Retrospective Analysis of Capecitabine and Radiation Therapy in the Treatment of Pancreatic Cancer

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KEY WORDS: pancreatic cancer, capecitabine (Xeloda), radiotherapy, thymidine phosphorylase

ABSTRACT

Purpose: To report our clinical experience with 25 patients receiving concurrent capecitabine and irradiation in the treatment of locally advanced or resected pancreatic cancer.

Methods and Materials: We reviewed the medical records of patients with pancreatic cancer who received treatment with capecitabine and irradiation for pancreatic cancer and received capecitabine 1200 to 1600 mg/m^2 orally twice daily Monday through Friday with concurrent radiation (5040-5400 cGy, 180 cGy, 5 days/week), followed by a 4-week rest, then 6 to 8 cycles of capecitabine alone 2000 to 2500 mg/m^2 twice daily for 14 days every 3 weeks (surgically resected), and capecitabine 2000 to 2500 mg/m^2 BID for 14 days every 3 weeks until progressive disease (unresected).

Results: The population consisted of 14 females and 11 males, with a median age of 64 years (range 37-80 years). Histology was adenocarcinoma in 23 patients and neuroendocrine tumor in 2 patients. One patient had resected tumor, 3 patients were resected with positive margins, 1 patient was resectable with poor performance status prohibiting resection, and 20 patients had unresected locally advanced disease. Median dose of capecitabine concurrent with radiation was 1500 mg/m^2/day (600-1600 mg/m^2/day) given orally in two divided doses, 5 days per week on days of treatment with radiation therapy. Patients received a median total radiation dose of 5040 cGy (4500-5040 cGy) over 6 weeks. Eleven patients were continued on capecitabine cycles after treatment with concurrent capecitabine and irradiation. The median number of cycles completed was 3, with one patient completing 8 cycles. Median survival was 14 months, with 18 patients surviving through the end of the study period. Median overall primary tumor response over the study period was –2% (-100%-100%). Five patients were taken to laparotomy after

treatment based on radiographic response and two patients were successfully resected. By the end of the study period, there were 4 complete remissions, 2 partial remissions, 6 stable disease, and 13 progressive disease. Grade 3 or 4 toxicity was observed mainly with gastrointestinal symptoms including nausea, vomiting, diarrhea, and anorexia. Three patients had G3 hand-foot syndrome, 1 patient had G3 peripheral neuropathy, 1 patient had G4 gastrointestinal bleed, and 1 patient had G3 radiation enteritis. There was one death directly related to treatment secondary to uncontrolled GI bleeding.

Conclusion: In patients with locally advanced pancreatic cancer, concurrent capecitabine and radiation had good survival response in patients and good tumor response. Toxicity of oral capecitabine was well tolerated.

INTRODUCTION

Standard treatment for locally advanced pancreatic cancer for several decades has been rapid infusion 5-fluorouracil (5-FU) delivered in conjunction with irradiation (XRT).[1] Both abdominal radiotherapy and 5-FU treatment are associated with gastrointestinal symptoms including diarrhea, nausea, vomiting, and intestinal fibrosis, sometimes leading to bowel obstruction. Regimens based on gemcitabine have been offered as an alternative to fluorouracil based treatment in this stage of malignancy, with recent studies indicating improved clinical response with gemcitabine.[2] However subsequent analysis of experiences with gemcitabine and concurrent irradiation shows a significant toxicity, arguing for ongoing pursuit of therapeutic regimens in the treatment of locally advanced, unresectable pancreatic cancer.[3] A recent meta-analysis of treatment for locally advanced pancreatic cancer proposes that 5-FU in conjunction with irradiation is the preferred chemotherapeutic agent, with gemcitabine viewed as an acceptable alternative. The preferred delivery of 5-FU, whether infusional or bolus, however, was not well established by the studies analyzed.[4]

Capecitabine (Xeloda; Roche Laboratories, Nutley, NJ), a pro-drug of 5-FU, is an oral fluoropyrimidine that has recently been shown in a phase II study to have activity in advanced and metastatic pancreatic cancer.[5] The conversion to 5-FU occurs in a 3-step process, the last of which may provide for tumor selectivity (Figure 1). The final conversion to 5-FU occurs through thymidine phosphorylase (TP). This anti-angiogenic enzyme, which is also known as the platelet-derived endothelial cell growth factor, tends to be found in higher concentrations in tumor tissue than in surrounding normal tissue[2]. This differential creates the potential for tumor selectivity and enhanced therapeutic index, which is demonstrated in vivo.[6] Additionally, thymidine phosphorylase has been shown to be upregulated in irradiated human tissue.[7] Since TP is differentially expressed in tumors versus normal tissue, it is anticipated that treatment-related toxicity may be diminished by the use of concurrent capecitabine with radiotherapy, further enhancing the therapeutic index of radiation.

