

## Intratumoral Administration of Streptococcal Preparation (OK-432) to Advanced Pancreatic Cancer\*

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(Received March 5, 1983)

*Key words: Intratumoral administration, Streptococcal preparation, Pancreatic cancer*

### ABSTRACT

Ten patients with advanced, unresectable carcinoma of the pancreas were treated with intratumoral high-dose injections of OK-432 and their therapeutic responses assessed from the clinical standpoint in the past four years since 1977. Following the treatment, 7 (78%) of 9 patients evaluated by the Karnofsky criteria fell under Category I, of whom 2 were classified under I-C. Five patients (50%) showed performance status scores of  $\geq 80$  (on the Karnofsky scale) following operation. A substantial to complete relief of pain was achieved in 3 (60%) of 5 patients who had complained of pain prior to surgery. The average survival period in the group of OK-432-treated patients did not differ significantly from that in a control group. However, a patient in the treated group is still living 13 months after operation. The results indicate that intratumoral high-dose OK-432 therapy is notably effective for prolongation of survival and for relief of pain with rarity and mildness of side effects.

### INTRODUCTION

Notwithstanding the recent progress in imaging diagnostic procedure with the advent and improvement of such techniques as ERCP, PTC, CT and US, the diagnosis of pancreatic carcinoma still entails some difficulty as compared to cancers of other organs. And, it is often the case that the tumor of the pancreas has already reached an advanced stage and is found no longer surgically curable when the existence of malignancy becomes obvious. Biliary diversion aimed at removal of biliary tract obstruction is the principal surgical approach at present in the treatment of patients with advanced pancreatic carcinoma, occasionally in conjunction with radiotherapy and/or chemotherapy. Therapeutic outcome, nevertheless, still miserable. This study was undertaken to assess usefulness of OK-432, a lyophilized streptococcal preparation<sup>11)</sup> with host-mediated immunopotentiating activity, as an adjuvant

therapy for prolongation of survival and pain relief in unresectable cases of advanced pancreatic carcinomas at stages III-IV by the stage classification of Hermreck et al.<sup>4)</sup> or stages II-III of the Vermont Tumor Registration<sup>7)</sup>, receiving intratumoral high-dose therapy.

### MATERIALS AND METHODS

Eighty-five patients were treated at this department for carcinoma of the pancreas, 74 for carcinoma of the head of the pancreas and 11 for that of the body and tail of the gland, during the period from 1965 to 1981. Tumors were resectable in 13 cases (15.3%), all being of the head of the organ. Since 1977 OK-432 therapy by intratumoral injection has been performed for unresectable carcinoma of the pancreas in a total of 10 cases (Table 1). These patients, 9 male and 1 female, ranged in age from 52 to 77 years (mean: 64.1 years). The tumor was located in the head of the pancreas in 8 cases and in the body of the

\* 児玉 求, 田中恒夫: 進行膵癌に対する溶連菌製剤 OK-432 の腫瘍内投与

**Table 1.** Patients treated with intratumoral administration of OK-432

Case	Age (y. o.)	Portion	Stage*	Stage**	Dosage of OK-432 (KE)	Procedure of Operation
1	52	Head	IV	III	100	Cholecystojejunostomy
2	55	Head	III	II	50	Cholecystojejunostomy
3	72	Body	IV	III	75	Exploratory laparotomy
4	73	Head	IV	III	50	Cholecystojejunostomy
5	58	Body	III	II	50	Neurotomy on the head of pancreas***
6	54	Head	IV	III	50	Neurotomy on the head of pancreas***
7	75	Head	IV	III	100	Choledochoduodenostomy
8	66	Head	IV	III	100	Cholecystojejunostomy
9	77	Head	III	II	75	Cholecystojejunostomy
10	59	Head	IV	III	25	Cholecystojejunostomy

\* : Classification of Hermreck

\*\* : The Vermont Tumor Registry

\*\*\* : Yoshioka and Wakabayashi

gland in 2 cases. By the stage classification of Hermreck et al., 3 patients had stage III tumors and 7 patients stage IV malignancies. There were 3 patients whose conditions were at stage II and 7 patients at stage III according to the Vermont Tumor Registration. Surgical procedures employed were cholecystojejunostomy in 6 cases, pancreas (Yoshioka and Wakabayashi<sup>14)</sup>) in 2 and exploratory laparotomy in 1.

