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A Multi-Institutional Phase II Trial of Preoperative Full-Dose Gemcitabine and Concurrent Radiation for Patients With Potentially Resectable Pancreatic Carcinoma

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Background: We report the results of a multi-institutional phase II trial that used preoperative full-dose gemcitabine and radiotherapy for patients with potentially resectable pancreatic carcinoma.

Methods: Patients were treated before surgery with three cycles of full-dose gemcitabine (1000 mg/m^2 intravenously), with radiation during the second cycle (36 Gy in daily 2.4-Gy fractions). Patients underwent surgery 4 to 6 weeks after the last gemcitabine infusion.

Results: There were 10 men and 10 women, with a median age of 58 years (range, 50–80 years). Nineteen patients (95%) completed therapy without interruption, and one experienced grade 3 gastrointestinal toxicity. The mean weight loss after therapy was 4.0%. Of 20 patients taken to surgery, 17 (85%) underwent resections (16 pancreaticoduodenectomies and 1 distal pancreatectomy). The complication rate was 24%, with an average length of stay of 13.5 days. There were no operative deaths. Pathologic analysis revealed clear margins in 16 (94%) of 17 and uninvolved lymph nodes in 11 (65%) of 17 specimens. One specimen contained no residual tumor, and three specimens revealed only microscopic foci of residual disease. With a median follow-up of 18 months, 7 (41%) of the 17 patients with resected disease are alive with no recurrence, 3 (18%) are alive with distant metastases, and 7 (41%) have died.

Conclusions: Preoperative gemcitabine/radiotherapy is well tolerated and safe when delivered in a multi-institutional setting. This protocol had a high rate of subsequent resection, with acceptable morbidity. The high rate of negative margins and uninvolved nodes suggests a

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significant tumor response. Preliminary survival data are encouraging. This regimen should be considered in future neoadjuvant trials for pancreatic cancer.

Key Words: Neoadjuvant therapy—Pancreas surgery—Gemcitabine and radiotherapy—Pancreas cancer.

Recommendations for combined-modality therapy in patients with potentially resectable pancreatic cancer often include the use of 5-fluorouracil (5-FU) with concurrent radiotherapy.[1] This may be delivered in either the neoadjuvant or the postoperative adjuvant setting.[2,3] Data suggest only a modest benefit associated with this therapy.[4–6] Clinical trials investigating a variety of gemcitabine-based chemoradiotherapy regimens were initiated several years ago. These trials were based, in part, on the activity of gemcitabine as the single most effective agent in patients with advanced pancreatic cancer, preclinical studies that demonstrated radiosensitization in pancreatic cancer cell lines, and the need for treatment strategies with greater efficacy than that provided by 5-FU–based chemoradiation.[7–9] The regimens investigated to date include gemcitabine dose escalation with conventional radiotherapy,[10,11] gemcitabine dose escalation with rapid fractionation,[12] the addition of gemcitabine to 5-FU and radiotherapy,[13] and full-dose gemcitabine with radiotherapy directed at the primary tumor alone.[14,15] These investigations have been primarily in patients with unresectable disease, and few patients have been investigated in multi-institutional phase II trials.

In most of these trials, emphasis was placed on the delivery of radiotherapy with gemcitabine dose escalation. We elected to further investigate the use of full-dose gemcitabine with modified radiotherapy in a multi-institutional phase II trial that allowed entry of patients with potentially resectable pancreatic cancer. Our selection of this regimen was based on experience gained in phase I trials and recognition that a regimen that emphasizes systemic treatment may provide an advantage over more conventional combined-modality approaches, considering the systemic nature of this disease, while still providing adequate local control through sensitization of a modest radiation dose. Prior clinical experience indicated that full-dose gemcitabine requires a reduction of the radiation dose and modification of the treatment volumes. Radiation dose escalation in an initial phase I trial was achieved by increasing the fraction size and keeping the duration of radiotherapy at 3 weeks.[14] The current trial investigated the use of full-dose gemcitabine before and after a novel chemoradiation regimen with full doses of gemcitabine delivered with concurrent radiotherapy (36 Gy in 2.4-Gy fractions to the primary tumor alone over 3 weeks). The trial was designed to include patients with clearly unresectable disease and a second cohort of patients with potentially resectable cancers. The inclusion of patients with potentially resectable disease was based on a previous single-institution experience with patients who underwent surgical resection after full-dose gemcitabine and concurrent radiotherapy.[15]

