Effectiveness of Chemotherapy for Advanced Adenocarcinoma of the Pancreas in Combined Modality Therapy

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Because it is difficult to diagnose at an early stage, pancreatic carcinoma is usually well advanced by the time it is diagnosed. The combined use of intraoperative radiotherapy, gastrointestinal and/or biliary tract bypass operation, celiac plexus nerve block, and chemotherapy is widely applied in treatment, with favorable results reported in some patients with advanced disease. To evaluate the efficacy of chemotherapy in such combinations, we compared the effect of 5-fluorouracil, its analogues, and mitomycin C on the survival of patients with advanced stage pancreatic cancer. We found no significant difference between the patients treated or not treated with these drugs. Clearly, there is a need for new agents having greater efficacy against pancreatic carcinoma.

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Key words: 5-fluorouracil, mitomycin C, intraoperative radiotherapy, bypass operation, celiac plexus nerve block

Introduction

The incidence of adenocarcinoma of the pancreas has steadily risen over the past 40 years (1, 2); it is now the fifth leading cause of cancer deaths in Japan. Surgery is the only curative modality for this disease. Even though new imaging methods, e.g., ultrasonography, computed tomography, magnetic resonance imaging, have made diagnosis easier, in many cases, the disease is already well advanced when it is discovered. For unresectable pancreatic cancer, combinations of chemotherapy, radiotherapy, bypass procedure and plexus nerve block are used, with some favorable results reported (3–6). Since there has been no study reported on the efficacy of chemotherapy in such combined therapy, we evaluated the response to 5-fluorouracil (5-FU), 5-FU analogues and mitomycin-C (MMC) used in combination modalities in treating patients with advanced pancreatic cancer, by evaluating the survival data.

Patients and Methods

We studied 49 patients (27 men, 22 women, aged 41–80 years) with histologically confirmed carcinoma of the exocrine pancreas. They were selected from 175 consecutive patients with pancreatic carcinoma admitted to the National Kyushu Cancer Center between May 1972 and April 1988. The cases of

islet-cell carcinoma were excluded. All 49 had extensive (Stage IV) disease not amenable to surgical resection (7). Gastrointestinal and/or biliary tract bypass operations had been performed in all 49 cases. Other treatments included intraoperative plexus nerve block, intraoperative radiotherapy (IORT) and/or chemotherapy using 5-FU, or a 5-FU analogue (Tegafur, Carmofur, Doxifluridine) with or without MMC as the combined modality therapy. Survival was calculated from the date of operation and was evaluated by the Kaplan-Meier method (8). Statistical differences were calculated by the Cox-Mantel method (9, 10). Differences were considered statistically significant when $p < 0.05$.

Results

Patients were divided into six groups according to their treatment combination (Table 1). Group 1 consisted of 7 patients who received a bypass operation; Group 2, 6 patients who received a bypass operation plus chemotherapy with 5-FU or an analogue; Group 3, 9 patients who received a bypass operation plus chemotherapy with 5-FU or an analogue plus MMC (Table 2). The 27 patients treated with both a bypass operation and IORT were divided into three groups: Group 4 (6 patients), Group 5 (12 patients), and Group 6 (9 patients) who received the same combination chemotherapy as Groups 1, 2, and 3 respec-

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Table 1. Treatment and Survival of Each Patient Group

Group	(n)	Bypass procedure	IORT	5-FU	MMC	Survival period (Days) Mean±SD
1	(7)	(+)				101.8±26.0
2	(6)	(+)		(+)		144.7±89.4
3	(9)	(+)		(+)	(+)	102.3±47.5
4	(6)	(+)	(+)			100.7±59.6
5	(12)	(+)	(+)	(+)		95.7±55.3
6	(9)	(+)	(+)	(+)	(+)	149.3±80.4

IORT: intraoperative radiotherapy, 5-FU: 5-fluorouracil or its analogue, MMC: mitomycin-C.