The dosage of intratumoral OK-432 therapy was 50 to 100 K. E.<sup>\*)</sup>, individualized according to age, surgical risk and body weight. Each dose of the lyophilized preparation was made up in about 10 ml of diluent and injected in several fractions into the tumor with a dental high-pressure injector. The tumor of the head of the pancreas was injected not only anteriorly but through the posterior aspect of the pancreas on Kocher's mobilization, the care being taken to avoid infusion of drug into extratumoral pancreatic tissue or blood vessels. The patients undergoing intratumoral OK-432 therapy did not receive any antitumor chemotherapeutic agents.

## RESULTS

Table 2 shows the clinical outcome in the 10 cases treated by intratumoral injections of OK-432. By Karnofsky's criteria<sup>6)</sup>, the prognosis was O-C in 2 cases, I-A in 2, I-B in 3 and I-C in 2, excluding the patient of Case 1 who died of gastrointestinal hemorrhage 40

**Table 2.** Clinical course after operation and evaluation of clinical responses

Case	Course after Operation	Karnofsky's Criteria	Performance Status (Karnofsky Scale)
1	Dead, 40 days.	—	20
2	Dead, 4 mos.	I-A	50
3	Dead, 3 mos.	I-A	70
4	Dead, 7 mos.	I-C	90
5	Dead, 7 mos.	I-B	80
6	Dead, 4 mos.	O-C	50
7	Alive, 13 mos.	I-C	100
8	Dead, 8 mos.	I-B	80
9	Dead, 6 mos.	I-B	80
10	Dead, 3 mos.	O-C	50

days after operation. The Karnofsky performance status index<sup>5)</sup> was 80 or greater in 5 cases and averaged 67 in the 10 cases. Of 5 patients who had complained of pain prior to surgery, 3 became substantially to completely relieved following the treatment.

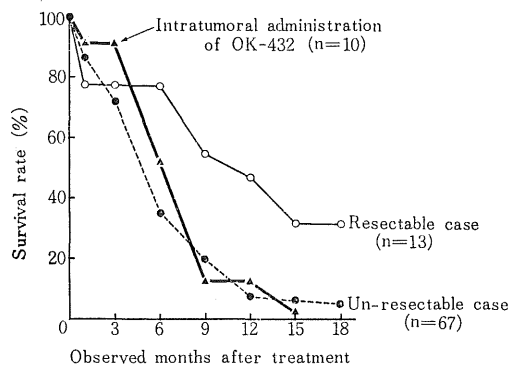
The patients treated with OK-432 had a mean survival period of  $5.6 \pm 3.2$  months, compared to  $5.4 \pm 5.0$  months in a group of 67 patients with non-resectable carcinoma of the pancreas not receiving OK-432 therapy; the intergroup difference did not reach statistical significance (Table 3). The cumulative survival rate determined by the method of Cutler<sup>2)</sup> also did not differ between the two groups (Fig. 1).

The intratumoral OK-432 therapy probably was most effective in Case 7 in the present

\*) K. E. = Klinische Einheit: 1 KE corresponds to 0.1 mg of lyophilized streptococcal constituent

**Table 3.** Mean survival period after operation in pancreatic cancer

Treatment	Number of case	Mean Survival Period mean ± S. D. (mos.)
Patients treated with OK-432	10	5.6 ± 3.2
Patients treated without OK-432	67	5.4 ± 5.0
Resected patients	13	17.5 ± 16.3



**Fig. 1.** Cumulative survival rate in cases of pancreatic cancer

series. The patient, female aged 75 years, had a fist-sized tumor in the head of the pancreas, extending beyond the pancreatic capsule with marked infiltration of the retroperitoneum and involvement of the proper hepatic artery and portal vein. As the tumor was unresectable, the patient was given intratumoral injections of 100 K. E. OK-432 along with cholecystoduodenostomy for relief of jaundice. The postoperative course was uneventful without development of any subjective symptoms or complications and the patient is now living 13 months following the operation.

Of the 10 patients receiving OK-432, 3 patients became febrile at 38.0°C on the day of the operation or the day following operation. None developed leucopenia and 1 patient showed leucocytosis as examined 7 days after surgery. One patient had elevation of serum amylase

**Table 4.** Side effect in patients treated with administration of OK-432

Case	Dosage of OK-432 (KE)	Fever (°C)	Leucocyte (/mm <sup>3</sup> )	Serum Amylase (Somogyi U.)
1	100	(-)	6700	73
2	50	(-)	4100	126
3	75	(-)	5500	174
4	50	(-)	6900	76
5	50	(-)	16700	78
6	50	38.4	6100	417
7	100	38.8	6500	100
8	100	38.3	7000	107
9	75	(-)	7200	61
10	25	(-)	7100	92

concentration following operation. All the side-effects were transient, posing no particular clinical problem (Table 4).

