Is adjuvant chemotherapy by continuous infusion 5-fluorouracil plus daily low dose cisplatin useful in advanced (stageIV) pancreatic cancer ?

Ikuo OIKAWA*, Koichi HIRATA, Fumitake HATA,
Tadashi KATSURAMAKI, Mitsuhiro MUKAIYA
and Kazuaki SASAKI

First Department of Surgery, Sapporo Medical University, School of Medicine
South 1, West 16, Chuo-ku, Sapporo 060-0061, Japan

ABSTRACT

Thirty-five patients were analyzed in this study to elucidate the usefulness of adjuvant chemotherapy by continuous infusion of 5-fluorouracil plus daily low-dose cisplatin after resection in advanced (stage IV) pancreatic cancer. The patients were divided into 3 groups : 8 patients were treated with the above therapy (group A), 16 patients with conventional chemotherapy (group B), and 11 patients received no chemotherapy whatsoever (group C). Mean survival time was longer in group A than in group B and C. These results were remarkable given that the patients had been diagnosed as stage IVb and curability C. Although the occurrence of adverse effects was higher in group A, none of them were severe.

We conclude in this retrospective study that continuous infusion of 5-fluorouracil plus daily low-dose cisplatin is effective adjuvant chemotherapy in the treatment of advanced cancer of the pancreas. Therefore, the prospective trial will be necessary in near future.

Key words : 5-fluorouracil, Cisplatin, Biochemical modulation, Advanced pancreatic cancer

INTRODUCTION

It is known that the prognosis for pancreas cancer is extremely poor. Even if curative resection has been carried out, the 5 years survival rate remains at approximately 5～15 % (1, 2). For patients with advanced pancreatic cancer,

*To whom requests for reprints should be addressed

surgery alone has not been effective because of a low rate of curative resection and a high incidence of liver metastasis (3). Therefore, it is widely accepted that these patients should receive adjuvant chemotherapy to prevent from liver metastasis after resection. Although several chemotherapies have been used as an adjuvant treatment after resection, the efficacy of chemotherapy in improving survival remains uncertain (4,5).

5-fluorouracil (5-FU) and cisplatin (CDDP) in combination has been shown to possess cytotoxicity against human neoplasms through the modulatory effect of CDDP to 5-FU (6, 7). In this study, we retrospectively elucidated the usefulness of adjuvant chemotherapy by continuous infusion of 5-FU plus daily low-dose CDDP (low-dose FP therapy) in advanced pancreatic cancer.

PATIENTS AND METHODS

Sixty-one patients with invasive ductal carcinoma of the pancreas received radical operation in our hospital between April 1992 and March 1997. Of these patients, we analyzed (Fig. 1) thirty-five who had been diagnosed as stage IV

	P0 H0 M0				P1,2,3 / H1,2,3 or M1
	n0	n1	n2	n3	
t1a tumor size ≦ 2.0 cm s0 + rp0 + pv0 + a0 + du0 + ch0,1	I	II	III	IVa	IVb
t1b tumor size > 2.0 cm s0 + rp0 + pv0 + a0 + du0 + ch0,1	II	II	III		
t2 Regardless of tumor size One or more positive factor(s) among s1 rp1 pv1 a1 du1,2,3 ch2,3	III	III	IVa		
t3 Regardless of tumor size One or more positive factor(s) among s2,3 rp2,3 pv2,3 a2,3	IVa				

Fig. 1 Classification of conclusive stage of pancreatic cancer according to the General Rules for the Study of Pancreatic Cancer of the Japan Pancreas Society. s, invasion of the anterior capsule of the pancreas; rp, retroperitoneal invasion; pv, invasion of the portal venous system; a, invasion of the artery; du, invasion of the duodenal wall; ch, invasion of the intrapancreatic bile duct; n, lymph node metastasis; P, peritoneal dissemination; H, hepatic metastasis; M, distant metastasis; 0, no evidence of invasion or metastasis; 1, suspicion of invasion or metastasis; 2, definite invasion or metastasis; 3, marked invasion or metastasis; n0, absence of lymph node involvement; n1, involvement of the primary group of lymph nodes close to the primary tumor; n2, involvement of regional lymph nodes distant from the primary tumor; n3, involvement of juxtaregional lymph node (from reference 7, with permission).

according to the General Rules of the Japan Pancreas Society (8). Patients were divided into three groups after resection according to the protocol of adjuvant chemotherapy. Group A (n=8) included patients treated with low-dose FP therapy. 5-FU was infused continuously at a dose of 500 mg/body for eight weeks, and CDDP at a dose of 5 mg/body was infused for one hour five times a week for eight weeks. The patients in group B (n=16) received a conventional chemotherapy, the detail of which are shown in Fig. 2. The eleven patients in group C received no chemotherapy whatsoever. The protocol for treatment was chosen in deference to the wishes of each patient or their family after informed consent had been obtained.

