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Postoperative chemotherapy including intraperitoneal and intradermal administration of the streptococcal preparation OK-432 for patients with gastric cancer and peritoneal dissemination: a prospective randomized study

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Abstract. We studied the effects on survival time of postoperative immuno-chemotherapy, including the streptococcal preparation OK-432, in patients with gastric cancer and synchronous peritoneal dissemination. The patients were prospectively randomized and a valid statistical assessment could be made for 109. Patients randomized to group B received therapy that is widely used in Japan to treat patients with gastric cancer: mitomycin C (MMC) and UFT, a combination of tegafur and uracil in a molar ratio of 1:4, for 1 year. Patients randomized to group A received the same drugs as were given to group B patients plus OK-432 i.p. for 7 days, beginning on postoperative day 0, and OK-432 by intradermal injection for 1 year, at 2-week intervals. There were no differences between the two groups in any known prognostic factor or in the dose of any drug administered except for OK-432. There was no difference in the toxicity rate between the groups. In this negative trial, there was no improvement in survival time with the addition of OK-432 to MMC and UFT for patients with gastric cancer and peritoneal dissemination.

Introduction

Peritoneal dissemination is a predominant route of metastasis for gastric cancer and, when present, significantly worsens the prognosis [19]. Reports of palliative gastric resection prolonging survival and alleviation of bleeding episodes and obstruction suggests that an aggressive approach may be benefical when primary and/or metastatic lesions are resected in patients with peritoneal dissemination [11, 16]. Tumor foci remain in these patients after gastric resection, and antitumor drugs are required to suppress tumor growth. As the doubling time of tumor cells in a small tumor focus is often shorter than that in a larger focus [5, 26], small tumor foci should be sensitive to antitumor drugs. Kano et al. [12] and Maehara et al. [18] found that early postoperative chemotherapy with a combination of mitomycin C (MMC) and a fluorinated pyrimidine, and/or PSK prolonged the survival of patients with advanced gastric cancer. As the survival rates were modest, more intense efforts are needed to improve the results.

OK-432, a lyophilized preparation of an attenuated strain of *Streptococcus*, has profound effects on host defense mechanisms, both experimentally and clinically [8, 31]. OK-432 stimulates natural killer cells and macrophages, and enhances the production of interferon [14, 21, 32, 33]. The antitumor activity of macrophages from malignant ascites was found to be lower than that of macrophages from benign ascites [15]. Torisu et al. [28] and Toge et al. [27] reported that the i.p. administration of OK-432 into malignant ascites related to a gastric cancer enhanced the antitumor effect of macrophages and reduced the amount malignant ascites fluid. Tsujitani et al. [30] found that i.p. administration of OK-432 not only increased the total number of peritoneal macrophages, but also enhanced their cytotoxic activity. We report here the effects on survival time of combination immuno-chemotherapy with MMC, UFT, and i.p. and intradermal (i.d.) administration of OK-432 in patients with synchronous peritoneal dissemination.

Materials and methods

Patients. All patients included in this prospectively randomized trial underwent gastric resection for gastric cancer with peritoneal dissemination. In all, 109 patients of 50 different clinics in Japan were enrolled in this study between October 1987 and September 1989. The patients were assigned at random to either group A or B on the day of

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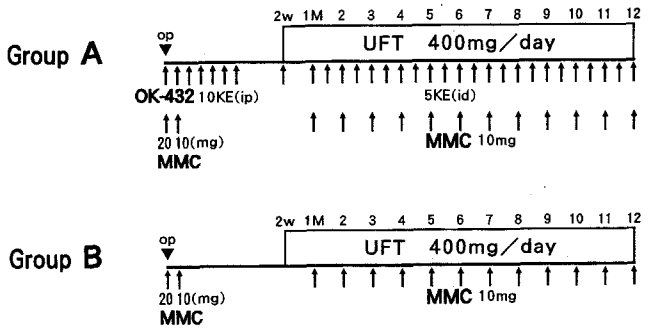