### DISCUSSION

Therapeutic outcome in cases of pancreatic carcinoma is generally recognized as one of the poorest among malignant tumors of various organs, and results of surgical treatment are frequently miserable; thus treatments have their limitations. Early detection of tumor naturally is most desirable but it is too frequent the case at present that the tumor is already in an advanced stage when its existence becomes obvious. A retrospective survey on therapeutic results in resectable cases of pancreatic carcinoma at eighteen principal medical institutions in the world was reported by Hermann<sup>8)</sup>, in Japan, Nakase<sup>10)</sup>, made a similar survey at 57 institutions (Table 5). The data show no conspicuous difference between Japan and the United States. The present results are virtually consistent with them, the resectability rate was as low as 15-20%, with a high mortality rate of 20-25% and a five-year-survival rate as low as less than 10% (Table 5). In view of the unfavorable prognosis after radical operations

**Table 5.** Results of pancreatoduodenal resection for pancreatic cancer

	Patients Resected	Resectability	Operative Mortality	5 Year Survivors
18 Institutions in World, by Hermann, 1978.	1005	15%	20%	39 (4%)
57 Institutions in Japan, by Nakase, 1977.	332	18%	25%	6 (2%)
Kodama, in Hiroshima, 1982.	13	14%	15%	1 (7%)

for carcinoma of the head of the pancreas, Crile<sup>1)</sup> made comparison of therapeutic results between palliative surgical treatment and pancreaticoduodenectomy, which revealed the former to be superior in respect of both the mean and maximal postoperative survival time.

Radiotherapy and chemotherapy have been undertaken as adjuvant therapies in the treatment of patients with unresectable malignant tumors of the pancreas. Pilepich et al.<sup>1)</sup> reported a significant increase in resectability rate by application of irradiation prior to surgical excision while Okawa et al.<sup>12)</sup> and Dgbelbower et al.<sup>9)</sup> observed effectiveness of radiation therapy performed in conjunction with surgery as a intra or postoperative supplement, respectively. Most studies have failed to demonstrate efficacy of anticancer chemotherapy in prolonging survival of the patient, but Mallinson and coworkers<sup>9)</sup> described a significant prolongation of survival in a group of patients receiving combined chemotherapeutic regimens consisting of 5-Fluorouracil, Cyclophosphamide, Methotrexate, Vincristine and Mitomycin C. However, radiotherapy, chemotherapy and their combined therapy have not been systematically established as yet and remain to be further explored.

In recent years, increasing attention has come to be directed toward anticancer immunotherapy aimed at enhancement of the immune function of the tumor-bearing host and OK-432 has been developed for this purpose. The objective of intratumoral injection of high-dose OK-432 seems to lie in achieving (1) a direct cytotoxic effect, (2) enhancement of specific immune function via degeneration and necrosis of tumor cells and (3) that of non-tumorspecific immune responsiveness. Intratumoral high-dose OK-432 therapy has been performed for prolongation of postoperative survival as well as for relief of pain in cancer patients at this department. Our past experience has shown that the evaluation of therapeutic responses to intratumoral administration of OK-432 from the clinical viewpoint often entails difficulty and presents no few problems.

The Karnofsky criteria have usually been employed for evaluation of clinical responses to anticancer chemotherapy. By these criteria, 7 (78%) out of 9 patients excluding the patient of Case 1 who died of gastrointestinal hemorrhage 40 days after surgery fell under Category

I following treatment, of whom 2 patients were classified under Category I-C. As for performance status after treatment, 5 (50%) of the 10 patients had normal activity with scores of  $\geq 80$  and the average score in the present series was 67. Thus, clinical benefit from the intratumoral OK-432 therapy was evident in both respects of Karnofsky criteria and performance status.

It is not infrequent that the patient with pancreatic cancer complains of deep, persistent abdominal pain which necessitate the use of narcotic analgesics. Moreover, the presence of malignant infiltration and metastases does not permit even surgical relief of pain, e.g. cephalic neurectomy, in many unresectable cases. A pain-relieving effect patients developed fever, 1 patient leucocytosis and 1 patient elevation of serum amylase activity. All these reactions were transient and posed no particular clinical problem. It is our impression that such adverse reactions may be avoided if sufficient precautions be observed to prevent leakage of intratumorally injected OK-432 into extratumoral pancreatic tissue or blood vessels.

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