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CLINICAL INVESTIGATION **Pancreas**

CAPECITABINE AND RADIATION THERAPY PRECEDED AND FOLLOWED BY COMBINATION CHEMOTHERAPY IN ADVANCED PANCREATIC CANCER

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Purpose: The primary objective of this study was to evaluate the tolerance and toxicity of radiation therapy (RT) and capecitabine in patients with advanced, unresectable pancreatic carcinoma. To control micrometastatic disease, combination chemotherapy (gemcitabine and cisplatin) before and after combined modality therapy (CMT) was planned.

Methods and Materials: Patients with unresectable or metastatic pancreatic cancer were eligible. Gemcitabine 1000 mg/m^2 and cisplatin 35 mg/m^2 were administered on Days 1 and 8 of a 21-day cycle for two cycles. RT was then given to a dose of 50.4 Gy in 1.8 Gy fractions. Patients were treated with capecitabine 1330 mg/m^2 daily during RT. After CMT, two additional cycles of gemcitabine and cisplatin completed the treatment.

Results: Twenty-three patients were treated. Eighteen patients completed CMT. One patient was removed from study during CMT for toxicity issues. Treatment delays and dose reductions were common during the final two cycles of gemcitabine and cisplatin as a result of myelosuppression. Median survival was 10.1 months (95% confidence interval [CI] = 7.6, 13.7) for all 23 patients and 12.8 months (95% CI = 8.2, 18.9) for 18 patients without metastasis.

Conclusion: Combined modality therapy with RT and capecitabine was well tolerated. Chemotherapy after CMT was difficult to complete owing to cumulative myelosuppression. Survival, response, and toxicity were comparable to infusional 5-fluorouracil and RT. © **2005 Elsevier Inc.**

Pancreatic cancer, Capecitabine, Radiation therapy.

INTRODUCTION

Pancreatic cancer is diagnosed in just over 30,000 people in the United States each year, with the incidence and mortality rates nearly matched (1). Of those that undergo surgical resection of limited disease, the 5-year survival approximates 20%, with some evidence that adjuvant treatment affects survival (2, 3). For the majority of patients presenting with locally advanced or metastatic disease, palliative options are limited to chemotherapy and radiation treatment. Current therapeutic approaches using these modalities in advanced disease have had a modest impact at best (4, 5).

Still, these modalities have shown promise as adjuvant therapy after surgery, as neoadjuvant therapy, and as a means of local tumor control and palliation. Patients treated with combined modality therapy (CMT) after surgical resection have improved survival compared with surgery alone (6–9). Patients treated neoadjuvantly have had evidence of pathologic response at resection, and rare patients with borderline or unresectable disease are subsequently resected after CMT (10–12). Our previous work in patients with advanced pancreatic cancer, using radiation therapy (RT) with full-dose gemcitabine ± cisplatin, attempted to maximize local and systemic disease control and suggested impact on patterns of and time to failure (11, 13). Despite these observations, CMT needs to be further developed and refined in pancreatic cancer.

Radiation therapy with concurrent 5-fluorouracil (5-FU) is a common approach worldwide in the treatment of pancreatic adenocarcinoma. Capecitabine is an oral prodrug of 5-FU that mimics intravenous infusion schedules as evidenced by similar serum drug levels and toxicity profiles (14–16). In a Phase II trial in advanced pancreatic cancer, capecitabine administered twice daily for 14 days, followed by a 7-day rest, was well-tolerated and demonstrated favor-

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able clinical effects as evidenced by time to progression, survival, and clinical benefit response (17). In a Phase I study without RT, capecitabine was well-tolerated continuously for 6 weeks and a dose of 1330 mg/m^2/day was recommended for Phase II testing (18). Initial investigations of oral fluoropyrimidine treatment in CMT have been concentrated in rectal cancer, where the approach appears tolerable and effective (19, 20). The use of an oral agent like capecitabine for CMT of pancreatic cancer is appealing, because it avoids the inconvenience of central venous catheterization and ambulatory pump delivery systems needed for infusions of 5-FU.