Fig. 1. Schedule for administration of chemotherapy

surgery. The protocol (Fig. 1) was as follows: the inductive regimen for group B included an i.v. injection of 20 mg of MMC [7] on the day of operation, 10 mg on postoperative day 1, and 10 mg every month thereafter for 1 year. For maintenance therapy, group B patients received UFT [18] (400 mg p.o.) daily for 1 year. The regimen for group A consisted in regimen B plus OK-432. At the time of the operation, a Nelaton tube was placed in the Douglas pouch and 10 KE (clinical units) of OK-432 was administered i.p. daily for 7 days (days 0–6), after which 5 KE i.d. injections were given every 2 weeks for 1 year. (For OK-432 1 KE is equivalent to 0.1 mg of lyophilized preparation of heat-killed *Streptococcus hemolyticus* [31].) Patients were selected on the basis of: (1) histological diagnosis of gastric cancer; (2) macroscopic diagnosis of peritoneal dissemination (P1 or P2) and no liver metastasis (H0); (3) macroscopic lymph node metastasis within the range of group 2 (N2), and extent of lymph node dissection (R) equal to or greater than N number ($R \geq N$); (4) age below 75 years and adequate organ system function; (5) no prior surgical therapy, radiation and/or chemotherapy; (6) no other evident synchronous or metachronous cancer; (7) informed consent to chemotherapy (obtained from patients or their family members prior to the surgery and drug treatments). All pathological diagnoses and classifications were evaluated according to the General Rules for the Gastric Cancer Study in Surgery and Pathology in Japan [9, 20]. In the case of P1, metastases were present in the adjacent peritoneum but apparently not in the distant peritoneum, and with P2, a few to several scattered metastases were evident in the distant peritoneum. Gastric resection based on lymph node dissection was classified as follows: R0, gastric resection including incomplete removal of group 1 lymph nodes; R1, gastric resection including complete removal of group 1 lymph nodes alone; R2, gastric resection including complete removal of groups 1 and 2 lymph nodes; R3, gastric resection including complete removal of groups 1, 2 and 3 lymph nodes. WHO criteria were used to define the toxicity of the postoperative chemotherapy [34].

The patient's general condition, bone marrow function, liver function, and serum carcinoembryonic antigen levels were evaluated at 2-week intervals in the outpatient department. At 2- to 6-month intervals, various radiologic imaging studies were done to assess the state of the tumor. The effect of immunochemotherapy was assessed according the survival time.

Drugs. The sources of the drugs were as follows: MMC from Kyowa Hakko; UFT from Taiho Pharmaceutical Co.; OK-432 from Chugai Pharmaceutical Co.

Statistical analysis. When this clinical trial was planned the size of sample recruited was expected to be about 60 patients for each group, on the assumption of a power of 80%, a one-tailed test at 5%, and survival proportions of 10% for the control group and 25% for the treatment group, respectively [3].

The BMDP Statistical Package program (BMDP; Los Angeles, Calif) for the IBM (Armonk, NY) 4381 mainframe computer was used for analyses [2]. The BMDP P4F and P3S programs were used for the chi-square and Mann-Whitney tests to compare data between the groups. The BMDP P1L program was used for the Kaplan and Meier method and the log rank test to analyze the survival time. The BMDP P2L program was used for multivariate adjustments for all covariates simultaneously, Cox regression analysis being used [1]. A P value of less than 0.05 was considered to be statistically significant.