Table 2. Patients in Groups 1, 2 and 3

No.	Age	Sex	Location*	Block**	Surgery	5-FU	MMC	Survival Period (Days)
Group 1								
1	44	M	B-T	(-)	D-J			91
2	80	M	B	(-)	CC-J, J-J			112
3	53	M	H	(-)	CC-J, J-J			112
4	48	F	B	(+)	G-J			145
5	54	M	H	(-)	G-J			94
6	70	M	B	(-)	G-J			52
7	74	M	B	(+)	G-J, CC-J			101
Group 2								
8	60	M	H-B	(-)	CC-J	5-FU 300 mg/day		109
9	65	F	H	(+)	CC-J	Carmofur 600 mg/day		80
10	56	F	H	(+)	G-J, CC-J	5-FU 300 mg/day		51
11	70	M	H	(-)	G-J	Tegafur 800 mg/day		327
12	57	M	H	(-)	G-J	Tegafur 800 mg/day		136
13	69	M	H	(-)	CC-J, J-J	Tegafur 600 mg/day		165
Group 3								
14	63	M	H	(+)	G-J, CC-J	Tegafur 600 mg/day	20 mg iv	116
15	72	F	H	(-)	CC-J	Tegafur 600 mg/day	50 mg iv	122
16	45	F	B	(-)	G-J, CC-J	Tegafur 600 mg/day	20 mg iv	81
17	49	F	B	(+)	G-J, CC-J	Tegafur 400 mg/day	20 mg iv	125
18	65	M	H	(-)	CC-J	Tegafur 600 mg/day	6 mg iv	211
19	71	F	H	(-)	CC-J	Doxifluridine 600 mg/day	6 mg iv	102
20	46	F	H-B	(-)	G-J	5-FU 300 mg/day	30 mg iv	56
21	55	F	H-B	(+)	G-J, CC-J	Tegafur 400 mg/day	10 mg iv	62
22	57	F	H	(-)	G-J, CC-J	5-FU 250 mg/day	10 mg iv	46

*location of the tumor in pancreas (H: head, B: body, T: tail), **celiac plexus nerve block, 5-FU: 5-FU or its analogue, MMC: mitomycin-C, D-J: duodenojejunostomy, CC-J: cholecystojejunostomy, J-J: jejunojejunostomy, G-J: gastrojejunostomy.

tively (Table 3). The survival period of each group is shown in Table 1.

To evaluate the effect of chemotherapy, the groups were

paired and the period of survival was examined as shown in Table 4. In pairs I and II, we compared the effect of 5-FU (or its analogue) or of 5-FU (or its analogue) plus MMC in patients

Table 3. Patients in Groups 4, 5 and 6

No.	Age	Sex	Location*	Block**	Surgery	IORT (Gy)	5-FU	MMC	Survival period (Days)
Group 4									
23	50	M	H	(-)	CC-J	30			203
24	49	F	H	(+)	G-J, CD-J	20			147
25	62	M	H	(+)	CD-J	20			43
26	61	F	H	(-)	G-J	20			38
27	73	F	T	(+)	CC-J	30			109
28	58	F	H	(+)	CD-J, J-J	25			64
Group 5									
29	62	M	H-B	(+)	G-J	27	Doxifluridine 1,200 mg/day		59
30	71	M	B-T	(+)	G-J	40	Tegafur 600 mg/day		199
31	72	M	B	(+)	G-J, CC-J	40	Tegafur 600 mg/day		110
32	66	F	B	(-)	G-J	35	Tegafur 600 mg/day		137
33	61	M	B	(-)	CD-J, CC-J	20	5-FU 250 mg/day		126
34	80	M	H	(-)	G-J	30	Tegafur 600 mg/day		92
35	55	F	H	(-)	G-J	18	Tegafur 400 mg/day		69
36	69	F	H	(-)	G-J, CC-J	30	Carmofur 200 mg/day		32
37	69	M	B	(-)	G-J, CC-J	20	Tegafur 600 mg/day		189
38	47	F	B	(+)	G-J, CC-J	15	Tegafur 800 mg/day		67
39	41	M	B	(-)	CD-J	25	Tegafur 600 mg/day		34
40	48	M	H-B	(+)	G-J	20	Carmofur 600 mg/day		34
Group 6									
41	72	M	B	(-)	CC-J	25	Tegafur 1,200 mg/day	10 mg iv	235
42	63	M	B-T	(+)	G-J	30	5-FU 200 mg/day	10 mg iv	90
43	69	M	B	(+)	G-J, CC-J	20	Tegafur 600 mg/day	10 mg iv	179
44	57	F	B-T	(+)	CC-J	30	Tegafur 400 mg/day	10 mg iv	83
45	75	F	B-T	(+)	CC-J	20	Tegafur 400 mg/day	8 mg iv	79
46	68	M	H	(+)	G-J, CC-J	25	Carmofur 300 mg/day	10 mg iv	105
47	62	M	B	(+)	CC-J	35	Tegafur 600 mg/day	20 mg iv	116
48	72	F	H	(-)	G-J	30	5-FU 300 mg/day	8 mg iv	332
49	63	F	B	(+)	G-J, CC-J	25	Tegafur 600 mg/day	10 mg iv	125