Control of distant disease remains a challenge in the treatment of pancreatic adenocarcinoma. Gemcitabine in combination with cisplatin has been studied in patients with advanced pancreatic cancer and demonstrated improved response rates, time to progression, and trends toward increased survival, as compared with gemcitabine alone (21–23). Full doses of each drug are possible given the nonoverlapping dose-limiting toxicities of each agent.

With these considerations, we designed a pilot study to evaluate the tolerability and toxicity of RT and capecitabine. In an effort to improve on distant disease control, combination chemotherapy with gemcitabine and cisplatin preceded and followed CMT. An objective of this trial was to provide pilot data with capecitabine/RT for subsequent Phase II or Phase III trials evaluating CMT with capecitabine and gemcitabine in patients with unresectable or resectable pancreatic cancer.

PATIENTS AND METHODS

Eligibility

Eligibility criteria for study entry included cytologic or histologic confirmation of pancreatic carcinoma. Patients were required to be unresectable, with or without distant metastases, as determined by helical computed tomography (CT) scan and surgical consultation. Pretreatment evaluation included a complete history and physical examination, baseline assessment of organ function, chest X-ray, and CT scan of the abdomen. Further eligibility criteria included age 18 or older, Zubrod performance status $\leq$2 and adequate organ function as defined by neutrophils $\geq$1500/mm^3, platelets $\geq$100,000/mm^3, serum creatinine $\leq$1.5 mg/dl and bilirubin $<$3 mg/dl. Patients with reproductive potential were required to use effective contraception during treatment.

Patients with a history of previous abdominal irradiation or chemotherapy for pancreatic cancer were ineligible. In addition, patients could not have another active systemic malignancy or any serious comorbid medical or psychiatric condition that might interfere with the safe delivery of therapy. The institutional review board of the University of Michigan Medical School (Ann Arbor, MI) approved the trial. Written informed consent was obtained from all patients before initiation of therapy.

Treatment

Protocol treatment consisted of two 21-day cycles of gemcitabine (Eli Lilly and Co., Indianapolis, IN) and cisplatin (Bristol-Myers Squibb, Princeton, NJ) followed by 5½ weeks of RT to the primary pancreatic tumor and regional lymph nodes, plus daily capecitabine (Roche Laboratories, Nutley, NJ). Upon completion of CMT, patients received two additional cycles of cisplatin and gemcitabine if the clinical course and toxicity permitted.

Initial chemotherapy consisted of gemcitabine 1000 mg/m^2 as a 30-min intravenous infusion, in combination with cisplatin 35 mg/m^2 as a 30-min infusion, administered 1 to 2 h after the gemcitabine on Days 1 and 8 of a 21-day cycle. Capecitabine plus RT followed the two cycles of combination chemotherapy. Capecitabine was administered 7 days per week as a daily dosage of 1330 mg/m^2 in two divided doses. Total daily dosage was calculated, and rounded to the nearest 500 mg. Morning and evening doses were taken 11 to 13 h apart with the odd tablet added to the morning dose, if necessary. Capecitabine was continued daily during the entire course of RT. After capecitabine and RT, patients completed treatment with two cycles of gemcitabine and cisplatin as above.

The initial radiation target included the primary tumor and draining lymph nodes. A 2- to 3-cm margin was included in all directions. The superior border of the fields was placed at the level of T10–T11 interspace to cover the celiac axis nodes. The inferior field border was placed at the level of L3 or lower to encompass the entire tumor. The right lateral border included the portal vein, the hepatic artery, and the common bile duct as well as the head of the pancreas with the appropriate margin. This was generally 4 to 5 cm to the right of the midline. The left lateral border extended 2 to 3 cm beyond the tumor. A cone down included the primary tumor with a 1.5-cm margin in all directions. All fields were treated each day, 5 days per week, using 1.8 Gy fractions. A total of 45 Gy was delivered to the initial fields with an additional 5.4 Gy delivered via the boost fields. A standard 3-field beam arrangement was used (posteroanterior and opposed laterals). Wedges were used for lateral fields to improve homogeneity. The equivalent of two-thirds of one kidney (at a minimum) had to be kept below 22.5 Gy. The dose to the spinal cord was limited to 45 Gy, and no more than one-half of the liver was allowed to receive more than 30 Gy.