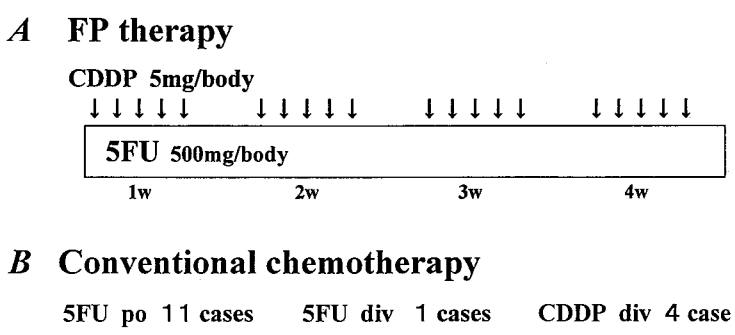

Fig. 2 Treatment protocol in each groups. po, per os; div, dripped intravenously.

To elucidate the feasibity and efficacy of each treatment, mean survival time was compared between each group not only for the total cases, but also for stage IVa or IVb and curability B or C, which had been classified according to the criteria of the Japan Pancreas Society (8). Also the frequency of adverse effect caused by treatment was compared between group A and B and scored according to the World Health Organization criteria (9).

Statistical analysis was performed by means of the X^2 test. Survival curves were calculated by the Kaplan-Meire method (10), and difference in survival rates were evaluated by a generalized Wilcoxon test (11). The Cox proportional hazards model was used to determine the significant variables related to survival (12). Statistical significance was defined as a p value (<0.05).

RESULTS

Background of patients

We compared the background of patients in each group as regards mean age, number of stage IVa and IVb, curability B and C. Mean age was 63.3 yrs. old in both group A and B, 60.5 yrs. old in group C. Althogh the number of stage IVa was higher in group B than in group A and C, there was no difference in the degree of curabirity between each group (Table 1).

Table 1 Patient background

	A	B	C	
Cases	8	16	11	
Age	63.3	63.3	60.5	NS
stage IVa	50%	63%*	36%	* p<0.005(between B and C)
IVb	50%	37%*	64%	* p<0.005 (between B and C)
curability B	50%	63%	55%	NS
C	50%	37%	45%	NS

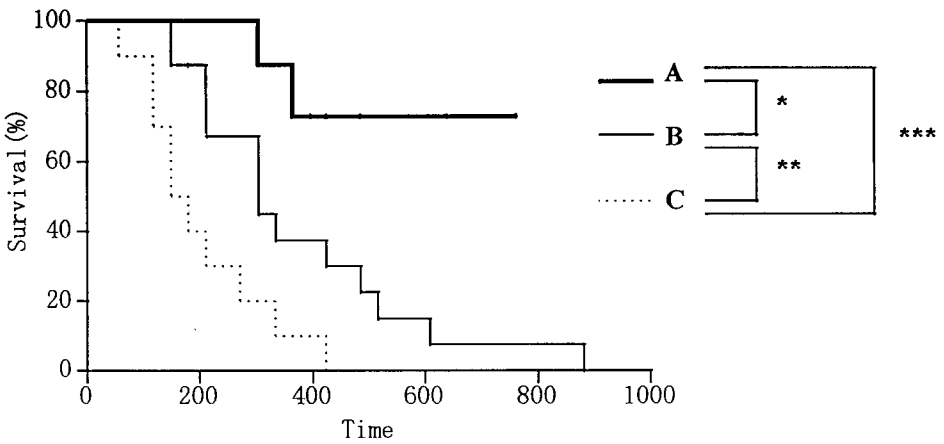

Fig. 3 Survival curves for all patients in each group. Mean survival time was 646.1±69.8 days in group A, 372.9±52.3 days in groupB, 202.5±33.4 days in group C.
* p<0.05; * *p<0.01; * * *p<0.005.

Mean survival time

The survival curve of each group is shown in Fig. 3. Mean survival time was 646.1±69.8 days in group A, 372.9±52.3 days in groupB, 202.5±33.4 days in group C, representing statistically significant differences between each group. The mean survival time of patients diagnosed as stage IVa showed no statistically significant difference among the three groups. However, mean survival time of patients diagnosed as stage IVb was longer in group A than in groups B and C. Mean survival time of patients diasnosed as curability B and C was longer in group A than in groups B and C. A statistical significance was observed between group A and C with regard to curability B and between each group with regard to curability C (Table 2).

Table 2 Mean survival time in each group

Group	Total cases	stageIV		Microscopical curability	
		IVa	IVb	B	C
A	646.1±69.8	629.0±107.8	439.8±39.2	629.0±107.8	439.8±39.2
	*	NS	*	NS	*
B	372.9±52.3 ***	406.7±68.5 NS	267.2±20.2 **	406.7±68.5 *	267.2±20.1 *
	**	NS	*	NS	**
C	202.5±33.4	242.0±72.2	176.2±22.1	226.8±52.1	166.0±17.1

*p < 0.05; **p < 0.01; ***p < 0.005.

Cumulative survival rate

Both 1-year and 2-year survival rates are shown in Table 3. The 1-year survival rate was 87.5% in group A, 37.4% in group B and 10.0% in group C. The 2-year survival rate was 73.0 % in group A, 7.5% in group B and 0% in group C. This represented a statistically significant difference for both 1 and 2 year survival rates, among each group.