Use of capecitabine as a radiation sensitizer offers several other theoretical advantages. Capecitabine is well absorbed orally and offers the possibility of continuous tumor exposure to tissue. A phase III study comparing capecitabine to 5-FU in colorectal cancer showed similar incidence of gastrointestinal side effects, decreased incidence of stomatitis, alopecia, and grade 3/4 neutropenia but increased incidence of hand-foot syndrome and uncomplicated hyperbilirubinemia. Efficacy was similar with both drugs.[8] An added advantage to

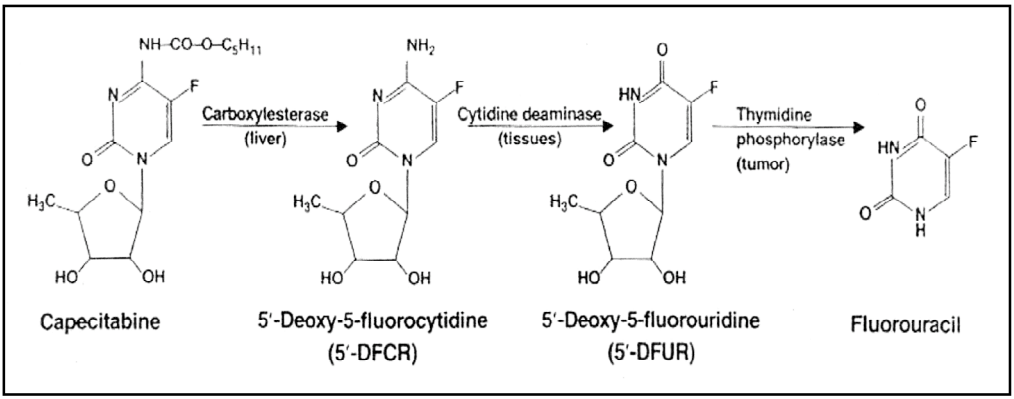

Figure 1. The enzymatic conversion of capecitabine to 5-FU occurs in a three-step process.

oral capecitabine is the elimination of catheter-related complications and convenience of oral administration. These data suggest that oral capecitabine may be an equally efficacious and a more tolerable treatment for locally advanced pancreatic cancer.

We report a retrospective analysis of the efficacy and toxicity of concurrent capecitabine and radiation in 25 patients with locally advanced (resected or unresectable) pancreatic cancer treated at the University of Alabama at Birmingham (UAB) during April 2002 through September 2003.

METHODS AND MATERIALS

This study was approved by the Institutional Review Board (IRB) at the University of Alabama at Birmingham, Birmingham, Alabama. We reviewed records of 25 patients with locally advanced or resected pancreatic cancer who were treated with capecitabine and concurrent radiation therapy. Patients were seen from April 2002 through September 2003. Twenty-four patients received treatment at the University of Alabama at Birmingham; one patient was initially seen at the University of Alabama at Birmingham, but received treatment at an outside facility. Patients were identified by medical oncologists at the University of Alabama at Birmingham. Information regarding patient characteristics, treatment duration and dosage, toxicity, and survival was obtained from medical charts and through the tumor registry at the University of Alabama at Birmingham.

Capecitabine

Patients received a 6-week course of oral capecitabine, divided in two daily doses on days of radiation, Monday through Friday, for 6 weeks' duration with concurrent radiation therapy. Patients received capecitabine doses of 1200 to 1600 mg/m^2/day in two divided doses per day (median dose 1600 mg/m^2/day). Capecitabine was rounded to the nearest dose, which allowed for dosing with standard 150 mg and 500 mg tablets. This 6-week chemoradiation was followed by a 4-week rest period. Patients who responded to capecitabine with radiation (responded either stable disease or response) were treated with then 6 to 8 cycles of capecitabine 2000 to 2500 mg/m^2 orally twice daily for 14 days every 3 weeks for the surgically resected patients, and capecitabine 2000 to 2500 mg/m^2 orally, twice daily for 14 days every 3 weeks (with 2 weeks on medication, 1 week off) until progressive disease for unresected patients.