The objectives of this phase II trial were (1) to evaluate the toxicity associated with this neoadjuvant regimen in a multi-institutional setting, (2) to determine radiographic, tumor marker, and pathologic responses to treatment, (3) to evaluate morbidity and mortality among patients who undergo resection after completion of therapy, and (4) to estimate overall survival in patients treated with this approach. We now report the results for patients entered onto the trial with potentially resectable pancreatic cancers.

PATIENTS AND METHODS

Eligibility and Evaluation

Between April 2002 and October 2003, 41 patients were entered onto this phase II trial from 5 participating institutions. Twenty patients were determined to have potentially resectable pancreatic cancers and make up the study population. Histological or cytological confirmation of adenocarcinoma of the pancreas was required. Patients with tumors in the head, uncinate process, and body or tail of the pancreas were eligible. Patients with tumors other than adenocarcinoma of the pancreas were excluded. Determination of resectability was based on helical computed tomography (CT) scan results by using criteria defined in the National Comprehensive Cancer Network guidelines for pancreatic cancer.[16] In borderline cases, further confirmation of resection potential with endoscopic ultrasonography or magnetic resonance imaging was required. Tumors were considered potentially resectable in the absence of extrapancreatic metastases and with no evidence of arterial encasement of the celiac and superior mesenteric arteries or occlusion of the superior mesen-

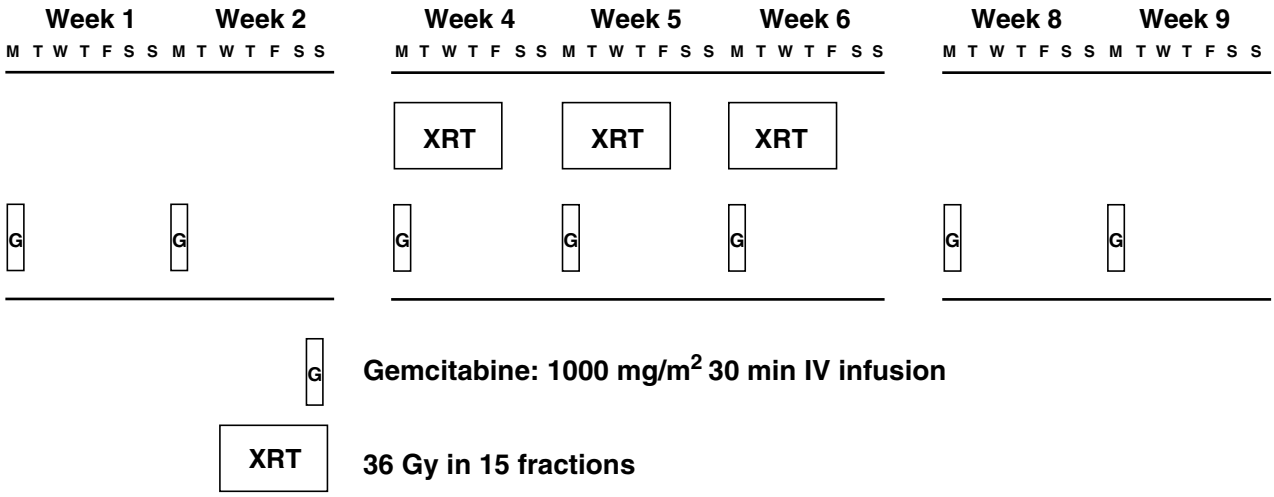

FIG. 1. Treatment schema of full-dose gemcitabine (1000 mg/m^2) and concurrent radiation (36 Gy in 2.4-Gy fractions). Gemcitabine was administered on days 1 and 8 of a 21-day cycle before and after a 28-day cycle of gemcitabine on days 1, 8, and 15 and concurrent radiation on days 1 to 19. XRT, radiotherapy.

