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Protracted 5-Fluorouracil Infusion with Concurrent Radiotherapy as a Treatment for Locally Advanced Pancreatic Carcinoma

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ABSTRACT

Bagkground: Radiotherapy plus bolus 5-fluorouracil (5-FU) is generally accepted as an effective treatment for locally advanced pancreatic carcinoma. To intensify the antitumor effect of chemotherapy, the authors administered protracted 5-FU infusion with concurrent radiotherapy. The aim of this study is to determine the feasibility and effectiveness of this combined therapy.

Methods: Twenty patients, all of whom had histologically confirmed exocrine pancreatic carcinoma that was nonresectable but confined to the pancreatic region, were enrolled in a Phase II trial of protracted 5-Fluorouracil infusion (200 mg/m^2 /day) with concurrent radiotherapy (50.4 gray in 28 fractions over 5.5 weeks). Chemotherapy began on the first day of irradiation and continued through the entire radiotherapy course. Thereafter, weekly infusions (500 mg/m^2) were administered until disease progression.

Results: Of the 20 patients, 17 (85%) completed the scheduled course of chemoradiotherapy. Grade 3 or more toxicity, graded according to World Health Organization criteria, was observed in 4 patients (20%). Two patients (10%) achieved partial response, and disease remained stable in 16 patients (80%). After the completion of combined therapy, serum CA 19.9 levels were reduced by more than 50% in 10 of 12 patients (83%) who had pretreatment CA 19.9 levels of 100 U/ml or greater. The median progression free survival and 1-year progression free survival rate were 4.9 months and 29.5%, respectively. The median overall survival and 1-year overall survival rate were 10.3 months and 41.8%, respectively.

Conclusion: This treatment showed moderate activity against locally advanced pancreatic carcinoma and was accompanied by an acceptable toxicity level.

Key Words: *Pancreatic neoplasms - Chemotherapy - Radiotherapy - Prognosis.*

INTRODUCTION

The prognosis of patients with pancreatic carcinoma is extremely poor because of the difficulty in the early detection of the disease and the little benefit from nonsurgical treatments. For patients with locally nonresectable disease, the results of previous randomized trials indicated that concurrent external-beam radiation therapy (EBRT) and 5-fluorouracil (5-FU) therapy resulted in significantly better survival as compared with EBRT alone [3,10] or chemotherapy alone [4]. In these trials, 5-FU was commonly administered by bolus injection. However, the optimal schedule for 5-FU administration in chemoradiation has not been established.

5-FU is an antimetabolite with a very short plasma half-life, and its major cytotoxicity occurs during the S-phase [8]. Therefore, protracted infusion increases the percentage of tumor cells exposed to 5-FU. To intensify systemic chemotherapy in the treatment of locally advanced pancreatic carcinoma, we employed protracted infusion of 5-FU with concurrent EBRT. This study aims to determine the feasibility and effectiveness of this combined therapy for locally advanced pancreatic carcinoma.

PATIENTS AND METHODS

Twenty patients with cytologically or histologically proven adenocarcinoma of the pancreas were enrolled in this study during the time period from November 1995 to March 1998. Eligibility criteria included locally advanced pancreatic carcinoma, an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, adequate bone marrow reserve indicated by a total white blood cell count of 3000/µl or

greater, a platelet count of 100,000/µl or greater, and adequate renal function as measured by a serum creatinine level of less than 1.5 mg/dl. 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 and within normal liver enzymes before the initiation of chemoradiation. Pretreatment staging included chest X- ray, ultrasonography, and dynamic computed tomography (CT) of the abdomen. The degree to which local tumor extent was not resectable was assessed by CT; the CT criteria included obstruction or bilateral invasion of the portal vein and/or tumor encasement of the celiac or superior mesenteric arteries.