Radiation therapy

CT image-based three-dimensional treatment planning was utilized to opti-

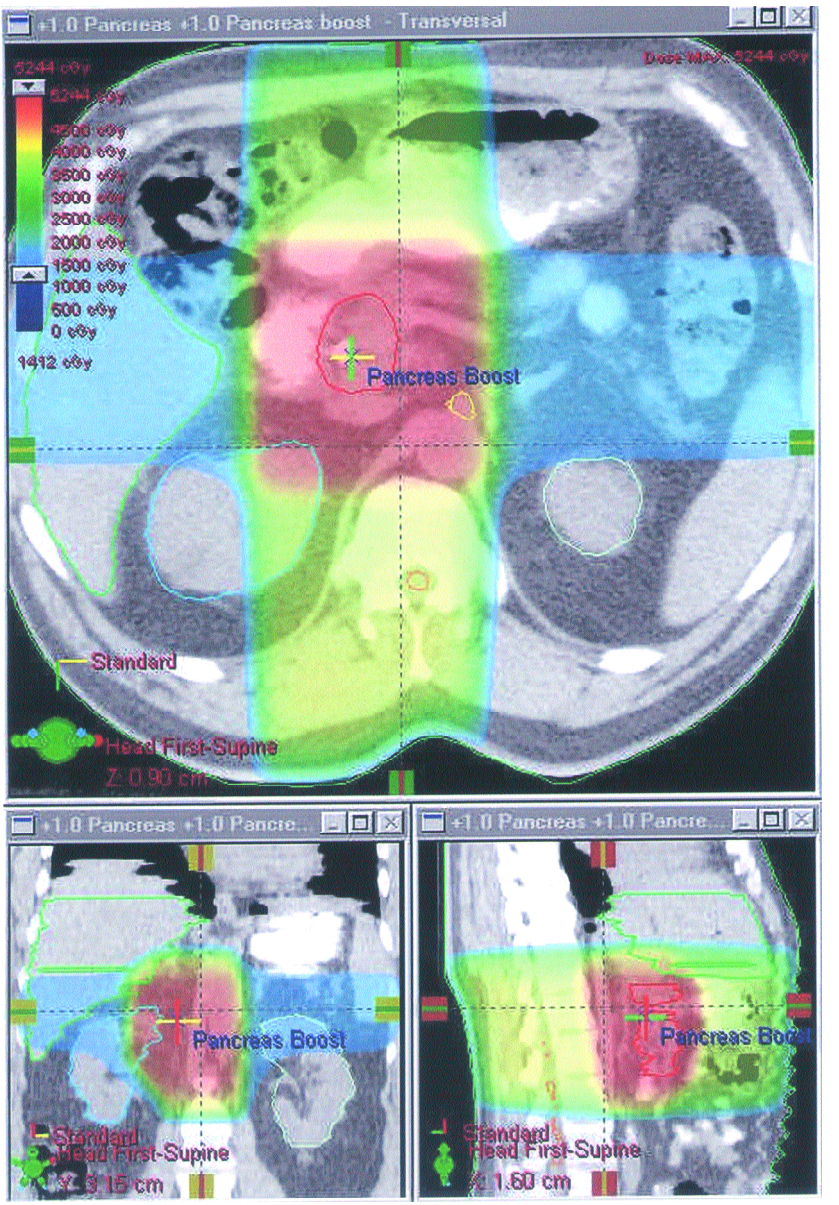

Figure 2. Three-dimensional treatment plan with color wash dose distributions identifying dose of tumor delivered to tumor volume and surrounding normal anatomical structures.

mize radiation treatment by facilitating identification of the target volume and surrounding normal structures (Figure 2). Attempts were made to minimize radiation dose to surrounding normal tissues while ensuring adequate dose to the target volume. CT simulation was performed with IV and oral contrast material to assist in localizing kidneys, liver, stomach, and intestines. Anatomical structures were contoured for dose-volume histogram (DVH) analysis. The intestines were defined as the contents within the peritoneal cavity,

excluding the stomach, spleen, liver, kidneys, aorta, and gross target volume (GTV) to allow for organ motion.