teric vein and portal vein confluence. Further eligibility criteria included age ≥18 years, a Zubrod performance status of ≤2, and adequate hematological, hepatic, renal, and cardiac function. Pretreatment evaluation included a complete history and physical examination, chest radiograph, and CT scan of the abdomen. Patients with a history of upper abdominal radiotherapy or chemotherapy were ineligible. Patients with obstructive jaundice underwent endoscopic biliary decompression before beginning treatment. The institutional review board of each participating institution approved the trial, and written informed consent was obtained from all patients before the initiation of therapy.

During the preoperative phase of treatments, patients underwent regular assessments of body weight and performance status and routine laboratory studies. Surgery was planned approximately 6 weeks after the completion of therapy, and all patients underwent repeat staging studies to exclude disease progression.

Treatment Regimen

Gemcitabine was administered as a 30-minute intravenous infusion at a dose of 1000 mg/m^2 on days 1 and 8 of a 21-day cycle before and after a 28 day cycle of gemcitabine (1000 mg/m^2 days 1, 8, and 15) and concurrent radiation. The planned course of radiation was 36 Gy in 2.4 fractions to the gross tumor alone on days 1 to 19 (Fig. 1). Dose adjustments of gemcitabine were made on the basis of the toxicity experienced, including the absolute granulocyte count (AGC) and platelet count, taken on the day of therapy. A full dose was delivered for AGC ≥1,000 μL and platelets ≥75,000 μL. A 25% dose reduction was given for AGC ≥500 and <1,000 μL and/or platelets between 50,000 and 75,000 μL, and the dose was held for AGC <500 μL or platelets <50,000 μL. If gemcitabine was held during combined therapy, radiotherapy was also held. Treatment was resumed, if delayed, when toxicity had resolved to grade ≤2. There was a 1-week break between cycles and after the completion of the third cycle. The occurrence of gastrointestinal dose-limiting toxicity prompted discontinuation of radiotherapy and gemcitabine (if noted on the day of planned infusion). The occurrence of toxicities grade ≥3 in other organ systems prompted discontinuation of therapy while appropriate evaluation was performed. Treatment was not resumed unless recovery to grade <3 toxicity occurred in ≤2 weeks.

Three-dimensional radiotreatment planning was used in all cases. Treatment planning CT was obtained on a helical scanner with both oral and intravenous contrast. The gross tumor volume was the primary tumor identifiable on CT scan. The clinical target volume was defined as the gross tumor volume plus .5 cm. The planning target volume was the clinical target volume plus .5 cm for daily patient setup variation. No prophylactic nodal irradiation was given. Treatment planning was performed with the isocenter calculated at 100% and the 95% line encompassing 99.5% of the planning target volume. The spinal cord was limited to a generally accepted tolerance dose, considering the change in fraction size.

No more than 50% of the combined renal function was to receive >20 Gy. Generally, a three-field nonaxial beam arrangement (opposed laterals with an anterior-inferior oblique) was used, as previously described.[14] Before radiotherapy was initiated, the original CT scans, digital reconstructed radiographs of the radiotherapy fields, treatment plans, and dose-volume histograms were centrally reviewed (W.S. and C.J.M.) and adjusted if necessary.

Assessment of Treatment Responses and Surgical Outcomes

Radiographical responses were determined by a comparison of pretreatment CT and presurgical scans. A partial response was defined as at least a 30% decrease in the longest diameter of the primary tumor, taking as a reference the baseline longest diameter. A complete response was the disappearance of the primary tumor. Progression was defined as at least a 20% increase in the longest diameter of the primary tumor or the appearance of one or more new lesions. Stable disease was defined as neither a tumor response sufficient to qualify as a partial response nor an increase sufficient to qualify as progressive disease.

