

Phase II Trial of Induction Gemcitabine/CPT-11 Followed by a Twice-Weekly Infusion of Gemcitabine and Concurrent External Beam Radiation for the Treatment of Locally Advanced Pancreatic Cancer

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Purpose: This phase II trial of induction irinotecan/gemcitabine followed by twice-weekly gemcitabine and upper abdominal radiation was initiated to determine the activity of this regimen in patients with unresectable pancreatic cancer.

Methods: Patients with locally advanced, nonmetastatic adenocarcinoma of the pancreas received 2 cycles of induction irinotecan (100 mg/m² IV) and gemcitabine (1000 mg/m² IV) on days 1 and 8 of each 3-week cycle. Following the induction, patients without disease progression received gemcitabine administered twice weekly (40 mg/m²/day) for 5 weeks concurrent with upper abdominal radiation (50.4 Gy over 5.5 weeks).

Results: From April 2000 to August 2003, 20 patients were entered into this study, 17 of whom were evaluable for treatment response. Characteristics included a median age of 67 years (range, 44–87 years) and 14 men (70%). Grades III and IV hematologic toxicity occurred in 25% and 5% of patients respectively and was primarily thrombocytopenia. No grade IV gastrointestinal toxicities or deaths due to therapy were observed. All therapy was completed in 8 patients, 7 patients were removed due to progression, 2 due to toxicity, 2 refused further treatment, and 1 was removed per the treating physician. The median time to progression and median survival was 5.1 months (95% CI, 3.2–6.7) and 8.8 months (95% CI,

6.4–10.1) respectively. Four patients (20%) were alive at 12 and 18 months.

Conclusion: Induction irinotecan/gemcitabine followed by twice-weekly gemcitabine and upper abdominal radiation is feasible in patients with locally advanced pancreatic cancer. This regimen, however, has only modest activity and should not be explored further.

Key Words: gemcitabine, irinotecan, radiation, pancreatic, cancer, locally advanced

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In 2004, an estimated 31,880 new cases of pancreatic cancer will be diagnosed in the United States, resulting in approximately 31,270 deaths from the disease. The overall 5-year survival rate for patients with pancreatic cancer is less than 5%, with little improvement in survival observed in the past 20 years.¹ Approximately two thirds of all pancreatic cancer patients have metastatic disease at the time of diagnosis,^{2,3} while the majority of the remaining patients have locally advanced, unresectable disease.^{4,5} Cures for patients with locally advanced/unresectable pancreatic cancer are anecdotal. In 1981 the Gastrointestinal Tumor Study Group (GITSG) published the results of a 3-arm randomized study comparing high-dose (60 Gy) radiation with or without 5-fluorouracil (5-FU) chemotherapy with moderate-dose (40 Gy) radiation with 5-FU. The median survival of both the high-dose and moderate-dose radiation groups receiving combined modality therapy exceeded that of the high-dose radiation alone group (40 weeks, 36 weeks, and 20 weeks respectively).⁶ As a result, several randomized trials utilizing combined modality therapy have attempted to improve on these results.^{7,8} With the exception of a report from the Eastern

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Cooperative Oncology Group,⁹ treatments incorporating 5-FU-based chemotherapy and radiation have yielded the best results and reflect the current standard of care.

Several centers are currently evaluating the use of neoadjuvant chemotherapy strategies in the setting of locally advanced pancreatic cancer in an attempt to improve systemic disease control. Chemotherapy delivered early in the course of therapy may potentially allow the oncologist to identify those patients with systemically aggressive disease who are destined to progress quickly and therefore are less likely to benefit from radiation treatments aimed at achieving local-regional tumor control. The challenge thus far, however, has been to discern a drug or combination of agents with consistent systemic activity in pancreatic cancer.