The maximum extent of the tumor and involved nodal areas (gross tumor volume, GTV), or tumor bed (marked with clips placed at the time of surgery), plus adjacent loco-regional nodes (celiac, peripancreatic, and portal), and para-aortic nodal areas at risk for residual microscopic diseases (clinical target volume, CTV) were also defined by CT.

Radiatherapy began on the first day of week 1 of capecitabine therapy. The initial target volume received 1.8 Gy/day delivered Monday through Friday for 25 fractions (45 Gy). Typically, the edges of the initial fields were defined superiorly 1.5 cm above the CTV, inferiorly to cover the para-aortic nodes to the L3-4 intervertebral space, laterally and anteriorly with a 1.5 cm margin around the CTV, and posteriorly by splitting the anterior vertebral bodies in half. After 45 Gy, an additional three to five 1.8 Gy fraction was delivered to the GTV or tumor bed with a 1.5 cm margin for a total dose of 50.4 to 54 Gy. External beam radiation therapy was delivered from high-energy linear accelerators with 15 MV photon beams. Patients received 4500 to 5040 cGy, median dose 5040 cGy to the tumor bed. Treatment fields were irradiated once daily, 5 days per week, at 180 cGy per fraction, over the course of 6 weeks.

Response Assessment

Survival was measured from date of treatment initiation. Disease response was measured according to the RECIST criteria. Assessments of tumor dimensions were performed prior to treatment, after treatment with capecitabine and radiation (6 weeks of chemoradiotherpy + 4-week rest) and then every three cycles (9 weeks). Response criteria were as follows: complete response, disappearance of all target lesions; partial response, at least 30% decrease in longest diameter; progressive disease, at least 20% increase in longest diameter; and stable disease, response falling between partial response and progressive disease.[9]

Toxicity Assessment

Patients were assessed weekly during chemo-radiation and every 3 weeks during capecitabine monotherapy. Acute 90 days from the start of radiation, side effects were documented using the NCI Common Toxicity Criteria (CTC) version 2.0.[10] Late (>90 days from the start of radiation side effects were evaluated and graded according to RTOG Late Radiation Morbidity Scoring Scale.

Statistical Methods

Patient characteristics were analyzed with frequency tables with groupings assigned respective percentage of the entire data set. Toxicity was analyzed with frequency tables with groupings assigned respective percentage of the entire data set. Survival was assessed with Kaplan-Meier survival analysis. Survival was measured from date of diagnosis until date of death or until the end of the study period for patients surviving through the end of the study period.

RESULTS

Patient Characteristics

Table 1 summarizes the patient characteristics. Twenty-five patients consisting of 14 females and 11 males, with locally advanced or resected pancreatic cancer, treated with capecitabine and irradiation were identified. Median age of the patient population was 64 years, range 37 to 80 years. Twenty-three patients had adenocarcinoma and 2 had neuroendocrine tumor of the pancreas. One patient had resected tumor, 3 patients were resected with positive margins, 1 patient was resectable with poor performance status prohibiting resection,

Table 1. Patient Characteristics

Characteristic	No	(%)
Age		
<65 years	13	(52)
≥65 years	12	(48)
Race		
White	23	(92)
African-American	2	(8)
Gender		
Female	14	(56)
Male	11	(44)
Histology		
Adenocarcinoma	23	(92)
Neuroendocrine	2	(8)
Stage		
I	2	(8)
IVA	23	(92)
Resection status		
Resected with (-) margins	1	(4)
Resected with (+) margins	3	(8)
Resectable, but inoperable d/t poor performance status	1	(4)
Locally advanced	20	(84)
Primary site		
Head	20	(80)
Body	3	(12)
Neck	1	(4)
Periampulla	1	(4)
Performance status		
ECOG 0	9	(36)
ECOG 1	13	(52)
ECOG 2	2	(8)
ECOG 3	1	(4)
Weight loss grade		
0	11	(44)
1	9	(36)
2	4	(16)
3	1	(4)
Pain grade		
0	9	(36)
1	13	(52)
2	2	(8)
3	1	(4)
New onset diabetes		
No	23	(92)
Yes	2	(8)
CA 19-9		
0-10	5	(20)
11-100	5	(20)
101-1000	6	(24)
>1000	7	(28)
Prior therapy		
None	22	(88)
Surgical resection	1	(4)
Chemotherapy for prior malignancy	2	(8)