Information regarding surgical therapy after the completion of the protocol therapy included the type of operation performed, the duration of the operation, estimated blood loss, complications, including the 30-day mortality rate, and the length of stay. Surgical complications were defined as postoperative problems that resulted in a longer stay, reoperation, or readmission. Designated pathologists at each institution examined resected specimens, and their review included an assessment of the histological treatment response, the size of the primary tumor, resection margins, and lymph node status. Survival was calculated from the date of treatment initiation to the date of death or last follow-up. Survival curves were calculated by using the method of Kaplan and Meier.[17]

RESULTS

Patient and Primary Tumor Characteristics

There were 10 male and 10 female patients (Table 1). The median age was 58 years (range, 50–80 years). Seventeen cancers originated in the head of the pancreas, one tumor involved the head and neck of the pancreas, and two tumors were located in the body of the pancreas. The median pretherapy tumor diameter, measured from the preregistration CT, was 3.0 cm (range, 1.0–5.0 cm). The treating surgeon determined the initial assessment of resection potential with subsequent confirmation by the trial's surgical principal investigator (M.S.T.). Fourteen patients were considered to have clearly resectable disease according to National Comprehensive Cancer Network guidelines, and six patients were considered to have borderline resectable disease secondary to partial venous encasement or tumor abutting either the superior mesenteric or hepatic arteries.

TABLE 1. *Clinical characteristics of patients who received neoadjuvant gemcitabine and radiotherapy*

Variable	Data
Median age, y (range)	58 (50–80)
Male/female	10/10
Tumor location	
Head or uncinate process	18
Body/tail	2
Pretreatment tumor size (cm)	
Median	3.0
Range	1.0–5.0
Full course of therapy completed	20/20
Hospitalizations	0/20
Mean weight loss after therapy (%)	4
Surgery within 6 weeks of last infusion	20/20

Chemoradiation Toxicity and Surgical Results

Chemoradiation was delivered on an outpatient basis in all 20 patients. Nineteen patients (95%) completed therapy without interruption. One patient experienced hematological toxicity that necessitated gemcitabine dose reduction in each of the first two chemotherapy cycles. This included grade 3 neutropenia on day 8 of the first cycle and grade 3 neutropenia on day 15 of the second cycle. There were no incidences of significant thrombocytopenia. One patient was treated with erythropoietin for anemia and required a subsequent reduction in the gemcitabine dose because of weight loss. No patient experienced nonhematological toxicity that warranted dose reduction during chemotherapy alone. One patient experienced grade 3 gastrointestinal toxicity during the combined chemoradiation phase of treatments that caused a 1-week delay in treatment. The mean weight loss after therapy was 4%. All 20 patients completed the planned course of chemoradiation (36 Gy). All patients underwent operation within 6 weeks of the last gemcitabine infusion (Table 1).

At the time of exploration, two patients were found to have hepatic metastases, and one patient had partial encasement of the hepatic artery with soft tissue infiltration around the celiac axis. Seventeen patients (85%) underwent pancreatic resections (Table 2).

TABLE 2. *Results of surgery after neoadjuvant therapy*

Variable	Data
Resection rate	17/20 (85%)
Standard pancreaticoduodenectomy	15
Pyloric-preserving	1
Distal pancreatectomy and splenectomy	1
Vascular resections/reconstructions	5/17 (29%)
Operation time (h)	
Mean	7.5
Range	5–10.5
Estimated blood loss (mL)	
Mean	768
Range	250–2200
Length of stay (d)	
Median	13.5
Range	7–47
Major complication rate (%)	24
Mortality rate (%)	0

TABLE 3. *Response to therapy*

Variable	Data
Radiographic responses by CT comparisons	
Stable disease	16 (80%)
Partial response	3 (15%)
Possible progression	1 (5%)
CA 19-9 levels, U, median (range)	
Before treatment	359 (15–9951)
After treatment	35 (ND–1254)*
Pathologic findings and responses	
Median tumor size	3.0 cm
Treatment effect noted	17/17/ resected
>90% tumor destruction[a]	4/17 (24%)
Resection margins negative (R0)	16/17 (94%)
Regional nodes negative	11/17 (65%)

CT, computed tomography; ND, not detectable.
[a] One complete partial response.
* $P < .05$.