The complementary toxicity profiles and different mechanisms of cytotoxicity provided the rationale for the development of a gemcitabine and irinotecan combination. Preclinical studies suggested a synergistic interaction between gemcitabine and irinotecan.^{10,11} In a phase I study with both drugs given on days 1 and 8 of repeated 3-week cycles, the maximum tolerated doses were gemcitabine 1000 mg/m² given during a 30-minute infusion immediately followed by irinotecan 100 mg/m² infused during 90 minutes.¹² A phase II study at the maximum tolerated dose and schedule defined by the phase I experience showed that the combination was active and had an acceptable toxicity profile.¹³

The strategy to combine radiation and twice-weekly gemcitabine comes from a number of preclinical reports of increased radiation sensitization when the gemcitabine is dosed more frequently.^{14–18} This resulted in several phase I/II trials combining upper abdominal radiation and twice-weekly gemcitabine, with each suggesting this combination is safe and active at gemcitabine doses in the range of 40 to 90 mg/m².^{19–22} In a preoperative trial from Joensuu et al,²³ the investigators observed a median survival of 25 months for patients taken to resection after receiving twice-weekly gemcitabine and radiation. While survival in the Cancer and Leukemia Group B trial of twice-weekly gemcitabine and radiation for inoperable patients was only comparable with that expected with 5-FU-based chemoradiation, the regimen did result in acceptable toxicity.²⁴

This study was initiated to evaluate the combination of induction gemcitabine/irinotecan followed by radiation with concurrent twice-weekly gemcitabine for patients with locally advanced, unresectable pancreatic cancer.

PATIENTS AND METHODS

Patient Population

Patients age 18 to 70 years with a surgically confirmed diagnosis of locoregional adenocarcinoma of the pancreas by either laparoscopy or laparotomy were eligible. Inclusion criteria were the following: Eastern Cooperative Oncology

Group performance status (PS) of 0 to 2, determination of disease extent by laparotomy or laparoscopy and radiographic imaging, no prior abdominal radiation or chemotherapy, and adequate bone marrow (absolute neutrophil count, 1500 cells/mm³, platelet count, \geq 100,000 cells/mm³, and hemoglobin, \geq 10 g/dL), kidney function (serum creatinine <2.0 mg/dL), and liver function (serum total bilirubin <2 mg/dL). Patients with prior malignancy were ineligible for the study with the exception of those who had had nonmelanoma skin cancer, in situ cancer of the cervix, or other cancer for which the patient had been disease free for \geq 5 years.

All patients provided written informed consent according to federal and institutional guidelines. Institutional review board approvals were obtained at all participating sites.

Treatment and Evaluation

A complete course of therapy was defined as a total of 14 weeks or 3 cycles. Cycles 1 and 2 (weeks 1–6) incorporated the induction portion of the trial. Patients received 2 cycles of induction chemotherapy consisting of irinotecan at 100 mg/m² IV over 90 minutes and gemcitabine at 1000 mg/m² IV over 30 minutes on days 1 and 8 of each 3-week cycle, along with appropriate premedications and hydration. During the chemoradiation portion of the study, gemcitabine was delivered IV at a dose of 40 mg/m² over 30 minutes, twice weekly on either Monday and Thursday or Tuesday and Friday during the radiation therapy. The radiation was delivered to an initial dose of 45 Gy in 180-cGy daily fractions to the tumor and peripancreatic nodal regions plus a 1.0 to 2.0-cm margin. The celiac axis was treated at the discretion of the radiation oncologist. The boosted volume included the original tumor volume with a 1.0-cm margin and received an additional 5.4 Gy in 180-cGy daily fractions. While 3-dimensional treatment planning was encouraged, the specific technique, design, and configuration of the fields were individualized based upon the volume and location of the disease. Four field beam arrangements and 10 to 15-mV photon energies were required. In general, a 4-field approach used anterior–posterior and left–right lateral beams. The spinal cord dose was limited to 45 Gy. To decrease hepatic irradiation, the anterior–posterior fields were generally weighted more heavily than the laterals.

Dose Modifications, Response, Toxicity Criteria

During the induction chemotherapy, patients had irinotecan and gemcitabine doses reduced or withheld if they experienced a nadir granulocyte count of less than 1500/ μ L or a platelet count of less than 100,000/ μ L. The irinotecan dose was reduced 75% in cases of grade 2 diarrhea, and was withheld in patients with grade 3 or grade 4 diarrhea. During concurrent chemoradiation, gemcitabine was withheld in patients experiencing grade 2 or higher hematologic toxicity until blood counts recovered.

