Clinical Benefit Response of Concurrent Chemoradiotherapy with Protracted 5-Fluorouracil Infusion in Patients with Locally Advanced Pancreatic Cancer

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Background: Pancreatic cancer is a highly virulent disease with a poor prognosis. Although objective tumor response to chemotherapy and/or radiotherapy is low, some patients show an improvement in their symptoms after treatments, without obvious tumor regression.

Methods: We assessed the clinical benefit of concurrent chemoradiotherapy with protracted 5-fluorouracil infusion in patients with locally advanced pancreatic cancer. Sixteen patients were enrolled in this study. The clinical benefit response to the chemoradiotherapy was evaluated by 2 indicators, including pain (intensity of pain and consumption of morphine) and performance status. A patient was defined to be a clinical benefit responder if 1 of these 2 variables was positive, and the other variable was positive or stable.

Results: Seven patients (44%) responded. Six patients (38%) were classified as stable, and 3 (19%) as nonresponders. The survival period in responders was significantly longer than that in nonresponders and stable patients.

Conclusion: Concurrent external-beam radiation therapy, with protracted 5-fluorouracil infusion, may be a meaningful treatment for locally advanced pancreatic cancer.

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INTRODUCTION

Pancreatic cancer is a virulent disease with a poor prognosis. Many patients with inoperable pancreatic cancer have various symptoms, such as severe pain, rapid weight loss, and fatigue.[1,2] The improvement of these symptoms is clinically beneficial for these patients.[3–5] Some patients have been relieved of these symptoms by chemotherapy and/or radiotherapy, though objective tumor responses have not been recognized. Recently, such clinical benefit response has been noted as a clinical endpoint for pancreatic cancer.[6,7]

Concurrent external-beam radiation therapy and 5-fluorouracil is generally accepted, based on previous randomized trials,[8–10] as the standard treatment for locally advanced pancreatic cancer. In this study, we administered concurrent external-beam radiation therapy, with protracted 5-fluorouracil infusion, in patients with locally advanced pancreatic cancer,[11] and assessed the clinical benefit of this treatment by measuring changes of pain and performance status before, during, and after chemoradiotherapy.

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PATIENTS AND METHODS

Eligibility

Patients with locally advanced pancreatic cancer were eligible for this study if they satisfied a number of criteria. It was necessary that patients had histologically confirmed adenocarcinoma. They needed to be between 15 and 75 years of age, with no prior irradiation or chemotherapy. Adequate hepatic (serum total bilirubin < 3.0 mg/dL, serum aspartate aminotransferase < 200 IU/L, alanine aminotransferase < 200 IU/L), hematologic (white blood cells > 3000/mm^3, platelets > 100,000/mm^3, hemoglobin > 10 g/mL), and renal function (serum creatinine < 1.5 mg/dL, BUN < 23 mg/dL) were required. Patients were required to meet at least 1 of the following additional criteria: a Karnofsky performance status of 50, 60, or 70, baseline morphine consumption of ≥ 10 mg/day, and a baseline pain intensity score of ≥ 20 (visual analog scale, range 0 [none] to 100 [intolerable]), as measured on a pain assessment card. Written, informed consent was obtained from all patients.

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Endoscopic or percutaneous biliary drainage was performed for patients with obstructive jaundice, and patients were required to have a serum total bilirubin level of less than 3.0 mg/dL before the initiation of chemoradiation. The possibility for resection of the local tumor was assessed by dynamic CT. Obstruction or bilateral invasion of the portal vein, and/or tumor encasement of the celiac or superior mesenteric arteries, was considered to exclude surgical resection.

Sixteen patients were enrolled in this study between November 1993 and June 1996. The patient characteristics before treatment are summarized in Table 1.

Chemoradiotherapy

Radiation therapy was delivered through 2 to 4 fields, as a single course of 50.4 Gy in 28 fractions over 5.5 weeks, using 10 to 14 MV photons (MM22; Scanditronix, Uppsala, Sweden). The radiation field included the primary tumor and a margin of 1 to 3 cm, covering the pancreaticoduodenal and celiac axis lymph nodes, defined by treatment-planning CT (GE9800; GE Medical Systems, Milwaukee, WI, USA), performed 1 or 2 days before treatment. The drug, 5-fluorouracil, was given from the first day of radiation and continued throughout the entire course of radiation, at a dose of 200 mg/m^2 per day, through a central venous catheter.

Toxicity was evaluated weekly according to standard WHO criteria.[12] Both radiotherapy and chemotherapy were suspended if grade 3 toxicity was encountered, and were resumed on recovery to grade 2 toxicity level. If there was a total delay of 2 weeks, due to toxicity for any reason, the combined treatment was abandoned. One week after the completion of chemoradiotherapy, maintenance chemotherapy of 5-fluorouracil (500 mg/m^2, bolus injection) was given weekly until disease progression, or unacceptable toxicity.

Follow-up CT was performed every 2 months after the chemoradiotherapy. Objective tumor responses were categorized as complete response, partial response, no change, or progressive disease, according to WHO criteria.[12]

Table 1. Characteristics of patients with locally advanced pancreatic cancer who were enrolled in this study.