Table 2. Number and Percentage of Patients with Capecitabine Toxicity

	Grade 1		Grade 2		Grade 3		Grade 4	
Toxicity	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Anemia	11	(44)	2	(8)	0	(0)	0	(0)
Neutropenia	2	(8)	1	(4)	0	(0)	0	(0)
Thrombocytopenia	0	(0)	0	(0)	0	(0)	0	(0)
Nausea	12	(48)	1	(4)	3	(12)	0	(0)
Vomiting	7	(28)	0	(0)	3	(12)	0	(0)
Diarrhea	10	(40)	1	(4)	4	(16)	0	(0)
Anorexia	2	(8)	4	(16)	0	(0)	2	(8)
Weight loss	6	(24)	4	(16)	0	(0)	0	(0)
Mucositis	1	(4)	1	(4)	0	(0)	0	(0)
Hand-foot syndrome	2	(8)	1	(4)	3	(12)	0	(0)
Peripheral nervous	0	(0)	1	(4)	1	(4)	0	(0)
GI bleeding	0	(0)	0	(0)	1	(4)	1	(4)
Radiation enteritis	1	(4)	0	(0)	1	(4)	0	(0)

and 20 patients had unresected locally advanced disease due to vascular involvement. Most patients were of performance status 0 to 1, with grade 0 to 1 weight loss and grade 0 to 1 pain associated with disease. Tumor marker CA 19-9 ranged with a relatively even distribution among different log ranges. Most patients did not have prior treatment for malignancy, but two patients did have prior treatment for breast cancer, both with chemotherapy, and one with hormonal therapy.

Treatment Delays and Modifications

Twenty of 25 patients completed the full 6 week course of capecitabine-radiotherapy at the intended dose without a break or dose reduction of therapy. Two patients mistakenly took half a dose for the first 3 weeks, and were then corrected by the treating physician to the intended dose for the last 3 weeks. One patient did not complete the intended 6-week course because of prolonged hospitalization secondary to malignancy related biliary obstruction. Two patients had breaks in treatment: one patient had capecitabine held for 3 days due to diarrhea, and one patient had capecitabine held for 2 weeks due to hyperbilirubinemia.

Eleven patients were continued on capecitabine monotherapy after conclusion of capecitabine-radiation. Median number of cycles completed was 3, with range from 1 to 8. Eight cycles (intended full course) were completed by one patient. Of the 11 patients who received capecitabine cycles, 7 patients had cycles held: 3 had cycles held due to diarrhea, 3 had cycles held due to grade 3 hand-foot syndrome, and 1 had capecitabine cycle length shortened due to physician decision. Capecitabine cycles were held from 1 to 4 weeks with resolution of symptoms. Of the 11 patients who received capecitabine cycles, 4 had doses decreased for symptoms: 3 patients for grade 3 hand-foot syndrome and 1 patient for grade 3 diarrhea, grade 2 mucositis, and grade 2 hand-foot syndrome.

Capecitabine was continued as treatment until certain endpoints were reached. Sixteen patients had progressive disease or inadequate response to treatment, including both patients with neuroendocrine histology, and were therefore discontinued on capecitabine and changed to an alternate treatment regimen. Most common agents used after failing capecitabine included gemc-

itabine as a single agent (> 70%), combination of gemcitabine with other agents such as irinotecan. Six patients were not stopped during the study period, and 2 of these 6 patients completed the intended 8 total capecitabine cycles. Two patients were discontinued on capecitabine due to physician decision in anticipation of side effects. One patient died due to disease before capecitabine cycle discontinuation.

Toxicity

Table 2 summarizes the toxicity of capecitabine when given with XRT. G3-4 toxicity was reported in 10 patients, related to vomiting, diarrhea, and hand-foot syndrome. Most common toxicities included G1-2 gastrointestinal side effects and G1-2 anemia. Gastrointestinal toxicity comprised of nausea, vomiting, diarrhea, weight loss, and anorexia. Most of patients developed G1-2 nausea or vomiting, while 12 patients developed cases of G3-4 nausea, vomiting, diarrhea, and anorexia. There were 10 cases of G1-2 weight loss but no G3-4 weight loss was noted. There were 3 cases of G3 hand-foot syndrome, 2 of which required holding dose of capecitabine. Hematologic toxicity consisted of 13 cases of G1-2 anemia and 3 cases of G1-2 neutropenia. No cases of thrombocytopenia were reported. Other toxicity included 3 instances of G1-2 hand-foot syndrome, 2 cases of G1-2 mucositis, and 2 cases of peripheral neuropathy. Peripheral neuropathy was of G3 in one patient manifested as gait ataxia, and G2 in the second presenting as perioral numbness and tingling of upper extremity. Both these patients had their symptoms resolved without discontinuation of capecitabine.[11] One case of G4 gastrointestinal bleeding occurred on capecitabine, requiring angiographic embolization. One case of G3 radiation enteritis is also reported here, though not directly related to capecitabine therapy.