Fifteen patients underwent a standard pancreaticoduodenectomy, one patient had a pyloric-preserving Whipple procedure, and one patient had a distal pancreatectomy and splenectomy. Five (31%) of the 16 patients who underwent pancreaticoduodenectomy required combined vascular resection and reconstruction. The mean operative time for the Whipple procedures was 7.5 hours (range, 5–10.5 hours), and the mean estimated blood loss for those patients was 768 mL (range, 250–2200 mL). The complication rate was 24%, with a median length of stay of 13.5 days (range, 7–47 days) in all patients who underwent resection. There were three major postoperative complications: one patient required re-exploration on day 1 after surgery for bleeding at the gastrojejunal anastomosis, one patient required re-exploration for delayed gastric emptying and revision of the gastrojejunal anastomosis, and a third patient required readmission for percutaneous drainage of a liver abscess. There were no operative deaths.

Response

The response to treatment was determined by comparisons of pretreatment and posttherapy radiographic changes and CA-19.9 levels (Table 3). Resected specimens were examined to determine the estimated degree of pathologic response, tumor stage, and margin status. Evaluation for disease status by helical CT 4 to 6 weeks after completion of the last cycle of gemcitabine showed stable disease in 16 patients (80%) and partial response in 3 patients (15%). One patient had a questionable development of hepatic metastases. Sixteen patients had a ≥50% reduction in CA-19.9 levels after therapy. The median CA-19.9 value before treatment initiation was 359 U (range, 15–9951 U). The median CA-19.9 value after neoadjuvant treatment and before surgery was 35 U (range, not detectable to 1254 U; $P < .05$).

The pathologic findings in the 17 patients who underwent resection are listed in Table 3. The median tumor size was 3.0 cm. One specimen contained no residual tumor, and three specimens revealed only microscopic foci of residual disease (Fig. 2). Surgical resection margins revealed no microscopic evidence of cancer in 16 (94%) of the 17 resected specimens. The regional lymph nodes in 11 (65%) of 17 patients were uninvolved by metastatic disease.

Patient Outcomes and Recurrence Patterns

The median follow-up for the entire cohort was 18 months (range, 11.5–30 months). The median overall survival and 2-year survival rate for the 17 patients treated with preoperative therapy and surgical resection were 26 months and 61%, respectively (Fig. 3). Of the patients who underwent resection, 10 developed recurrent disease at a median time of 8 months from the operation (range, 3–16.5 months). Sites of recurrence were distant metastases in eight patients and locoregional disease in two patients. Seven patients (41%) remain alive with no evidence of recurrent disease, and among the four patients with either a complete pathologic response (one patient) or only scattered residual microscopic foci of disease (three patients), three remain alive with no evidence of disease at 14, 23.5, and 24 months from surgery.

DISCUSSION

Despite significant advances in preoperative staging and surgical resection for localized pancreatic cancer, most patients are not cured by pancreaticoduodenectomy alone. The treatment strategy of