Characteristic	Value[a]
Sex	
Male	9 (56%)
Female	7 (44%)
Karnofsky performance status	
50	1 (6%)
60	1 (6%)
70	8 (50%)
80	4 (25%)
90	2 (13%)
Baseline morphine requirement (mg/d)	
100–	2 (13%)
50–99	2 (13%)
10–49	2 (13%)
0–9	10 (61%)
Baseline pain intensity score	
60–	0 (0%)
40–59	5 (31%)
20–39	7 (44%)
0–19	4 (25%)
Site of primary tumor	
Head	4 (25%)
Body/tail	12 (75%)
Median CEA (range, ng/mL)	3.7 (1.1–32.7)
Median CA 19–9 (range, U/mL)	684 (1–42540)

CEA, carcinoembryonic antigen; CA, carbohydrate antigen. [a]Table values are numbers of patients (%), unless otherwise indicated.

Evaluation of Pain

Each patient recorded their pain intensity on a visual analog scale shown on a daily pain assessment card. The baseline measurement of pain intensity is the mean of the pain intensity scores of 3 days, immediately prior to starting treatment. The pain-intensity measurement was computed each week by taking the mean of the daily pain-intensity scores of the previous week.

A rating of positive was an improvement of ≥ 50% from baseline, sustained for ≥ 4 weeks, assuming a minimum pain score of ≥ 20, negative was a worsening from baseline, sustained for ≥ 4 weeks, and any other result was considered to be "stable."

The consumption of morphine taken by the patient as an analgesic was recorded daily. The dose of morphine taken per os or per anum was converted to one-third the dose equivalent of an intravenous dose. The baseline measurement of morphine consumption was the mean of the morphine consumption scores for 3 days, immediately prior to starting treatment. The morphine consumption measurement was computed each week by taking the mean of the daily morphine consumption scores of the previous week. A rating of positive was a decrease of ≥ 50% from baseline, sustained for ≥ 4 weeks, assuming a minimum morphine consumption of ≥ 10 mg/day, negative was any increase from baseline, sustained for ≥ 4 weeks, and any other result was considered to be "stable."

Pain was evaluated by measuring changes from the baseline in pain intensity and analgesic consumption. Each patient was categorized as positive, stable, or negative for each of these 2 pain-related indices. If at least 1 of the 2 pain-related indices was positive, without the other being identified as negative, the overall pain-improvement classification was positive. A patient who was stable according to both indices was classified as stable overall. All others were considered to have a negative response.

Evaluation of Karnofsky Performance Status

Karnofsky performance status was recorded weekly by 2 physicians. The baseline measurement of Karnofsky performance status was recorded immediately prior to starting treatment. Each patient's response was categorized as positive (improvement of ≥ 20 points from baseline, sustained for ≥ 4 weeks, for patients with Karnofsky performance status of 50, 60, or 70), negative (worsening of ≥ 20 points from baseline, sustained for ≥ 4 weeks) or stable (any other result).

Clinical Benefit Response

To be classified as a clinical benefit responder, a patient had to achieve a positive status in at least 1 of the 2 measures of pain, or in the Karnofsky performance status, without being identified as negative in the other. A patient who was stable on 2 measures was classified as stable on the clinical benefit response. All others were considered clinical benefit nonresponders. The period of response lasted from the date the clinical benefit response was first recorded, to the date thereafter on which at least 1 of the measures of pain, or the Karnofsky performance status, was worse than baseline.

Survival

Survival curves were calculated by the Kaplan-Meier method,[13] and the difference between survival curves was evaluated using the log-rank test.[14,15]

RESULTS

Tumor Response and Toxicity of the Chemoradiotherapy

Treatment-related toxicity is summarized in Table 2. One patient (6%) achieved partial response, 12 (75%) remained the same, and 3 (19%) showed progressive disease, demonstrated by the development of distant metastases.

Pain and Clinical Benefit Response

The pain improvement response is shown in Table 3. Seven patients (44%) were classified as positive in the overall pain-improvement classification. Six patients (38%) were stable, and 3 (19%) were negative.

Table 4 shows the clinical benefit response. Seven patients (44%) were clinical benefit responders. The median duration of the responses in these patients was 5.0 (range, 1.4 to 13.2) months. Overall, 6 patients (38%) were classified as stable, and 3 (19%) as nonresponders.

Table 2. Treatment-related toxicity of concurrent chemoradiotherapy, with protracted 5-fluorouracil infusion, in patients with locally advanced pancreatic cancer.

Toxicity	Grade			
	1	2	3	4
Leukocytopenia	4 (25)	3 (19)	0	0
Anemia	4 (25)	4 (25)	0	0
Thrombocytopenia	2 (13)	0	0	0
Nausea/vomiting	8 (50)	0	2 (13)	0
Diarrhea	4 (25)	0	0	0
Mucositis	4 (25)	1 (6)	1 (6)	0
Liver dysfunction	3 (19)	1 (6)	1 (6)	0

Table values are numbers of patients (%).

