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Irinotecan/Gemcitabine Followed by Twice-Weekly Gemcitabine/Radiation in Locally Advanced Pancreatic Cancer

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ABSTRACT:

Early clinical studies combining irinotecan (CPT-11, Camptosar) and gemcitabine (Gemzar) have yielded encouraging results. Gemcitabine administered via a twice-weekly schedule results in an enhanced radiation-sensitizing effect. This multi-institution phase II trial of induction irinotecan/gemcitabine followed by twice-weekly gemcitabine and upper abdominal radiation has been initiated to determine the activity of this regimen in patients with unresectable pancreatic cancer. Patients received two cycles of induction irinotecan (100 mg/m IV) and gemcitabine (1,000 mg/m IV) on days 1 and 8 of each 3-week cycle. Following the induction therapy, patients without disease progression received twice-weekly gemcitabine at 40 mg/m and radiation. Nine patients have been enrolled in the study to date. Median patient age was 71 years (range: 65-85 years). The major toxicity observed thus far was grade 3/4 neutropenia. Grade 3/4 nonhematologic toxicity was rarely observed and included dehydration (12%) and diarrhea (12%), which were likely related to the irinotecan. No treatment-related deaths have occurred. These preliminary data suggest that this regimen is well tolerated. Although the data are limited, tumor progression during the induction chemotherapy has not been observed thus far (radiographically or biochemically [CA-19-9]). [ONCOLOGY 16(Suppl 5):25-28, 2002]

In 2002, an estimated 30,300 new cases of pancreatic cancer will be diagnosed, and 29,700 people will die from the disease. The overall 5-year survival rate for patients with pancreatic cancer ranges from less than 1% to 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]

Several chemotherapeutic agents have been evaluated either alone or in combination in patients with metastatic pancreatic cancer, but the results continue to be disappointing: reproducible objective response rates range from 0% to 20% and median survival times are less than 6 months.[6-9] Results for patients presenting with locally advanced (nonmetastatic) unresectable disease have also been disappointing. The combination of concurrent fluorouracil (5-FU) and ionizing radiation therapy for patients with unresectable disease has resulted in a twofold increase in median survival: approximately 10 months vs 5 months.[10-12] Despite these limited benefits, many consider external beam radiation and concurrent 5-FU as the standard therapy for locally advanced pancreatic cancer.

In an attempt to improve systemic disease control, which could possibly impact overall survival, investigators at several centers are testing neoadjuvant chemotherapy strategies. Such strategies have potential advantages for patients with pancreatic cancer. The morbidity of definitive chemoradiation is not insignificant, and can thwart the possibility of using systemic chemotherapy. In addition, preoperative chemotherapy allows the oncologist to identify those patients with aggressive disease who are destined to progress quickly—specifically, patients with micrometastatic disease who are less likely to benefit from a course of locoregional chemoradiotherapy. While induction chemotherapy has several potential advantages, a challenge for investigators is to discover a regimen with consistent activity in pancreatic cancer.

Irinotecan/Gemcitabine for Advanced Pancreatic Cancer

Results of phase I and II clinical trials have demonstrated that single-agent irinotecan (7-ethyl-10-[4-(1-piperidino)-1-

piperidino]carbonyloxycamptothecin [CPT-11, Camptosar]), a camptothecin analog, has activity in pancreatic cancer. In previously untreated patients with advanced pancreatic cancer, Sakata et al reported an 11% partial response rate (4 out of 35 patients) using irinotecan at 100 mg/m²/wk or 150 mg/m² every other week.[13] Wagener et al observed three partial responses among 32 patients (9%) with pancreatic cancer who received irinotecan at 350 mg/m² by 30-minute intravenous infusion every 3 weeks.[14] Response durations were 7.2, 7.5, and 7.8 months.

In contrast, O'Reilly et al evaluated topotecan (Hycamtin), another topoisomerase I inhibitor, in 27 previously untreated advanced pancreatic cancer patients, and noted no responses.[15] Scher et al, however, reported three (10%) partial responders in a similar patient cohort receiving a comparable topotecan dosing schedule. Additional information on this combination has been discussed by Rocha Lima et al elsewhere in this supplement.