Capecitabine was held in 7 patients (3 due to diarrhea, 3 due to grade 3 hand-foot syndrome, and 1 instance for G4 bleeding). Other delays or alteration in therapy were unrelated to toxicity. Six patients were hospitalized for side effects related to capecitabine; one hospitalization was for G4 bleeding noted above, the rest were for gastrointestinal side effects. Toxicity was controlled with symptomatic treatment on outpatient basis.

One possible treatment-related death occurred and was attributable to uncontrolled GI bleeding. This bleeding occurred within the radiation port as a late complication, while the patient was receiving post-radiation capecitabine monotherapy (approximately 3 months following completion of capecitabine-radiotherapy).

RESPONSE AND SURVIVAL

Chemo-radiotherapy

After initial treatment with capecitabine and radiation (6-week chemo-radiotherapy), 2 of 20 patients with unresected, locally advanced tumor were converted to radiographically resectable disease (2 complete response). Two other patients with locally advanced unresectable disease exhibited a partial response of 29% and 42%, respectively. Eight patients exhibited stable disease, and 10 patients exhibited progressive disease, of whom 1 showed an increase in tumor size by 100%, the other 9 exhibited metastatic disease in the liver. All the patients with resected tumor (either negative or positive margins) had no radiological evidence of recurrent disease at the end of 6-week chemo-radiotherapy.

Mono-chemotherapy

Eleven patients received further treatment with capecitabine cycles alone. With continued capecitabine therapy, 3 patients with locally advanced unre-

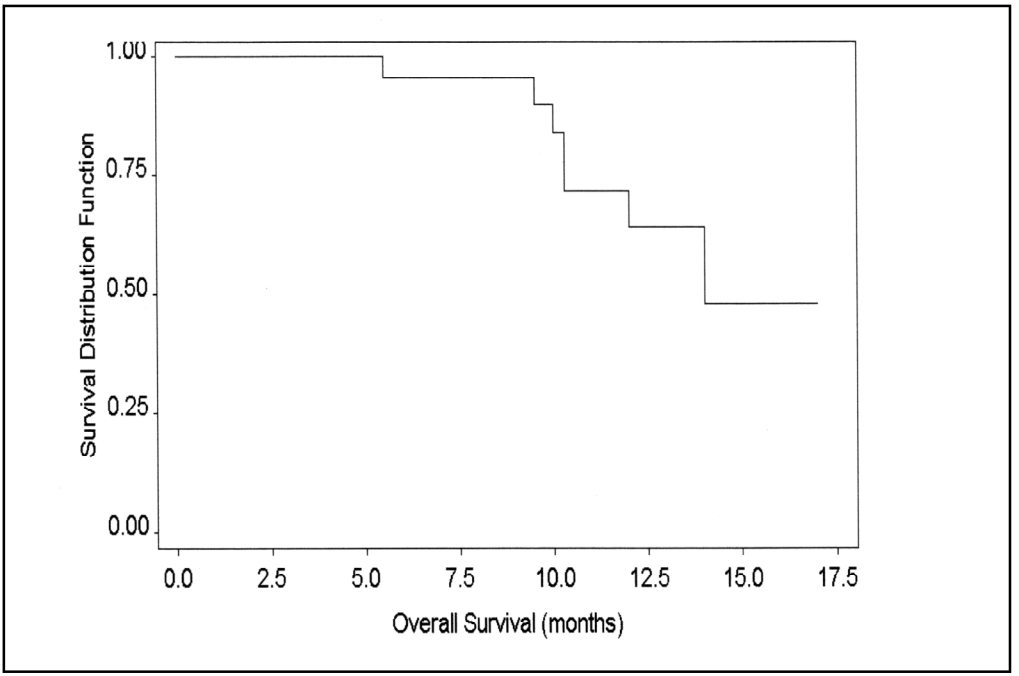

Figure 3. Kaplan-Meier survival curve for 25 patients treated with capecitabine and irradiation.