Relationship between Clinical Benefit Response and Tumor Response

Among the 7 clinical benefit responders, 1 attained a partial tumor response, and 5 had no change in tumor response. Although the 1 remaining clinical benefit responder showed progressive disease, demonstrated by development of liver metastasis, he became pain free without analgesic medication, and recovered his strength after the chemoradiotherapy. He was considered to have had an effective response from the therapy.

Survival

Of the 16 patients studied, 13 died during this analysis. The survival curves for the 7 clinical benefit responders and the 9 nonresponders and stable patients are shown in Fig. 1. The 6-month and 1-year survival rates and the

Table 3. Pain improvement response.

Pain intensity	Morphine consumption			
	Positive	Stable	Negative	Total
Positive	3	4	0	7
Stable	0	6	2	8
Negative	0	0	1	1
Total	3	10	3	16

	Overall pain improvement			
	Positive	Stable	Negative	Total
Number of patients (%)	7 (44)	6 (38)	3 (19)	16 (100)

Table 4. Clinical benefit response.

	Performance status			
Pain	Positive	Stable	Negative	Total
Positive	4	3	0	7
Stable	0	6	0	6
Negative	0	2	1	3
Total	4	11	1	16

	Overall pain improvement			
	Response	Stable	Nonresponse	Total
Number of patients (%)	7 (44)	6 (38)	3 (19)	16 (100)

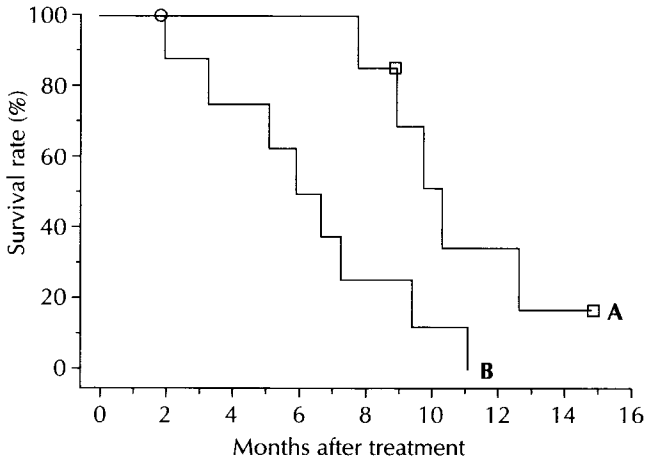

Fig. 1. Clinical benefit of chemoradiotherapy. Survival curves for responders with a clinical benefit (**A**) and nonresponders and stable patients (**B**).

median survival time were 100%, 34%, and 10.3 months, respectively, in the responders, and 50%, 0%, and 5.9 months, respectively, in the others. There was a significant difference in survival between the 2 groups ($P < 0.05$).

DISCUSSION

Pancreatic cancer has increased in incidence over the last few decades. This disease, with its poor prognosis, is the fifth most common cause of death among patients with malignant disease in Japan. Many patients with inoperable pancreatic cancer have symptoms of severe pain, fatigue, and loss of weight. The improvement of these symptoms is clinically beneficial in these patients. Although objective tumor response to chemotherapy and/or radiotherapy is low, the symptoms of several patients have improved after treatment, without obvious tumor regression.[16] Recently, the clinical benefit response has been noted as a clinical endpoint for pancreatic cancer.[6,7] We also reported a clinical benefit, resulting from systemic chemotherapy with 5-fluorouracil and cisplatin, for advanced pancreatic cancer.[17]

This study showed that about half of the patients (44%, 7 of 16), who received chemoradiotherapy for locally advanced pancreatic cancer, obtained a clinical benefit. The clinical benefit response rate of 5-fluorouracil and cisplatin therapy was 19% (4 of 21), as we reported.[17] About 25% of patients with advanced pancreatic cancer obtained the clinical benefit from treatment with gemcitabine.[18,19] Chemoradiotherapy seems to have more effect on the clinical benefit response than chemotherapy alone. However, these clinical benefit response rates may have been affected not only by treatment modality, but also by the extent of tumor spread. Most patients receiving these systemic chemotherapy regimens had more advanced disease than did the patients in this study.

An objective tumor response is usually used as the primary clinical endpoint of chemotherapy and/or radiotherapy. However, imaging modalities may not be sufficiently sensitive to precisely assess pancreatic tumor regression, because the boundary between pancreatic cancer and noncancerous parenchyma is irregular and obscure, primarily due to its invasive growth.[20,21] In contrast, the clinical benefit response was assessed simply and rapidly, and the longer survival time among the clinical benefit responders supports the clinical benefit response as being a reliable indicator for evaluation of the treatment of pancreatic cancer.

The concurrent chemoradiotherapy was well tolerated in patients with locally advanced pancreatic cancer. In addition, about half of the patients who received this treatment obtained a clinical benefit. This combined therapy may be a meaningful treatment for locally advanced pancreatic cancer.

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