Table 3 Cumulative survival rate in each group

	Cumulative survival rate	
	1 yrs.	2 yrs.
A	87.5%	73.0%
	*	**
B	37.4% *	7.5% **
	*	*
C	10.0%	0%

*p < 0.05; **p < 0.005.

Frequency of adverse effect

The frequency of adverse effects, the main ones being thrombocytopenia in group A and appetite loss in group B, were higher in group A than in group B. Although one case in group A resulted in the interruption of chemotherapy because of the occurrence of mild thrombocytopenia, no severe adverse effects were observed in the other cases (Table 4).

Table 4 Frequency of adverse effects in groups A and B

	A	B	
Frequency of adverse effects	**38%**	**6%**	**$p<0.005$**
appetite loss	**0%**	**6%**	
thrombocytopenia	**38%**	**0%**	
grade 1	**25%**	**6%**	
grade 2	**13%**	**0%**	
grade 3	**0%**	**0%**	
grade 4	**0%**	**0%**	
Death caused by adverse effect	**0%**	**0%**	**NS**

Multivariate analysis

Multivariate regression analysis was conducted to identify the independent prognostic value of each variable studied. Treatment protocol alone was identified as a factor with significant relevance to survival in this analysis (Table 5).

Table 5 Multivariate analysis (Cox's proportional hazards model)

Variable	Odds ratio	95% confidential interval	p value
Treatment protocol	**20.040**	**3.102-129.468**	**$p<0.005$**
H factor	**9.294**	**0.320-269.572**	**NS**
D < N	**3.293**	**0.228-47.530**	**NS**
stage	**2.908**	**0.489-17.282**	**NS**
ew factor	**1.818**	**0.169-19.495**	**NS**
Age	**1.212**	**0.429-3.423**	**NS**
Sex	**0.897**	**0.242-3.330**	**NS**
P factor	**0.296**	**0.010-8.824**	**NS**
curability	**0.180**	**0.006-5.675**	**NS**

* Treatment protocol (A, B, C)
H factor (+, −)
D < N (yes, no)
stage (IVa, IVb)
ew factor (+, −)
Age (60 ≦, 60 >)
Sex (male, female)
P factor (+, −)
curability (B, C)

DISCUSSION

The patients with locally advanced pancreatic carcinoma might have had small metastases of the liver or regional lymphnodes, which could not be detected by preoperative imaging diagnosis or surgical exploration (13). For these patients, surgery alone was recognized to be limitted and has not been effective in improving survival rates. Although several chemotherapies as adjuvant treatments after resection, most of which were single agent chemotherapies, have been tried, no effective regimens have been reported (4,5).

It is a matter of common knowledge that the reasonable chemotherapy is scheduled to maximize antitumor effects while minimizing toxicities. Recently, the synergism between 5-FU and CDDP has been reported in both experimental models and clinical cases (6,14). It is thought that CDDP enhances the antitumor effect of 5-FU by increasing the availability of the reduced folate necessary for tight binding of fluorodeoxyuridylate, a 5-FU metabolite, to deoxythymidylic acid synthase (14). On the other hand, 5-FU is an antimetabolite with a very short plasma halflife, and it causes major cytotoxicity during the S-phase (15). It has been also reported that continuous infusion of 5-FU increases the percentage of tumor cells exposed to 5-FU, resulted in fewer toxicities with a higher response rate than bolus 5-FU (16). From these facts, we hypothesize that the combination of continuous infusion of 5-FU and CDDP infusion is a promising chemotherapy.

In this study, the mean survival time of patients treated with low-dose FP therapy was longer than that of patients treated with conventional chemotherapy and that of those without chemotherapy. It's effect was especially remarkable in patients diagnosed as stageIVb or curability C, with whom there was a high probability that residual tumor might remain.. As this study was performed retrospectively and the numbers of patients were small, a large randomized-trial will be necessary in the near future to confirm the effects of this regimen. However, the results from multivariate regression analysis in these cases indicate the efficacy of this regimen as an adjuvant chemotherapy for patients with advanced pancreatic cancer.

The frequency of adverse effects associated with this regimen was higher than that associated with conventional chemotherapy. However, except for one case who was required to suspend the treatment at grade 2 due to thrombocytopenia, the toxicities of the other cases were almost mild. Although nephrotoxicity due to bolus infusion of CDDP has been reported occasionally (17), we did not observe nephrotoxicity in our cases. In our regimen, it is not necessary to infuse CDDP at dosage levels which result in nephorotoxicity, becaese it is infused as a modulator to 5-FU. Other study in which continuous or prolonged

CDDP infusion was given aslo showed a lower degree of toxicities than in bolus regimens in patients with lung cancer, accompanied by at least the same level of efficacy (18). In view of the low toxicity, it might be possible to prolong the treatment or to continue the treatment on an outpatients basis.

In conclusion, we have identified low-dose FP therapy as an useful regimen against advanced pancreatic cancer. Because of the improvement in survival time and low rate of toxicity, we have confidence that this is a feasible and effective approach and can be considered in the routine care and treatment of pancreatic cancer.

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