the radiation therapy during the first 2 weeks of the regimen, they were frequently unable to tolerate subsequent administration of gemcitabine at the intended dose. Given the many patients who suffered from nausea and vomiting (with or without abdominal pain), we believe that injury to intestinal mucosa was common. Consistent with this hypothesis, two patients were endoscopically documented to have mucosal injury either while receiving treatment or shortly after the therapy was completed. This observation is similar to the mucosal toxicity observed in patients with head and neck cancers treated with a combination of gemcitabine and radiation therapy (14, 23).

It is interesting to note that patients who received the highest dose of gemcitabine (500 mg/m²/week) had a lower occurrence of grade 3 or 4 hematological toxicity, but all of the patients had grade 3/4 gastrointestinal side effects. Conversely, patients treated at either 350 mg/m²/week or 400 mg/m²/week were more likely to develop grade 3 myelosuppression. We postulate that the 500-mg/m²/week dose led to severe mucosal injury that precluded continued therapy on schedule. The patients assigned to receive either 350 or 400 mg/m²/week were more likely to receive gemcitabine on a weekly basis and, therefore, were more prone to develop hematological toxicity. Although gastrointestinal toxicity was also common in this group, myelosuppression was likely related to the higher cumulative dose of gemcitabine.

These results suggest that when gemcitabine is given weekly with concomitant radiation therapy to a dose of 30 Gy in 10 fractions, the MTD of gemcitabine is 350 mg/m²/week for 7

weeks. This is approximately one-third the recommended dose of gemcitabine when administered as a single agent for the treatment of advanced pancreatic cancer.

Because pancreatic cancer is a disease characterized by local-regional failure and early dissemination to distant sites, our original goal was to design a regimen that delivered a therapeutic dose of radiation therapy to the pancreatic head while maintaining a dose of gemcitabine that would have both radiosensitizing effects and potential systemic activity. Because the delivered doses of gemcitabine in this study were between 350 mg/m²/week and 500 mg/m²/week, it would be expected that peak plasma concentrations would be at least 30–50 nM (13). This exceeds the concentration of gemcitabine required to yield radiosensitization *in vitro* (11, 12). The responses observed in the locally advanced tumors treated on this trial suggest that gemcitabine at these doses is a clinically relevant radiosensitizing agent. More problematic is the issue of whether these weekly doses of gemcitabine have a systemic anticancer effect. Because most patients with metastatic pancreatic cancer are treated with maximal doses of gemcitabine, the lowest weekly dose with systemic activity is unknown. In this study, a single patient treated at 350 mg/m²/week was retrospectively considered to have a metastatic peritoneal implant that responded to therapy. This suggests that for certain patients gemcitabine doses of 350–400 mg/m²/week may have some systemic activity.

Although median survival for the entire group of 18 patients was less than that reported previously for patients with locally advanced pancreatic cancer, the survival of the responding patients was considerably better (6). Caution is advised when interpreting these results, however, given the small numbers of patients treated and the selective nature of the patients treated on this trial. One primary reason for studying gemcitabine with radiation therapy in patients with locally advanced disease was the desire to improve radiosensitization for patients with resectable tumors in an effort to have an impact on pathological response. Moreover, because gemcitabine may have better systemic activity than 5-FU, it is hoped that the time to the development of gross metastatic disease may be prolonged with the use of gemcitabine as part of a preoperative regimen. Therefore, this study has served as the foundation for our next preoperative chemoradiation protocol for patients with resectable disease. On the basis of our anticipation that smaller radiation fields could be used, current patients with resectable pancreatic cancer are being enrolled in a Phase II trial combining 30 Gy of radiation with weekly gemcitabine at 400 mg/m². Overall, the tolerance of this program has been good (24).

Other reports of the combination of gemcitabine with radiation therapy for pancreatic cancer have been published recently (25).⁴ Of note, differing schedules of radiation therapy and gemcitabine have been used in these studies. McGinn *et al.* (25) have been conducting a Phase I study of weekly gemcitabine in combination with 5040 cGy of external beam radiation therapy in patients with unresectable tumors. At a dose level of 500 mg/m²/week, the MTD of gemcitabine has not been

reached. It is possible that the lower, more conventional radiation/fraction (180 cGy) allows for a higher dose of gemcitabine to be delivered. Of note, the radiation field size used in the McGinn *et al.* (25) study encompasses the pancreatic tumor with a 2–3-cm margin.⁴ In our protocol, the field was designed to have a 3–5-cm margin and to include the pancreaticoduodenal, celiac, and porta hepatis nodes. This may also explain differences in MTD, because in this trial a large volume of normal mucosa would be at risk for radiation injury. However, because gemcitabine is such a potent radiosensitizer, radiation dose/fraction may be the primary reason for the lower MTD observed with our regimen compared with other weekly schedules of gemcitabine combined with radiation.

Blackstock *et al.* (26) have used lower doses of twice-weekly gemcitabine in combination with 5040 cGy. In that study, the MTD of twice-weekly gemcitabine was less than 60 mg/m². As suggested by Mason *et al.* (22), frequent delivery of gemcitabine with external beam radiation may cause a marked increase in cytotoxicity of normal tissues, specifically the gastrointestinal mucosa encompassed within the radiation therapy field. On the basis of the significant toxicity observed in our study and that of Blackstock *et al.* (26), combinations of gemcitabine with radiation for pancreatic cancer should be delivered in the context of an approved clinical trial. Additional studies of the combination of gemcitabine with radiation are warranted to determine the dose and schedule of concomitant therapy that optimizes the therapeutic index of this promising regimen.

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⁴ C. J. McGinn, personal communication.

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