Radiation therapy was delivered through 2-4 fields as a single course of 50.4 gray (Gy) in 28 fractions over 5.5 weeks, using 6 or 10 MV photons (SL75-5 and SL15 Philips LINAC). The radiation field included the primary tumor and a margin of 1-3 cm covering the pancreaticoduodenal and celiac axis lymph nodes, defined by treatment-planning CT localization (Philips Oncology support system) 1 or 2 days before treatment. 5-FU was given from the first day of radiation and continued through the entire course of radiation at a dose of 200 mg/m^2/day.

The toxicity of the treatment was scored weekly according to World Health Organization (WHO) criteria [11]. Both radiotherapy and chemotherapy were suspended if Grade 3 toxicity was encountered, and both resumed when recovery to Grade 2 toxicity level was achieved. If there was a total of 2 weeks' delay due to toxicity for any reason, the combined treatment was abandoned. One week after the completion of chemoradiotherapy, maintenance chemotherapy of 5-FU (500 mg/m^2, bolus injection), was given weekly until disease progression.

Follow-up CT was performed every 2 months to assess objective tumor response according to WHO criteria [14]. Local disease progression was the diagnosis when the primary tumor was enlarged on CT (if there was 25% increase in size) or when obstructive jaundice occurred after treatment. Serum CA 19.9 level was measured by an immunoradiometric assay.

Statistical Analysis

The correlation between CA 19.9 before and after treatment with survival was done by the non parametric U test.

Progression - free and overall survivals were measured from the first day of treatment, and the survival rate was calculated by the Kaplan-Meier method [5].

RESULTS

Patient characteristics are listed in (Table 1). Seventeen patients (85%) received the full regimen of chemoradiotherapy, although two patients required temporary interruption (at 4 and 14 days, respectively) due to gastrointestinal toxicity. One patient discontinued treatment after 30.6 Gy because of hepatic toxicity, one after 46.8 Gy because of severe nausea/vomiting, and one after 12.6 Gy because of disease progression. Manifestations of treatment-related toxicity are summarized in (Table 2). No life-threatening toxicity was observed, but 4 patients (20%) developed Grade 3 toxicity. Nausea/vomiting and mucositis of Grade 3 toxicity were observed in 2 patients and 1 patient, respectively. Grade 3 hepatic toxicity was observed in 1 patient, but liver functions recovered to initial levels without specific treatment 1 week after the termination of chemoradiation. Hematological toxicity was frequent but mild. Eight patients showed Grade 2 hematological toxicity, but none of the patients discontinued therapy because of this toxic effect. Late radiation-related toxicity, such as gastrointestinal bleeding, was not observed, even though the median follow-up duration reached 293 days (range: 59-647 days).

Two patients (10%) achieved partial response, 16 (80%) remained stable, and 2 (10%) showed progressive disease .After the completion of combined therapy, the serum CA 19.9 level was reduced more than 50% in 10 (83%) of 12 patients who had a pretreatment level of 100 U/ml or greater, with mean value of 284.833 and SD ±2577.741u/ml.After treatment, the mean value was 1228.5 and SD ±2439.1u/ml (Table 3). There was a signifcant correlation between CA19.9 before and after treatment (Tables 4,5). The percentage range of responders was 83.30% and nonresponders 16.70%. Disease progression and death from cancer were documented in 16 and 14 patients, respectively, at the time of analysis (median observation time was one year). The initial sites of disease progression are listed in (Table 6). Dis-

tant metastases were evident in 20% and were the main cause of disease progression. Progression - free survival and overall survival curves are shown in Fig. (1). The median progression free survival time and 1-year progression free survival rate were 4.9 months and 29.5%, respectively. The median overall survival time and 1-year overall survival rate were 10.3 months and 41.8%, respectively.