Dose adjustments for toxicity

Based upon blood counts on the day of treatment, full doses of gemcitabine and cisplatin were delivered for Absolute Neutrophil Count (ANC) $\geq$1000/mm^3 and platelets $\geq$75,000/mm^3; but a 30% dose reduction for both drugs was given when ANC $\geq$500/mm^3 and $<$1000/mm^3 and/or platelets $>$51,000/mm^3 and $<$75,000/mm^3. A cycle was delayed or a treatment was dropped (Day 8 of a cycle) for ANC $<$500/mm^3, platelets $\leq$50,000/mm^3, or grade $\geq$3 nonhematologic toxicity. A treatment cycle could begin when toxicity resolved to $\leq$ Grade 1. If $\geq$ Grade 3 nonhematologic toxicity was observed at any point, or a dose was dropped because of hematologic toxicity, then subsequent cycles of both gemcitabine and cisplatin doses were reduced by 30%. Cisplatin was held for a serum creatinine $\geq$1.4 mg/dL on the day treatment was due, and the dose was reduced by 30% for all subsequent treatments. If patients experienced $\geq$ Grade 2 neurotoxicity or nephrotoxicity from cisplatin, cisplatin was discontinued and treatment with gemcitabine alone was administered.

Combined modality therapy with radiation plus capecitabine was continued provided weekly blood counts demonstrated a white blood cell count $\geq$2000/mm^3 and platelet count $\geq$50,000/mm^3. Both treatments were held for a white blood cell count $<$2000 or platelets $<$50,000 and treatment resumed once the blood counts recovered to the above parameters. Grade $\geq$3 diarrhea, nausea, anorexia, radiation dermatitis or Grade $\geq$2 vomiting resulted in

CMT interruption and reduction of capecitabine dose by 1000 mg/day once toxicity resolved to ≤ Grade 1. A second interruption of treatment despite capecitabine dose reduction resulted in permanent discontinuation of capecitabine and completion of RT. Patients experiencing ≥ Grade 2 stomatitis/esophagitis and/or hand-foot syndrome had capecitabine held and continued with radiation alone. Capecitabine therapy was resumed when drug-specific toxicity resolved to ≤ Grade 1. Criteria for removal from protocol treatment included evidence of progressive disease, patient refusal to continue therapy, treatment interruption >2 weeks, or unacceptable toxicity which despite protocol-specified adjustments, required treatment cessation.

Assessment of toxicity and response

Patients were examined at least once weekly during the course of RT, and at least on one occasion during each cycle of gemcitabine and cisplatin. All toxicities encountered during the study were evaluated using the National Cancer Institute Common Toxicity Criteria Version 2.0 (http://ctep.cancer.gov/reporting/ctc.html). Patients returned for an evaluation of acute toxicity after the last dose of chemotherapy. Helical CT scan was performed on the patients after completion of CMT and again after completion of all therapy. Response was assessed using the Response Evaluation Criteria in Solid Tumors (24).

Statistical considerations

The study intent was to evaluate CMT in 15 patients. Three of the initial 15 patients enrolled did not begin CMT, so the study was amended and an additional 8 patients were accrued. Survival was measured from the day of registration on study until death from any cause. The time to treatment failure was measured from the day of registration on study until disease progression, removal from treatment as a result of toxicity, refusal, or death from any cause. Statistical analyses were performed in SAS v9.1. Survival curves were produced using the product-limit (Kaplan-Meier) method. Confidence intervals for median survival were determined using the sign test. Likelihood ratio confidence intervals were reported for binomial proportions.