Use of a gemcitabine/irinotecan combination regimen seems attractive, based on the complementary toxicity profiles, different mechanisms of cytotoxicity, and overlapping antitumor activity spectra of the two compounds.[16]

Concurrent Radiation and Gemcitabine

Early results of limited phase I/II trials that combined radiation and gemcitabine have been reported.[17-20] Data from a phase I study from Wake Forest University/University of North Carolina Chapel Hill determined that the maximum tolerated dose of concurrent twice-weekly gemcitabine with upper abdominal radiation was 40 mg/m² given each Monday and Thursday of the radiation.[21] The preliminary Cancer and Leukemia Group B report of this regimen in the phase II setting indicated that it was safe and feasible. While only four local (in-field) failures were observed, systemic disease progression limited median survival to 13.7 months and 7.8 months in patients with Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 1 to 2, respectively. These data support that gemcitabine/irinotecan is an active systemic regimen in pancreatic cancer and that radiation with concurrent twice-weekly gemcitabine provides effective local tumor control for patients with locally advanced pancreatic cancer. The phase II trial reported herein is assessing the effects of these regimens used in combination for patients with locally advanced, unresectable pancreatic cancer. The trial objectives are to determine time to disease progression, local control, and survival for patients receiving induction gemcitabine/irinotecan followed by twice-weekly gemcitabine and concurrent radiation.

Materials and Methods

Patient Eligibility and Treatment

Eligibility criteria are outlined in <u>Table 1</u>. Patients with nonmetastatic, unresectable pancreatic cancer were eligible for study entry. ECOG performance status of 1 to 2 and life expectancy of at least 6 months were required, as were normal laboratory assessments of granulocyte, hemoglobin, platelet, and serum creatinine levels. All patients provided written informed consent.

Patients received two cycles of induction chemotherapy consisting of irinotecan at 100 mg/m² IV over 90 minutes and gemcitabine at 1,000 mg/m² IV over 30 minutes on days 1 and 8 of each 3-week cycle along with appropriate premedications and hydration. Following induction therapy, patients without disease progression received twice-weekly gemcitabine at 40 mg/m² on each Monday and Thursday of the radiation (Figure 1).

Radiation therapy consisted of an initial 45 Gy in 180-cGy daily fractions delivered to the tumor and peripancreatic nodal regions plus a 1.0- to 2.0-cm margin (to account for setup variation, patient motion, and tumor volume uncertainty). The celiac axis was treated at the discretion of the radiation oncologist. An additional 5.4-Gy boost was delivered in 180-cGy daily fractions to the original tumor volume with a 1.0-cm margin. The fields were individually designed and configured based on tumor volume and location. Four-field beam arrangements and 10- to 15-mV photon energies were required. In general, a four-field approach utilized anterior-posterior and left and right lateral beams. The spinal cord dose was limited to 45 Gy.

Dose Modifications and Response and Toxicity Criteria

During induction chemotherapy, patients had irinotecan and gemcitabine doses reduced or withheld if they experienced a nadir granulocyte count of less than 1,500/µL or a platelet count of less than 100,000/µL (<u>Table 2</u>). The irinotecan dose was reduced 75% in cases of grade 2 diarrhea, and was withheld in patients with grade 3 or 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 (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 greater than 2 weeks, or if they refused to participate.

Results

Patient Characteristics

Nine patients have been enrolled in the study to date, seven of whom completed therapy as planned: one patient refused further therapy after the first dose while a second patient is currently under treatment. Neither patient is assessable for toxicity or survival. The median patient age was 71 years (range: 65-85 years) and 33% of patients were female. Performance status was 0 in four patients and 1 in five patients.

Efficacy

Two of eight patients (29%) had an objective response to treatment. No complete responses were observed. All of the seven evaluable patients have progressed, with liver metastasis (n = 4) as the most common site of failure, followed by the lungs. One patient has progressed in the radiation field (14%) as the initial failure site. Median overall survival in this preliminary analysis is 9 months from registration (10 months from diagnosis). The median pretreatment CA-19-9 level was 426 U/mL (range: 15-14,167 U/mL). A reduction in CA-19-9 from pretreatment of greater than 50% was observed in two patients, and that greater than 35% was observed in another two patients.

Toxicity

Seven patients were assessable for toxicity. The major toxicity was grade 3/4 neutropenia (n = 3). Grade 4 thrombocytopenia and anemia occurred infrequently. Grade 3/4 nonhematologic toxicity was rarely observed and included dehydration (12%) and diarrhea (12%), which were likely related to the irinotecan. No treatment-related deaths have occurred. Four of the seven patients required dose reductions or held doses. Two patients did not complete induction chemotherapy as planned due to neutropenia but did go on to receive the concurrent twice-weekly gemcitabine and radiation. Four patients have completed all 10 doses of twice-weekly gemcitabine, with thrombocytopenia representing the dose-limiting toxicity.

Conclusions

This is a preliminary report of a multicenter, phase II study of induction irinotecan/gemcitabine chemotherapy followed by radiation and twice-weekly gemcitabine in patients with locally advanced pancreatic cancer. These early results indicate that this approach is safe in such patients. The observed grade 3/4 toxicities were limited to those expected in patients receiving irinotecan and gemcitabine, and were primarily gastrointestinal and hematologic in nature. Although the data so far are limited to eight patients, no local tumor progression has been demonstrated radiographically, biochemically (CA-19-9), or clinically during the induction chemotherapy.

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