Table 1. Comparison of clinicopathological characteristics between patients in groups A and B

Variable		Group A (n = 54)	Group B (n = 55)	P value
Age (years)		56.3±10.9*	59.3±11.5	0.084
Sex	Male	31	31	1.000
	Female	23	24	
Location of tumor	Upper	15	22	0.405
	Middle	23	16	
	Lower	13	15	
	Whole stomach	3	2	
Tumor maximal diameter (cm)		10.4±3.8*	9.5±3.8	0.258
Peritoneal dissemination	P1	16	27	0.060
	P2	38	28	
Macroscopic appearance	Localized	2	8	0.127
	Infiltrative	49	43	
	Unclassified	3	4	
Histology	Differentiated	10	18	0.139
	Undifferentiated	44	37	
Histological serosal invasion	Negative	13	11	0.778
	Positive	41	44	
Histological lymph node metastasis	Negative	4	4	1.000
	Positive	50	51	
Lymphatic involvement	Negative	3	0	0.235
	Positive	51	55	
Vascular involvement	Negative	22	17	0.384
	Positive	32	38	
Gastrectomy	Total	38	39	1.000
	Partial	16	16	
Lymph node dissection	R1	1	3	0.400
	R2	39	34	
	R3	14	18	
Splenectomy	None	30	33	0.783
	Present	24	22	

*, mean ± standard deviation

Results

Clinicopathological features

The clinicopathological details of the 109 eligible cases (100%: 54 in group A; 55 in group B) are shown in Table 1. There were no significant differences between the groups in the distribution of prognostic factors or the extent of surgery.

Doses of drugs

Table 2 shows the median doses of MMC, UFT and OK-432 administered to each group. The number of patients

Table 2. Doses[a] of drugs

Drug	Group A (n = 54)	Group B (n = 55)	P value
MMC (mg)	80.0 (50.0, 120.0)	70.0 (48.0, 120.0)	0.351
UFT (g)	64.8 (17.0, 109.3)	79.2 (36.4, 119.2)	0.271
OK-432 (KE)	138.0 (108.8, 172.5)	–	–

MMC, mitomycin C; UFT, a combined oral preparation of tegafur and uracil in a molar ratio of 1:4; OK-432, an immunomodulator
[a] Median doses (25th percentile, 75th percentile)

Table 3. Toxicities

Toxicity	Group A (n = 54)	Group B (n = 55)	P value
Hematologic			
Hemoglobin (<9.4 g/dl)	16	10	0.196
WBC (<3,000 /μl)	12	7	0.251
Platelet (<70,000 /μl)	12	6	0.155
Gastrointestinal			
Liver (GOT >100 U)	8	4	0.307
Stomatitis	1	3	0.651
Appetite loss	22	21	0.812
Nausea, vomiting	14	13	0.866
Diarrhea	4	2	0.623
Renal (BUN >40 mg/dl)	2	1	0.961
Fever	6	3	0.433

who were actually able to take all the prescribed therapy was 3 in each group. There was no significant difference between the groups in the doses of MMC and UFT administered; the addition of OK-432 in group A was the only difference in drug therapy.

Survival rates for patients in groups A and B

Figure 2 shows the survival curves for the 54 patients in group A and the 55 in group B. The log rank test of the two survival patterns revealed a P value of 0.415. The 1-year survival rate was 50.0% for group A and 56.4% for group B; the 2-year survival rate was 20.4% for group A and 22.6% for group B; and the 3-year survival rate was 11.7% for group A and 13.3% for group B.

Multivariate analysis

Multivariate analysis for the factors listed in Table 1 showed independent prognostic factors to be grade of peritoneal dissemination (P1 or P2; relative risk 2.10) and serosal invasion (none or present; relative risk 1.82), and not immuno-chemotherapy. The prognosis was poorer for patients with P2 dissemination and with serosal invasion.

Toxicity

Table 3 summarizes the toxicity with a grade of over II, according to WHO criteria [34]. Various side effects occurred in each group, as did hematologic toxicities; the rates of hematologic toxicities and liver dysfunction were higher in the group A patients, but the difference did not reach statistical significance. There was no difference between the groups with respect to other side effects.