RESULTS

Patient characteristics and treatment received

Between January 2002 and November 2003, 23 patients were registered to the study. The median age of study participants was 61 years (range, 39–74 years). There were 9 men and 14 women. Baseline Zubrod performance status was 0 in 13 subjects, 1 in 8 subjects, and 2 in 2 subjects. Eighteen patients had an elevated baseline CA 19-9 (median value in all 23 patients, 2538 U/mL; range, 3 to 209,252 U/mL). Five patients had metastatic disease at the time of protocol entry. Patient characteristics are summarized in Table 1.

Table 1. Patient characteristics

Number of patients	23
Sex (men/women)	9/14
Race (Caucasian/African American)	21/2
Median age, years (range)	61 (39–74)
Zubrod performance status (0/1/2)	13/8/2
Initial stage (locally advanced/metastatic)	18/5

Twenty-one patients completed the initial two cycles of gemcitabine and cisplatin. One patient developed azotemia with a first infusion and died from a pulmonary embolus 10 days from treatment initiation. A second patient developed Grade 2 nephrotoxicity and a significant decline in performance status after a single dose of cisplatin which prevented further study treatment. During cycle 1 or 2, 8 patients (38%) required dose reductions of gemcitabine and cisplatin, and 5 of those 8 had a delay in therapy as a result of neutropenia or thrombocytopenia, or both.

Of the 21 patients who completed the initial two cycles of chemotherapy, 18 completed CMT. Two patients had serious adverse events (pulmonary embolism, biliary obstruction with bacteremia) and did not begin CMT. One patient developed infectious colitis during CMT and was removed from protocol.

Twelve of 18 patients completed post-CMT chemotherapy, receiving two cycles of cisplatin plus gemcitabine. Of the 6 who did not complete chemotherapy, 2 patients had persistent thrombocytopenia, 1 patient had continuing diarrhea, and 1 patient demonstrated a marked decline in performance status precluding the additional chemotherapy. One patient sought treatment at another institution, and 1 patient suffered third-degree burns in an unrelated accident after completing CMT. During post-CMT chemotherapy, 9 of 12 patients (75%) required dose reductions and 6 required treatment delays for myelosuppression.

The median time to treatment failure was 4.6 months. Patients failed treatment as a result of disease progression (11), adverse events deemed related to treatment (5), events unrelated to treatment (4), and patient choice to stop therapy (1). Three patients demonstrated isolated, local tumor progression in the pancreas as the first evidence of disease progression 5.6, 12.3, and 20.3 months from the start of treatment. Two patients have not progressed at 17.0 and 28.6 months from study initiation.

Toxicity

All 23 patients were evaluable for toxicity, with the worst toxicity experienced per patient during combination chemotherapy shown in Table 2 and during CMT shown in Table 3. With the initial two cycles of combination chemotherapy, 4 patients (17%) experienced Grade 4 hematologic toxicities (neutropenia), one with associated neutropenic fever. No hemorrhagic complications were reported. Four patients had Grade 2 nephrotoxicity; 1 patient with diabetes developed Grade 3 peripheral neuropathy from cisplatin.

Of the 19 patients who received radiation and capecitabine, treatment was discontinued in one because of Grade 3 infectious colitis. A second patient had worsening diarrhea (Grade 3) and, despite interruption of CMT and dose reduction of capecitabine, the diarrhea persisted; RT was completed without chemotherapy. Three patients had interruption of CMT, 1 developed a Grade 3 skin rash, 1 had Grade 3 nausea and vomiting, and 1 developed Grade 3 *Clostrid-*

Table 2. Toxicity summary: worst toxicity experienced with gemcitabine/cisplatin per patient (n = 23)

Toxicity	Grade 0–1	2	3	4
Anemia	4	15	4	0
Thrombocytopenia	11	4	8	0
Leukopenia	3	5	12	3
Neutropenia	4	5	8	6
Neutropenic fever	21	0	2	0
Neuropathy	22	0	1	0
Nausea/vomiting	17	3	3	0
Diarrhea	22	0	1	0
Sepsis	22	0	0	1
DVT/PE	19	1	2	1*
Nephrotoxicity	19	3	1	0
Fatigue/decline in PS	18	3	2	0

Abbreviations: DVT = deep venous thrombosis; PE = pulmonary embolism; PS = performance status.