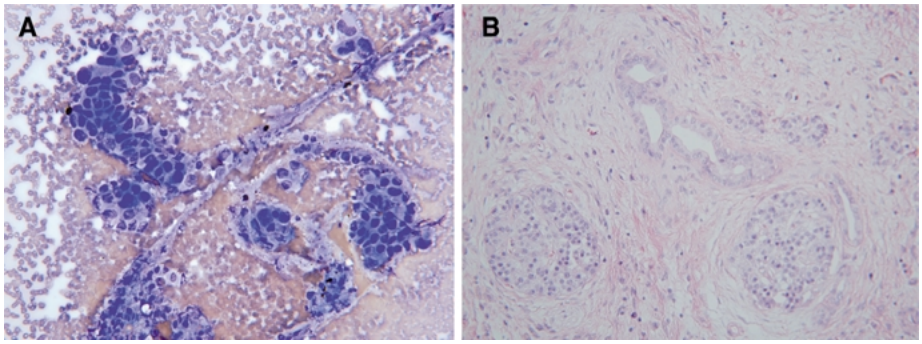

FIG. 2. Pretreatment cytological analysis and postsurgical pathologic specimen in a patient with a complete pathologic response after neoadjuvant chemoradiation. (**A**) Pretreatment aspiration cytological specimen demonstrating malignant glandular cells arising in the head of the pancreas. (**B**) Surgical specimen demonstrating posttherapy changes consistent with parenchymal fibrosis and acinar atrophy, but no evidence of residual malignancy.

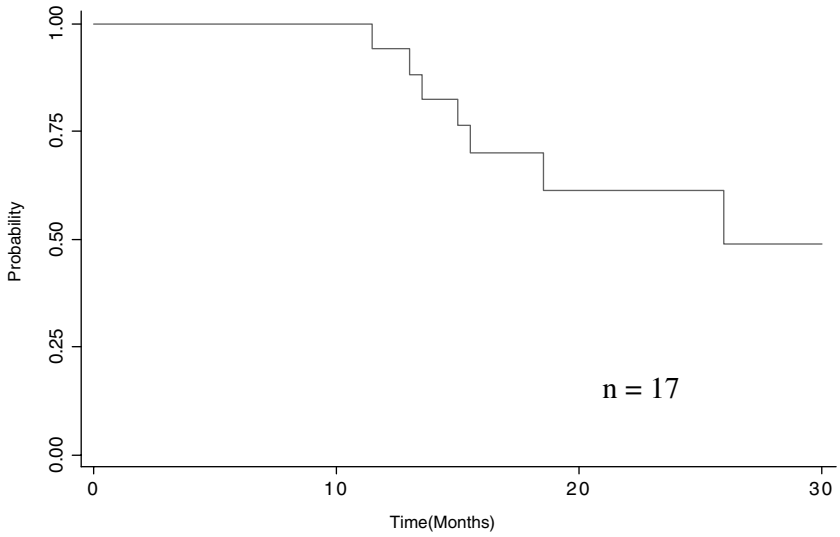

FIG. 3. Kaplan-Meier overall survival curve for patients treated with neoadjuvant gemcitabine/radiotherapy followed by pancreatic resection (n = 17). The median follow-up was 18 months (range, 11.5–30 months).

combined-modality therapy in pancreatic cancer is based in large part on data from serial Gastrointestinal Tumor Study Group trials that investigated 5-FU–based chemoradiotherapy.[1,18,19] A benefit of combined-modality therapy was observed compared with radiotherapy alone in patients with unresectable disease and compared with observations in patients who had undergone surgical resection. These studies provided the basis for clinical trials investigating adjuvant and neoadjuvant approaches in patients with localized pancreatic cancer for the next 20 years. Potential advantages of neoadjuvant therapy in pancreatic cancer patients have been well described and include the possibility of delivering full courses of chemotherapy and radiation without the potential delays caused by surgical complications and prolonged recovery times. A second potential advantage of neoadjuvant therapy is the avoidance of surgery in patients with rapidly progressive disease found on repeat staging studies after chemoradiation and before surgery.[20,21] Concerns regarding the safety of pancreaticoduodenectomy after chemoradiation have not been manifested in prior trials with either increased complication or mortality rates.[20–23] Unfortunately, clinical trials using 5-FU–based neoadjuvant chemoradiation have not resulted in significantly improved survival rates.[20–23] The use of gemcitabine with concurrent radiation represents an alternative approach to improve outcomes in patients with pancreatic cancer.