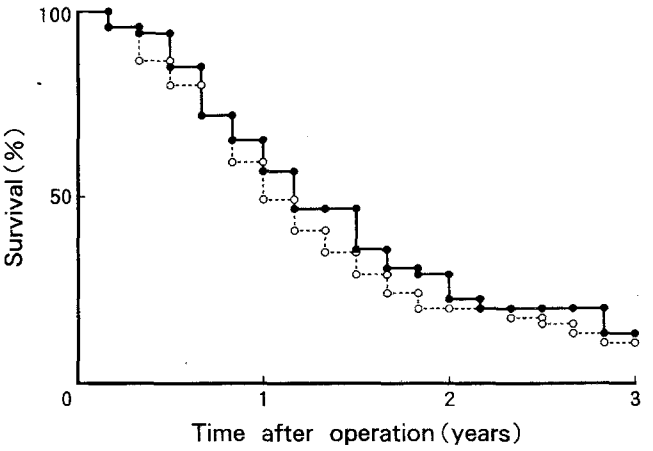

Fig. 2. Survival curves for patients in groups A and B. There were 54 patients in group A (●) and 55 patients in group B (○)

Discussion

Patients with advanced gastric cancer with peritoneal dissemination are usually treated by palliative resection. Aggressive perioperative treatment, including i.p. injection of antitumor drugs, and/or hyperthermic perfusion have also been prescribed for these patients [4, 6]. In attempts to design the optimal chemotherapeutic regimen, modification of the immune response of the host also has to be considered. OK-432 was developed in Japan as a biological response modifier [31] and has a stimulatory effect on lymphocyte-mediated and macrophage-mediated immunity [8, 10] and also exerts direct cytostatic and cytotoxic activities on malignant cells [23, 24]. The i.p. administration of OK-432 leads to reduction or disappearance of cancerous ascites and tumor cells in gastric cancer, by enhancing peritoneal effector cell activities and by inhibiting the induction of suppressor cell activities [15, 27, 28]. OK-432 may also prevent peritoneal recurrence in patients with gastric cancer invading the serosa and with no lymph node metastasis [30]. Therefore, in the present prospective study, we investigated the effect of OK-432 with MMC and UFT on the survival time of patients with gastric cancer and peritoneal dissemination: P1 or P2 according to the General Rules for the Gastric Cancer Study in Surgery and Pathology in Japan [9, 20]. The combination of MMC and UFT was found to be effective for these patients [18]. While OK-432 did not add significantly to the toxicity of this regimen, it also failed to demonstrate any significant clinical effect in terms of survival when administered i.p. and i.d. At least at the dose given in this study, OK-432 does not have an additive effect against peritoneal dissemination. As Toge et al. [27] observed that the immune effects of OK-432 administered i.p. were dose-dependent, larger doses and more frequent administration of OK-432

may be required. For patients in whom malignant ascites disappeared following i.p. injection of OK-432, delayed-type skin reactions were better after the treatment than before [29]. Clinical trials based on changes in the immune response of the patients are needed to determine the effect of this immunochemotherapy.

With respect to the chemosensitivity of gastric cancer tissues, undifferentiated cancers are relatively sensitive to anticancer drugs, i.e. to Adriamycin, MMC, cisplatin and 5-fluorouracil [17]. These undifferentiated lesions are dominant in the case of peritoneal metastases [19]. Okada et al. [22] reported that a regimen of cisplatin together with a 5-day continuous infusion of 5-fluorouracil was effective and less toxic for patients with advanced gastric cancer and peritoneal dissemination. Effectiveness of i.p. cisplatin was noted in cases of gastric cancer with peritoneal dissemination [13]. One study showed that the combined effect of i.p. cisplatin and OK-432 against murine malignant peritonitis was positive [25]. Therefore, studies with cisplatin, fluorinated pyrimidine and OK-432 will need to be done to determine whether the survival time of patients with gastric cancer and peritoneal dissemination can be prolonged.

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