Standard Response Evaluation Criteria in Solid Tumors (or RECIST) criteria were used for response determination. Toxicity was graded according to National Cancer Institute Cancer Therapy Evaluation Program Common Toxicity Criteria, version 2.0. Patients were removed from the study if they had disease progression, unacceptable toxicity as determined by the treating physician, or a treatment delay of more than 2 weeks, or if they refused to participate. Patients were evaluated for response either clinically or radiographically following the induction chemotherapy but prior to the chemoradiation, then every 2 months the first year and then every 3 months. Weekly complete blood cell counts were required during treatment, and the use of myeloid growth factors was discouraged. CA-19-9 levels were collected prior to therapy. Disease progression was defined as the appearance of any new lesions on radiographic studies or in patients experiencing complications consistent with local–regional progression of disease, including new gastric outlet obstruction, duodenal obstruction, new bile duct obstruction, a decline in PS of at least 1 level, or the new development of ascites not associated with gemcitabine therapy.

Statistical Design and Analyses

The statistical analysis was performed at the Comprehensive Cancer Center of Wake Forest University Statistical Center. The Kaplan–Meier method was used to estimate the overall survival and failure-free survival distributions.²⁵ Overall survival was measured from the date of study entry until death due to any cause. Failure-free survival was measured from date of study entry until disease progression or death from any cause. The log-rank test was used to test differences in time-to-event distributions between patient subgroups.

RESULTS

Patient Characteristics

Patient registration and data collection were managed by the Wake Forest University Statistical Center. Data quality was ensured by careful review of all data by the Statistical Center staff and the study chairperson. The first early review of the data was planned after 60 patients were to be accrued. However, 7 of the first 20 patients (35%) experienced disease progression during the induction chemotherapy, which prompted an analysis of the first 20 patients. In addition, a phase III trial reported by Roche Lima et al²⁶ indicated the addition of irinotecan to gemcitabine in metastatic pancreatic patients provided no survival advantage. Given the clinical results in the first 20 patients and the data from Roche Lima et al,²⁶ the study was stopped when it was deemed the primary end point, an anticipated 3-month improvement in median survival, was not likely to be achieved.

The pretreatment characteristics of the patients entered onto this trial are listed in Table 1. Twenty patients were

TABLE 1. Patient Characteristics

Characteristic	
Total	20
Age	
Median (range)	67 (44–87)
≥60 years	16 (80%)
Gender	
Female	6 (30%)
Male	14 (70%)
Race	
African American	3 (15%)
White	17 (85%)
Performance Status	
0	4 (20%)
1	13 (65%)
2	3 (15%)

accrued to this study between April 2000 and August 2003. Eighty percent of the patients (16 of 20) were accrued at the Comprehensive Cancer Center of Wake Forest University, 2 were accrued by the Upstate Community Clinical Oncology Program (CCOP), and 2 by the Southeastern Cancer Control CCOP. Patients ranged in age from 44 to 87 years (median age, 67 years); 80% were 60 years old or older. Seventy percent of the patients were male; 85%, white; 20% were PS 0, 65% were PS 1, and 15% were PS 2.

Toxicity

Toxicities are summarized in Table 2. Most patients (16 or more) experienced some degree of hematologic toxicity, primarily thrombocytopenia. Other common toxicities included nausea and vomiting, diarrhea, and malaise/fatigue, each of which occurred in more than half the patients. Of the 12 patients not completing therapy, 2 were removed for toxicity. Grade III gastrointestinal toxicities were observed in 8 patients, 3 during the induction CPT-11/gemcitabine chemotherapy. No correlation with radiation treatment volume

TABLE 2. Toxicities

Toxicity	Grade II (%)	Grade III (%)	Grade IV (%)
Hematologic			
Neutropenia	20	20	5
Thrombocytopenia	40	5	0
Anemia	55	0	0
Nonhematologic			
Nausea and Vomiting	5	35	0
Diarrhea	0	20	0

and the development of a grade III gastrointestinal toxicity during the chemoradiation portion of the study could be determined. Mean radiation treatment volume for patients experiencing a grade III toxicity ($n = 5$) was $136 \pm 17.6 \text{ cm}^2$ versus $154 \pm 23.4 \text{ cm}^2$ for all other patients. No gastrointestinal bleeding or perforations were observed.