sectable tumor were thought to be radiologically converted to a resectable disease. Of these 3 patients, only 1 was successfully taken for possible resection after careful evaluation of the scans by a team composed of a radiologist, radiation oncologist, medical oncologists, and surgical oncologists. Four patients had stable disease during treatment with capecitabine cycles alone, and 5 patients exhibited progressive disease, comprised of 2 recurrences after resection with (+) margins, 2 progressions to metastatic disease, and 1 patient with an increase in tumor size by 28%. However, in spite of a 28% increase in size, the patient's tumor was converted to resectable, and the patient was taken to laparotomy.

Surgical Resection

Of the 20 patients with locally advanced, unresected disease, 5 had radiographic improvement of disease sufficient to take patients to laparotomy for tumor resection. Only 2 of the 5 patients taken to laparotomy were successfully resected. The other 3 patients were not resected due to intraoperative findings prohibiting resection, including inflammatory adhesions in one and residual disease encasing vasculature in the rest. Operative findings in the former patient showed extensive fibrosis primarily at the tumor sites, but not in the surrounding normal tissues.

Overall Response

Overall response to therapy was 4 complete remissions, 2 partial remissions, 6 stable disease, and 13 progressive disease. Average duration of treatment within each group was 7.3 months (range 2.2-13.0 months) for the complete remissions, 5.4 months (range 2.2-8.5 months) for the partial remissions, 5.2 months (range 2.3-9.0 months) for the stable disease group, and 4.1 months (range 2.0-14.0 months) for the progressive disease group, respectively. One patient with stage I resected disease remained in complete remission over 13 months of treatment. Two patients with resected

disease but positive margins progressed with treatment after 6.2 and 14 months, respectively. Five patients with unresectable locally advanced disease were converted to resectable disease and taken to resection. Of these, only 1 was successfully resected.

Survival

Survival was measured from date of initial treatment until date of death or until the end of the study period. Figure 3 depicts the Kaplan-Meier survival curve for the population. Median survival was 14 months, with 50% of patients reaching the endpoint of death at 14 months. Survival ranged from 3.75 months to 17 months. Average survival was 10.3 months, with a standard deviation of 3.5 months. Seven of the 25 patients reviewed expired before the end of the study period, indicating that median and mean survival times are underestimations of actual survival.

DISCUSSION

Pancreatic adenocarcinoma is the fourth most common cause of adult cancer death. About 50% of patients present with metastatic disease, 20% with resectable disease and the remaining 30% of patients are diagnosed with incurable, locally advanced unresectable but nonmetastatic pancreatic cancer.[1,4] Earle et al recently performed a systematic review of the literature including MEDLINE, CANCERLIT, and Cochrane Library databases to evaluate the current evidence regarding treatment of incurable, locally advanced, unresectable but nonmetastatic pancreatic cancer and produced an evidence-based practice guideline.[4] Eight randomized trials were obtained that met the inclusion criteria. Current recommendations are to offer combined chemotherapy and radiotherapy to suitable patients. The preferred chemotherapeutic agent to combine with radiotherapy is bolus or infusional 5-fluorouracil, but the optimal mode and duration of 5-fluorouracil delivery is unclear. Chemotherapy alone with gemcitabine is an acceptable alternative. Survival in the series of patients treated with fluoropyrimidine is similar to treatment with capecitabine in our patients. Fisher et al report a median survival of 7 months in patients with locally advanced pancreatic cancer treated with infusional 5-FU.[12] Moertel et al report a median survival of 7.5 months.[1] Median survival with treatment with concurrent capecitabine and irradiation was 14 months. In our study, among 20 patients with unresected tumor and who were otherwise eligible candidates for resection, 5 patients sustained a radiological response indicating laparotomy for resection. Of these, 1 patient was successfully resected. One patient who was successfully resected with negative margins maintained complete remission through the end of the study period for an overall survival of 17 months.