Gemcitabine is a deoxycytidine analogue (2′,2′-difluoro-2′-deoxycitidine or dFdCyd) and has been shown to provide a survival advantage over 5-FU in patients with locally advanced (unresectable) or metastatic pancreatic cancer, as well as symptomatic relief in patients with metastatic pancreatic cancer in

whom prior treatment with 5-FU has failed.[7,24] In addition, laboratory studies have demonstrated potent radiosensitization with gemcitabine in human cancer cell lines, including pancreatic cancer cell lines.[8,9] Since 1996, phase I trials have investigated the use of gemcitabine with concurrent radiotherapy in patients with locally advanced pancreatic cancer. Initial trials attempted to determine the maximum tolerable dose of gemcitabine when it was delivered once weekly, concurrent with a relatively conventional course of radiotherapy (50.4 Gy in 1.8-Gy fractions).[18] Considering the clinical benefit associated with the use of gemcitabine as a systemic agent, an alternative strategy used a standard dose of gemcitabine (1000 mg/m^2/week) and investigated the tolerable radiation dose that could be delivered to the primary tumor (without inclusion of the regional lymph node basins).[14] The goal of this approach was to maximize the systemic drug effect while providing local control through sensitization of a modest radiation dose. Escalation of the radiation dose was achieved by increasing the fraction size, thus keeping the duration of radiation at 3 weeks. After completion of this phase I trial, McGinn et al.[14] concluded that 36 Gy in 2.4-Gy fractions was the recommended dose for phase II investigation. Toxicity data from this trial and the prior trials of gemcitabine dose escalation with more conventional radiotherapy suggested that the volume of normal tissue radiated in gemcitabine-based chemotherapy regimens was the most critical consideration.[10–14] Therefore, radiation fields in this study were planned with three-dimensional radiotherapy planning and covered only the gross target volume with a 1-cm margin (i.e., there was no elective nodal radiotherapy). The current trial design consisted of a 21-day cycle of gemcitabine (1000 mg/m^2 days 1 and 8) before and after a 28-day cycle of gemcitabine (1000 mg/m^2 days 1, 8, and 15) delivered with concurrent radiotherapy (36 Gy in 2.4-Gy fractions to the primary tumor alone, days 1–19). Finally, data from a single-institution study at the University of Michigan demonstrated the feasibility of surgical resection after gemcitabine and radiation with acceptable toxicity and no operative deaths and served as the rationale to use this regimen in the neoadjuvant setting.[15]

The primary goal of this trial was to determine whether the single-institution experience that indicated the safety and potential efficacy of this novel chemoradiotherapy regimen could be demonstrated in a multi-institutional setting. Evaluation of acute toxicity demonstrated that this regimen was remarkably well tolerated. All 20 patients completed a full course of therapy. Only one patient experienced grade 3 gastrointestinal toxicity that necessitated a delay in treatment, none required hospitalization for acute toxicity, and all went to surgery within 6 weeks of the last chemotherapy infusion. These results compare favorably to those from previous neoadjuvant trials, which demonstrated hospitalization rates between 9% and 43% and dose-limiting toxicity rates between 20% and 50%.[3,20–23] Explanations for this acceptable toxicity profile include extremely strict inclusion criteria of patients with acceptable performance status and tumors that were truly likely to be resectable and, most importantly, the modification in radiation treatment fields. Prophylactic nodal irradiation was excluded, thereby minimizing the large volume of healthy tissue treated.