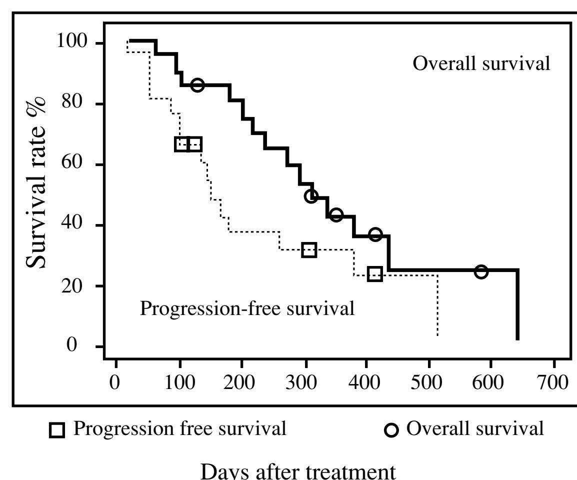

Fig. (1): Progression free survival and overall survival of the 20 patients treated with radiation and protracted 5-fluorouracil infusion.

Table (1): Patient characteristics

Characteristic	No. of patients (%)
Gender	
Male	12 (60)
Female	8 (40)
Median age year (range)	61 (37-75)
Mean± SD	62.16±11.48
ECOG performance status	
0	10 (50)
1	6 (30)
2	4 (20)
Tumor location	
Head	5 (25)
Body-tail	15 (75)
Median CEA, ng/ml (range)	4.0 (1.1-32.7)
Median CA 19-9, U/ml (range)	277 (1-8810)

ECOG : Eastern Cooperative Oncology Group;
CEA : Carcinoembryonic antigen;
CA 19.9: Carbohydrate antigen 19.9.

Table (2): Treatment-related toxicity, according to WHO criteria

Toxicity	No. of patients (%) Grade 2	3
Leukopenia	4 (20%)	0
Anemia	6 (30%)	0
Nausea/vomiting	1 (5%)	2 (10%)
Mucositis	2 (10%)	1 (5%)
Liver dysfunction	1 (5%)	1 (5%)

No Diarrhea , No Thrombocytopenia
WHO: World Health Organization.

Table (3): Changes in CA 19.9 in 12 patients with elevated CA 19.9 (>100U/ML).

	Before	After	Survival
Mean	2084.833	1228.5	297.0833
SD	2577.741	2439.133	171.7955

% Of Responders 83.30%
% Of Non-responders 16.70%

Table (4): Correlation between CA 19.9 before treatment and survival.

		Before	Survival
Correlation Coefficient	Before	1.000	-923*
	Survival	-.923*	1.000
Sig.	Before		.000
	Survival	.000	
N	Before	12	12
	Survival	12	12

* Correlation is significant

Table (5): Correlation between CA 19.9 after treatment and survival.

		Survival	After
Correlation Coefficient	Survival	1.000	-.741**
	After	-.741**	1.000
Sig.	Survival		.006
	After	.006	
N	Survival	12	12
	After	12	12

** Correlation is significant

Table (6): Initial site of disease progression.

	No. of patients (%)
None	4 (20)
Local	6 (30)
Peritoneum (ascites)	4 (20)
Liver	4 (20)
Local and peritoneum	1 (5)
Liver and peritoneum	1 (5)

Table (7):Comparison of studies involving chemoradiotherapy for locally advanced pancreatic carcinoma.

Chemotherapy					Grade 3 or worse toxicity		
Study	RT	Concurrent	Maintenance	Median survival(wKs)	Overall	Leukopenia	Reference no.
GITSG	60 Gy	5- FU (bolus)	5- FU	39	No data	18%	2
	40 Gy	5- FU (bolus)	5- FU	40	No data	16%	
GITSG	60 Gy	5- FU (bolus)	5- FU	37	36%	No data	10
	40 Gy	Doxorubicin(bolus)	Doxorubicin, 5- FU	33	53%	No data	
GITSG	54 Gy	5- FU (bolus)	SMF	42	50%	36%	3
Current Study	50.4Gy	5- FU (protracted)	5- FU	44	20%	0%	

GITSG: Gastrointestinal Tumor study group; R: Radiotherapy; Gy: Gray; SMF: Streptozotocin, mitomycin, and 5- Fluorouacil.