The major benefit of capecitabine lies in its favorable toxicity profile. A retrospective analysis of capecitabine in the treatment of a series of gastrointestinal malignancies recently showed incidence of gastrointestinal toxicity and hand-foot syndrome to be comparable to that infusional 5-FU. This study reviewed a number of different tumor types, and the treatment period with capecitabine was during radiation only without analyzing ongoing treatment with cycles of capecitabine monotherapy.[13] Our study also indicated that most toxicities were gastrointestinal, with relatively no grade 3/4 hematologic toxicities. However, over 50% of the patients did experience grade 1/2 anemia. An important consideration of oral therapy is vomiting sufficient to prevent absorption of oral medication. In this series, 12% of patients had grade 3/4 vomiting during treatment, but patients were able

to maintain oral capecitabine. Toxicity comparisons of 5-FU and capecitabine are perhaps best analyzed by looking at experiences with other malignancies, namely colorectal malignancies. A phase III study comparing oral capecitabine to 5-FU in colorectal cancer showed significantly less diarrhea, stomatitis, nausea, alopecia, and grade 3/4 neutropenia with capecitabine, although grade 3 hand-foot syndrome and grade 3/4 hyperbilirubinemia were more frequent with capecitabine.[14] This is in comparison with a similar study in which gastrointestinal side effects were similar with capecitabine and 5-FU.[5]

Secondly, a phase II study has evaluated the efficacy of capecitabine in patients with metastatic or unresectable, locally advanced pancreatic cancer.[5] Forty-two patients were treated with oral capecitabine 1,250 mg/m^2 administered twice daily (2,500 mg/m^2/d) as intermittent therapy in 3-week cycles consisting of 2 weeks of treatment followed by 1 week without treatment. Ten (24%) of 42 patients experienced a clinical benefit response (95% confidence interval [CI], 12.1% to 39.5%) as evidenced by improvement in pain intensity, analgesic consumption, and/or Karnofsky performance status. Three (7.3%) of the 41 patients with measurable disease had an objective response (partial). The median time to objective response was 85 days (range, 47 to 91 days) and duration of response was 208, 260, and 566 days for the 3 responding patients. One patient with nonmeasurable but assessable disease had improved residual disease with a positive clinical benefit response, for a total of 4 responses among the 42 assessable patients, for an overall response rate of 9.5% (90% CI, 3.3% to 20.5%). Capecitabine was generally well tolerated.[5]

Thirdly, there is also evidence that that ionizing radiation may increase the therapeutic index of capecitabine. Data from human cancer xenograft studies suggest that radiation upregulates TP in tumor tissue.[7] A single fraction of radiation (2.5 to 5 Gy) resulted in significant increase in TP at 6, 9, and 18 days after exposure in 4 of 5 xenograft models. A 9.4 fold increase in tumor TP levels was observed after whole body irradiation, but no increase in liver TP levels was found. An increase in tumor levels of Tumor Necrosis Factor-alpha, another known upregulator of TP, was also observed to precede the increase in tumor TP levels, suggesting that this mechanism is involved. The investigators also demonstrated the effects of combined capecitabine-XRT on tumor growth using a WiDr human colon cancer models, which is known to be refractory to 5-FU due to low TP levels. The tumor regrowth delay after capecitabine-XRT appeared to be more than additive. In contrast, the tumor regrowth delay after 5-FU-XRT was less than additive.[7]

The major pitfall, as related to any oral agent, is in patients controlling their medication. In this study, 2 patients made mistakes in dosing, which were corrected 3 weeks into their 6-week course of treatment. A close diary was followed on each visit in which patients were asked to write down the time they take their capecitabine and sign. A recent retrospective analysis of receipt of treatment for locally advanced pancreatic cancer indicated that only 44% of patients in a series of 1,696 patients received treatment.[15] It is not clear that oral treatment for pancreatic cancer would significantly raise the number of patients treated as the risk factors cited in that study would not necessarily be corrected by an oral treatment.

In conclusion, capecitabine can be safely and conveniently administered with concurrent radiotherapy in the treatment of locally advanced and

resected pancreatic cancer. Oral capecitabine has good bioavailability, did not have problems associated with intolerance of oral medication, and had a tolerable side effect profile. Tumor response and survival were comparable if not better to standard treatment with infusional 5-FU, although to test this rigorously, a phase III trial comparing the two treatment routes would have to be studied. Additionally, capecitabine has the convenience of oral administration and avoidance of catheter related problems. We are currently performing a phase I/II study to determine if TP is upregulated by administering radiation prior to capecitabine in locally advanced unresectable pancreatic cancer.[16] We also aim to evaluate the role of TNF-alpha, if there is any.

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