Investigators at M. D. Anderson Cancer Center reported significant gastrointestinal toxicity (43%) when weekly gemcitabine was delivered at doses ≥350 mg/m^2 with concurrent rapid fractionation (30 Gy in 3-Gy fractions). Treatment volumes reported with rapid fractionation included the primary tumor with a 3- to 5-cm margin, as well as the porta hepatis and celiac lymph nodes.[12] Relatively larger radiation fields were also used in a phase I Eastern Cooperative Oncology Group trial that examined the use of gemcitabine with concurrent protracted venous infusion of 5-FU and radiation (59.4 Gy in 1.8-Gy fractions) in locally advanced disease.[13] Despite low doses of gemcitabine (50 and 100 mg/m^2), significant gastrointestinal toxicity was seen in three of seven patients, and radiation field size was implicated in the toxicity encountered. Results from this trial indicate improved tolerance and decreased toxicity with full-dose gemcitabine when appropriate modifications in the delivery of radiation are made.

The current trial also confirmed the favorable response rates of this regimen demonstrated in the University of Michigan experience reported by Ammori et al.[15] In that study, pathologic evaluation revealed no evidence of malignancy in the surgical margins or regional lymph nodes in six of the nine patients who underwent resection after preoperative gemcitabine and radiation. Two patients had $<10\%$ viable-appearing tumor cells present, and one patient had destruction of 50% to 90% of tumors cells seen. The remaining patients all had some degree of tumor response, and the degree of fibrosis was considered to be extensive in six of the nine patients. A significant local treatment response was also seen in the preoperative gemcitabine/radiation trial at M. D. Anderson, with 58% of resected specimens showing at least

50% tumor cell kill.[25] There were also two pathologic complete responses—something not seen in any of their previous 5-FU–based protocols.[25] In the current trial, some degree of treatment response was seen in each resected specimen, and 4 (24%) of the 17 patients had >90% tumor destruction, with 1 complete pathologic response. Three of these patients remain alive with no evidence of recurrent or metastatic disease.

Single-institution trials using 5-FU–based neoadjuvant chemoradiation have reported resection rates between 53% and 70% for localized pancreatic cancer.[3,20–23] Hoffman et al.[22] reported a resection rate of 45% in a multi-institutional Eastern Cooperative Oncology Group trial that examined continuous infusional 5-FU, mitomycin, and conventional radiation (50 Gy in 1.8-Gy fractions). In the M. D. Anderson trial noted previously, the resection rate with gemcitabine and 30 Gy by using the rapid fractionation technique was 74%.[25] By using gemcitabine dose-escalation schemes and relatively fixed-dose conventional radiation, Fox Chase Cancer Center reported a resection rate of 65% in 63 patients variously treated since 1996.[26] In the pilot study of the current regimen performed at the University of Michigan, the resection rate was 52%.[15] The resection rate in the current multi-institutional trial was 85%. Also notable was the high rate of margin-negative resections (94%) and uninvolved lymph nodes (65%). This was especially encouraging considering that one of the tenets of this protocol was to limit gastrointestinal toxicity by foregoing prophylactic regional nodal irradiation. It seems from these studies that gemcitabine-based chemoradiation may result in a high rate of successful pancreatic resections and may be associated with a higher rate of margin-negative, node-negative resections than 5-FU–based chemoradiation or surgery alone. In addition, standard parameters of surgical quality, such as operative times, estimated blood loss, length of stay, and morbidity and mortality rates, were not appreciably different from those in previous reports of combined-modality trials in resectable pancreatic cancer; this supports the safety of this regimen.

In conclusion, this neoadjuvant trial of full-dose gemcitabine with concurrent radiation was well tolerated and safe when delivered in a multi-institutional setting. This regimen had a high rate of subsequent resection with acceptable morbidity rates. The high rate of clear margins, uninvolved lymph nodes, and pathologic responses suggests significant treatment effects, and preliminary survival data are encouraging. This design has the major advantage of providing full-dose systemic therapy to patients with early-stage (resectable) disease. These patients, who are likely to have the lowest systemic disease burden, may ultimately experience the greatest benefit from a neoadjuvant combined-modality regimen that emphasizes systemic therapy and maintains the benefit of local disease control with reduced risk of treatment-related toxicity. This novel combination of gemcitabine and radiotherapy should be considered in future clinical trials for patients with potentially resectable pancreatic cancer.

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