*location of the tumor in pancreas (H: head, B: body, T: tail), **celiac plexus nerve block, IORT: intraoperative radiotherapy, 5-FU: 5-FU or its analogue, MMC: mitomycin-C, CC-J: cholecystojejunostomy, G-J: gastrojejunostomy, CD-J: choledochojejunostomy, J-J: jejunojejunostomy.

who received the bypass operation. In pairs III and IV, we compared the effect of 5-FU (or its analogue) or 5-FU (or its analogue) plus MMC in patients who received a bypass operation plus IORT. The Kaplan-Meier survival plots for these pairs are shown in Fig. 1 and 2. No significant difference in survival was found in any of the pairs (I–IV).

Table 4. Group Pairs Used in Comparing Survival

Pair No.	Group		Group
I	1	vs	2
II	1	vs	3
III	4	vs	5
IV	4	vs	6

vs: versus.

Fig. 1. Survival curves for Group 1, Group 2 and Group 3 patients. ----- Group 1, — Group 2, - - - - - Group 3.

Fig. 2. Survival curves for Group 4, Group 5 and Group 6 patients. ----- Group 4, — Group 5, - - - - - Group 6.

Discussion

Even though imaging techniques such as ultrasonography, computed tomography and magnetic resonance have made the diagnosis of pancreatic cancer easier, the disease is usually advanced by the time it is discovered. Involvement of major abdominal vasculature or lymph nodes makes many patients unsuitable candidates for definite surgery. In such patients with advanced disease, combined modality therapy may include IORT, a gastrointestinal and/or biliary tract bypass operation, celiac plexus nerve block and chemotherapy (3–6). Since Abe and Takahashi (3) reported the effectiveness of IORT, it has been performed at our hospital. With this method, a 15–40 Gy “boost” is delivered directly to the surgically exposed tumor by an electron beam through a field-limiting cone, thus avoiding injury to neighboring tissue. Dobelbower and colleagues reported data from 720 cases with unresectable pancreatic cancer treated with IORT. Median patient survival time was 5.8–13.5 months (11).

5-FU is the most extensively studied chemotherapeutic agent in pancreatic cancer. In Japan, 5-FU and its analogues, Tegafur, Carmofur, and Doxifluridine, are administered orally as maintenance therapy after surgery in the hope of prolonging survival. However, an increase in survival has not been confirmed when chemotherapy has been used in combined modality therapy. In the present study, we statistically evaluated the effect of 5-FU, its analogues, and MMC using survival curves, and found no significant differences in survival between patients who were taking these drugs and those who were not. The advanced islet-cell carcinoma was excluded from the present study, because this tumor frequently shows indolent progression even after metastasis has occurred (12).

Many agents have been used to combat pancreatic cancer, including 5-FU, MMC, adriamycin and streptozocin. Carter and Comis (13), analyzing 212 patients treated with 5-FU, reported an overall positive response rate of 28%. The antibiotic, MMC, given as monotherapy is to exhibit activity comparable to that of 5-FU; 12 of 44 patients (27%) achieved a response (14). The introduction of new chemotherapeutic agents has progressed slowly, in part because the response rate is highly variable. For instance, in trials with 5-FU, responses have ranged from 0% to 67%. This wide range has variously been attributed to differences in patient selection, criteria used to define a response, or the small number of patients studied in uncontrolled trials. However, the most recent review indicates that 5-FU is the only agent with a response rate exceeding 20% (15). This response rate is not very high. Moreover, no standard chemotherapy regimen for pancreatic cancer has been established.

We conclude that chemotherapy using 5-FU, or its analogues, and MMC failed to prolong the survival of patients with advanced adenocarcinoma of the pancreas. We urge efforts be renewed to develop more effective agents for use as combined modality therapy for patients with pancreatic cancer.

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