Survival and Patterns of Failure

All patients are off study. Eight completed therapy as specified in the protocol, 7 were removed due to progression, 2 were removed due to toxicity, 2 refused further treatment, and 1 was removed per the physician's decision. Two patients remain alive, 1 with and 1 without disease progression. Seventeen of the 20 patients were evaluable for tumor response. There were no complete responders. Two patients (12%) exhibited partial responses (95% CI, 1–36). Eleven patients (65%) had stable disease and 4 (24%) progressed initially. Fifteen patients eventually experienced disease progression. The majority of patients failed in the liver (43%) as the first site of disease progression. Four others died of their disease and are considered to have progressed halfway between their on-study date and their date of death.

The median time to progression was 5.1 months (95% CI, 3.2–6.7) with a range from 0.3 to 24.7 months. Sites of progression were documented for 14 patients. The pancreas, liver, and pleural effusion were the most common sites of progression. The median survival for all patients was 8.8 months (95% CI, 6.4–10.1) with a range from 0.6 to 24.7 months. Four patients (20%) were alive at 18 months post-treatment. Kaplan–Meier estimated survival and time-to-progression curves are shown in Figure 1. Neither age nor race nor gender was significantly associated with either time to progression or survival. The median survival for patients completing the induction chemotherapy was only slightly improved to 9.6 months (95% CI, 8.6–10.4).

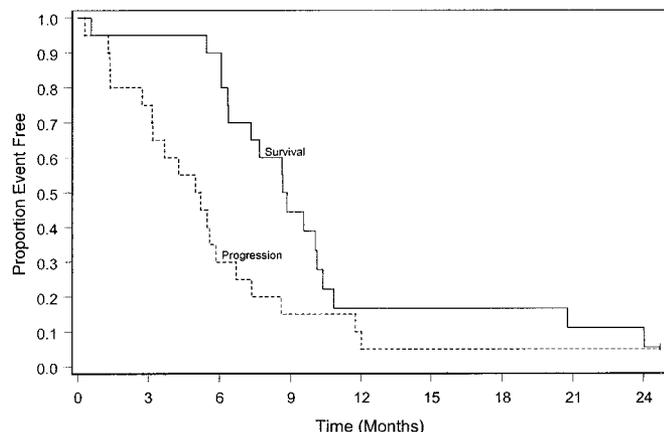


FIGURE 1. Kaplan-Meier progression free and overall survival.

DISCUSSION

This multicenter phase II study evaluated the feasibility and efficacy of induction irinotecan/gemcitabine followed by radiation and twice-weekly gemcitabine with respect to response, time to progression, and survival in patients with locally advanced pancreatic cancer. As presented in the introduction, the series of GITSG trials have established that bolus 5-FU and concurrent radiation yields a median survival in the range of 8 to 10 months and reflects the current standard of care. Limited data would suggest 5-FU delivered via a protracted venous infusion (200–250 mg/m² daily) during radiation is comparable with bolus 5-FU.²⁷

In this trial we elected to proceed with 2 21-day cycles of induction chemotherapy. Most patients with locally advanced pancreatic cancer receiving definitive chemoradiation will progress systemically prior to death. By initiating 2 cycles of neoadjuvant chemotherapy prior to the chemoradiation, we hoped to delay the systemic progression of disease for those patients with chemosensitive disease. This strategy potentially allows us to define patients who are likely harboring occult metastatic disease at the time of treatment and who are not likely to benefit from a local–regional treatment modality. The median survival for patients able to complete the induction chemotherapy, however, was only slightly improved, from 8.8 months to 9.6 months, emphasizing the challenge of discovering a systemically active chemotherapy regimen for this disease.