DISCUSSION

The rationale for protracted infusion of 5-FU is to increase the percentage of tumor cells exposed to the drug during the S-phase [8]. Moreover, protracted infusion can deliver a higher dose of 5-FU than the conventional bolus injection schedule. Therefore, protracted infusion may be a reasonable administration schedule for the enhancement of antitumor effect. In fact, protracted infusion of 5-FU showed a higher response rate than a bolus injection regimen in metastatic colon carcinoma patients. [7,12]. The dose intensity of 5-FU in the present treatment protocol was 1400 mg/m^2 /week, whereas the Gastrointestinal Tumor Study Group (GITSG) administered the treatment at an intensity of less than 500 mg/m^2 /week by bolus injection. [3,4,9]. Therefore, the main objective of this work was to reduce or delay the development of distant metastases due to the chemotherapeutic effect on nonirradiated sites.

However, our study failed to show that protracted 5-FU infusion reduced distant metastases as compared to bolus injection of 5-FU in conventional regimens. Patterns of disease progression (Table 6) and progression free survival (Fig.1) after this therapy were similar to those observed in previous studies (Table 7). More effective systemic therapy, which includes new active drugs and combined chemotherapy, might be necessary to reduce distant metastases and subsequently improve long term survival.

Among the new agents currently being tested for pancreatic carcinoma, the most promising one is gemcitabine. A randomized trial revealed that patients treated with this drug had significantly more favorable survival than those treated with 5-FU [11].

Because gemcitabine also acts as a radiosensitizer, [6], chemoradiotherapy with this agent may have an impact on the treatment of locally advanced pancreatic carcinoma.

The toxicity associated with this regimen seemed to be mild. In the current study, Grade 4 toxicity was not observed, and the percentage of patients with Grade 3 or worse toxicity was low (20%) as compared with percentages previously reported for concurrent chemoradiation (Table 7). Leukopenia was found to be the major treatment-associated toxicity when bolus 5-FU therapy schedules were used [2,4,10], In the GITSG trial, leukopenia with white blood cell counts of less than 2000/ul occurred in 16-18% of the patients. With our treatment, however, hematological toxicity was frequent but mild, and gastrointestinal toxicity was the only cause of treatment interruption. In view of the low toxicity, it might be possible to increase the radiation dose to 60 Gy or more and/or increase the dose of 5-FU that is continuously administered.

Recently, the ECOG reported a Phase I study of protracted 5-FU infusion with concurrent radiation therapy (59.4 Gy in 33 fractions) for the treatment of pancreaticobiliary tumor [13]. Their recommended dose of 5-FU was 250 mg/m^2 /day, and none of the patients developed Grade 3 toxicity at 5-FU doses below 250 mg/m^2 /day. This discrepancy in toxicity between the ECOG trial and our study might arise from differences in patient characteristics in the two trials, including ethnic differences. Moreover, the ECOG trial included cholangiocarcinoma patients (36%), who had a relatively small radiation field usually limited to the right upper quadrant of the abdomen. Therefore, these patients might escape the toxic effect on the gastrointestinal tract associated with radiation exposure.

It should be noted that serum CA 19.9 decreased to less than 50% from the baseline level of 100 U/ml or greater in 10 of 12 patients . Among these 10 patients, 2 showed partial response, and the remaining 8 demonstrated no change. In the latter group, the cancer might actually be responding to therapy, but not actively enough for visible tumor shrinkage. Alternatively, imaging modalities might not be sufficiently sensitive for precise assessment of tumor regression because the boundary between pancreatic carcinoma and noncancerous parenchyma is irregular and indistinct, mainly due to its invasive growth **[1,15]**.

Although marked improvement in survival was not observed in patients receiving protracted 5-FU infusion with concurrent radiotherapy as has been observed in response to conventional chemoradiation, this treatment showed moderate activity against locally advanced pancreatic carcinoma, accompanied by an acceptable toxicity level.

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