* Died of pulmonary embolism.

ium difficile colitis. Fourteen patients (74%) completed CMT without delay and with nothing more than mild toxicity. Grade ≥3 hematologic toxicity was not observed during CMT. After completion of CMT, 2 patients had persistent Grade 2 thrombocytopenia (<75,000 platelets) and were removed from study.

Of the 12 patients who completed the final two cycles of chemotherapy, 3 experienced Grade 4 hematologic toxicities (neutropenia), 1 with associated fever. One patient developed liver abscesses that required percutaneous drainage and intravenous antibiotics. Two patients developed hemorrhagic gastritis associated with Grade 3 thrombocytopenia during post-CMT chemotherapy.

Hospitalization for adverse events was required 15 times in 13 different patients, during or within 30 days of treatment. The most common reasons for hospitalization were deep venous thrombosis ± pulmonary embolism (3), pain control (3), cholangitis (2), and upper gastrointestinal bleeding (2).

Table 3. Toxicity summary: worst toxicity experienced with XRT/capecitabine per patient (n = 19)

Toxicity	Grade 0–1	2	3
Thrombocytopenia	17	2	0
Nausea/vomiting	16	2	1
Diarrhea	18	0	1
Infectious colitis	17	0	2
Rash	18	0	1
Fatigue/decline in PS	16	2	1

Abbreviations: PS = performance status; XRT = radiation therapy.

Response and survival

Nineteen patients underwent at least one CT scan after completion of RT, and 5 experienced an objective partial response (response rate 26%; 95% confidence interval [CI] = 9%, 51%). No complete response was observed. Of the 16 patients with an initial elevated serum CA 19-9 and at least one repeat value at 6 weeks, 7 achieved a ≥50% reduction in that serum marker after protocol therapy (44%; 95% CI = 20%, 70%). Three of those patients had a >50% reduction after the initial two cycles of chemotherapy, the remaining 4 after CMT. Five additional patients who completed therapy had normal CA 19-9 levels (<39.9 U/mL) before and throughout the treatment. Resection was performed in 2 patients (1 Whipple, CT stable disease, baseline normal CA 19-9; 1 total pancreatectomy, CT stable disease, CA 19-9, 94% reduction to normal range), and 2 additional patients were explored but could not be resected (1 response by CT and CA 19-9, 1 stable by CT, baseline normal CA 19-9). Both resected patients expired without clinical evidence of disease recurrence at 12 and 19 months.

Four patients with nonmetastatic, unresected disease are alive, 2 free of disease progression (17.0 and 28.6 months) and 2 with progressive disease (14.4 and 29.4 months). The median survival for all 23 patients was 10.1 months (95% CI = 7.6, 13.7, Fig. 1). The median survival of the 18 patients without metastasis was 12.8 months (95% CI = 8.2, 18.9). The median survival of the 11 patients with baseline normal CA 19-9 or a >50% reduction with treatment was 14.2 months (95% CI = 12.0, undefined).

DISCUSSION

The primary chemotherapeutic agent used concurrently with radiation treatment in pancreatic cancer remains 5-FU, delivered by infusion or bolus injections. Reports describing capecitabine concurrently with RT to the upper abdomen are scarce. Vaishampayan *et al.* have reported clinical benefit with capecitabine in combination with radiotherapy in a number of gastrointestinal malignancies, including pancre-

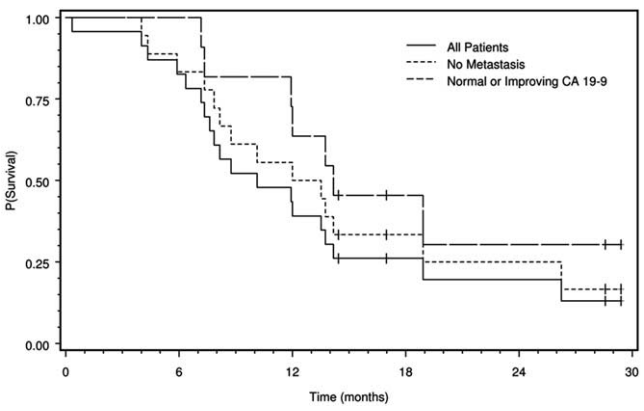

Fig. 1. Product-limit (Kaplan-Meier) survival curves for all patients, patients without metastases, and patients with baseline normal or 50% reduction in CA 19-9.

atic adenocarcinoma (25). Increasingly, capecitabine is being employed with safety and efficacy in combination with RT in patients with rectal cancer (26, 27).