The systemic activity of gemcitabine/irinotecan in patients with advanced pancreatic cancer was initially reported in 2 phase II trials. Rocha Lima et al¹³ reported a 24% partial response rate among 45 patients with unresectable or metastatic pancreatic cancer receiving 1000 mg/m² gemcitabine and 100 mg/m² irinotecan on days 1 and 8 every 21 days. Stathopoulos et al,²⁸ employing a similar 21-day treatment schedule but a higher dose of irinotecan (300 mg/m²) that is only given on day 8, reported an objective overall response rate of 25% and a very encouraging median time to progression of 7 months. The subsequent phase III trial results reported by Roche Lima et al,²⁹ however, were disappointing. In that randomized trial of 342 patients, the addition of irinotecan to standard-dose gemcitabine provided no survival advantage. The median time to progression and median survival for patients receiving irinotecan and gemcitabine were 3.5 months and 6.3 months respectively versus 3.0 months and 6.6 months respectively for patients receiving single-agent gemcitabine. Our experience in this trial would also suggest this regimen has only modest activity in patients with locally advanced disease. Approximately one third of patients progressed during the 6 weeks of induction irinotecan/gemcitabine chemotherapy.

The lack of improved systemic efficacy when combining gemcitabine with other agents in the setting of metastatic pan-

creatic cancer is not unique to the Rocha Lima trial. Louvet et al,³⁰ in a 326-patient trial comparing single-agent gemcitabine with a gemcitabine/oxaliplatin doublet, observed an improved response rate and progression-free survival, but not a statistically significant overall survival advantage (median survival of 7.1 months with single-agent gemcitabine vs 9.0 months with gemcitabine/oxaliplatin; $P = 0.13$). In 4 separate recently reported phase III trials, the first testing a gemcitabine/5-FU doublet, the second a gemcitabine/cisplatin doublet, the third a gemcitabine/alimta doublet, and the fourth a gemcitabine/topoisomerase-1 inhibitor doublet, no survival advantage was seen over single-agent gemcitabine.^{31–34}

Currently, a number of investigators are integrating novel, molecularly targeted therapies into standard regimens. An initial experience comes from Kindler et al,³⁵ who recently reported the results of a phase II trial evaluating gemcitabine and bevacizumab, a recombinant humanized monoclonal antibody to the vascular endothelial growth factor (VEGF). In this trial of 42 patients with advanced/metastatic pancreatic cancer, the investigators report an encouraging median time to progression time of 5.8 months and a median survival of 9.0 months. This regimen is currently being evaluated in a phase III study against single-agent gemcitabine (Cancer and Leukemia Group B 80303). In a related experience, Xiong et al³⁶ recently reported the results of an M.D. Anderson phase I/II study evaluating cetuximab, a chimeric monoclonal antibody to the epidermal growth factor receptor (EGFR) in patients with measurable locally advanced or metastatic pancreatic cancer. All patients were chemotherapy naive and had immunohistochemical evidence of EGFR expression. Patients were treated with cetuximab at an initial dose of 400 mg/m², followed by 250 mg/m² weekly for 7 weeks. The gemcitabine was administered at 1000 mg/m² for 7 weeks, followed by 1 week of rest. In subsequent cycles, cetuximab was administered weekly, and gemcitabine was administered weekly for 3 weeks every 4 weeks. The investigators report acceptable toxicity and an encouraging median survival duration of 7.1 months. One-year progression-free survival and overall survival rates were 12% and 31.7% respectively. Clearly additional studies with other innovative molecularly targeted compounds and strategies need to be completed.

In conclusion, this phase II study confirms the feasibility and generally acceptable overall toxicity profile of induction irinotecan/gemcitabine followed by twice-weekly gemcitabine concurrently with upper abdominal radiation therapy. The activity of this regimen, however, is only modest and comparable with those results achieved with 5-FU-based chemoradiation. Future studies for patients with locally advanced pancreatic cancer will likely build on the encouraging results reported by Kindler et al³⁵ and Xiong et al,³⁶ and will incorporate agents that target VEGF and EGFR.

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