The primary goal of this study was to determine the safety and tolerability of radiation and capecitabine in patients with advanced pancreatic cancer. Fourteen of 19 patients completed CMT without delay or dose reduction and only mild toxicity. Three patients required a one-week delay of treatment and capecitabine dose reduction, but were able to complete treatment without further difficulty. This favorable experience supports continued development and use of capecitabine in combination with RT in pancreatic cancer.

Capecitabine is an appealing agent to combine with RT. Preclinical data have demonstrated up-regulation of thymidine phosphorylase in tumor cells in response to RT (28). Thymidine phosphorylase is the final enzymatic step in the conversion of capecitabine to 5-FU (29). This up-regulation of thymidine phosphorylase in response to radiation may lead to increased intratumor levels of 5-FU and clinical synergy with capecitabine, as compared with an infusion of 5-FU.

We chose a dose of capecitabine that had been reported from Phase I and Phase II trials as tolerable when used continuously for up to 6 weeks (18). In rectal cancer, a total daily dose of capecitabine at 1650 mg/m^2 with RT has been reported to be well-tolerated (26). However, as compared with the pelvis, CMT to the upper abdomen is associated with increased toxicities. The North Central Cancer Treatment Group reported that the maximum tolerated and recommended doses of 5-FU for CMT were lower with upper abdominal radiation compared with pelvic radiation (30). Furthermore, improved efficacy of combined modality treatment has not been demonstrated to be related to intensification of the chemotherapy dose. Toxicities during CMT noted in our study were not likely to have been capecitabine-dose-related, and we believe that the dose of 1330 mg/m^2 is reasonable for continued investigation. Others have described the use of 1600 mg/m^2 in divided doses Monday through Friday, with a drug holiday on the weekend (31). We would suggest that the convenience of oral administration obviates the need for interruption of chemotherapy.

In this pilot trial, we elected to use combination chemotherapy with gemcitabine and cisplatin to enhance distant (and local) disease control based on Phase II and Phase III data with this combination (21–23). The combination was well tolerated before CMT, but myelosuppression and upper gastrointestinal ulceration with bleeding complicated post-CMT therapy. We have modified the sequencing of these therapies to accommodate these observations. For patients in the postoperative setting or for those with advanced unresectable disease and not treated on a clinical trial, we deliver all intended chemotherapy before treatment with radiation plus capecitabine.

At the University of Michigan, we have been investigating full-dose gemcitabine with modified RT (fraction size, total dose and treatment volumes) in pancreatic cancer (11, 13, 32). This approach requires precise definition of the target volume to minimize sensitization of normal tissues and does not treat regional nodal basins prophylactically. We have previously reported gemcitabine-based RT in the postoperative setting; however, the removal of the primary tumor and hence the target for radiation makes this approach more difficult in the adjuvant setting (32). Capecitabine-based radiation permits fields that include the tumor bed and regional nodal basins, and has become our preferred adjuvant treatment approach. The relative efficacy of RT with gemcitabine or capecitabine as neoadjuvant treatment or primary therapy for unresectable disease remains to be determined by randomized Phase II or Phase III trials.

In summary, capecitabine plus RT was well tolerated with apparent comparable efficacy to 5-FU infusion. Combination chemotherapy with gemcitabine and cisplatin before CMT is feasible but is not recommended as post-CMT treatment because of the toxicity. A treatment program using four cycles of gemcitabine and cisplatin followed by CMT with capecitabine could be considered as it may be better tolerated but warrants further investigation.

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