Cancer Chemother Pharmacol (1981) 7:5–10

Cancer Chemotherapy and Pharmacology

Original Articles

A Controlled Study of Maintenance Chemoimmunotherapy vs Immunotherapy Alone Immediately Following Palliative Gastrectomy and Induction Chemoimmunotherapy for Advanced Gastric Cancer

Tokai Cooperative Study Group for Adjuvant Chemoimmunotherapy of Stomach Cancer*

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Summary. *A randomized trial of surgical adjuvant chemoimmunotherapy was conducted in patients who had undergone palliative gastrectomy for previously untreated advanced stomach cancer. First, all patients received the same induction chemoimmunotherapy with MFC (mitomycin C, 5-fluorouracil, and cytosine arabinoside) plus OK-432 for 6 weeks after surgery. The patients were then randomized to receive either chemoimmunotherapy with MFC plus OK-432 (group A) or immunotherapy with OK-432 alone (group B) for maintenance. The survival rate of patients was significantly higher in group B (44 cases) than in group A (39 cases) during the first 9 months after the start of induction therapy ($P < 0.05$). A further division of patients in terms of carcinoma histology revealed a difference in survival rate only in patients with an undifferentiated histology (poorly differentiated adenocarcinoma and signet-ring cell carcinoma), and not in those with a differentiated histology (papillary, tubular, and mucinous adenocarcinomas). These results indicate that simple immunotherapy with OK-432 is better for maintenance than chemoimmunotherapy involving MFC, particularly in patients with undifferentiated gastric carcinomas.*

Introduction

In an attempt to improve the survival rate of advanced gastric cancer patients, we became interested in the combined application of chemotherapy and immunotherapy. In 1973, we established the Tokai Cooperative Study Group for Adjuvant Chemoimmunotherapy of Stomach Cancer. The Tokai district consists of four prefectures on the Pacific side in central Japan. The study group involved 20 institutions in the area.

Our initial trial in 1973 was an attempt to evaluate the possible role of postoperatively administered

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immunotherapy combined with chemotherapy in gastric cancer patients undergoing palliative surgical resection. Immediately after operation patients were randomized to one of the following two regimens: (A) Chemoimmunotherapy with MFC [10] plus OK-432 [11, 15]; and (B) chemotherapy with MFC alone. MFC is a combination of mitomycin C, 5-fluorouracil, and cytosine arabinoside, and OK-432 is a streptococcal preparation (NSC-B116209) widely used in Japan for immunotherapy. MFC was given IV once weekly for 4 weeks and then bi-weekly for the next 20 weeks; OK-432 was administered IM daily for the first 4 weeks and once weekly for the rest of the study period. For convenience, we termed the intensive treatment given in the first 4 weeks 'induction' and the continued but less intensive treatment given in the second period 'maintenance.'

This preliminary study, involving 27 patients treated according to regimen A and 19 treated according to regimen B, suggested that chemoimmunotherapy with MFC and OK-432 might be more effective than chemotherapy with MFC alone [12]. At 10 months after operation, 77% of the regimen A patients were suviving, whereas only 50% of the regimen B patients were surviving. Although evidence was statistically of borderline significance ($P < 0.10$), we considered the data suggested a supportive role of immunotherapy in postoperative adjuvant treatment of gastric cancer.

A second study, conducted since 1976, includes a total of 95 patients and constitutes the subject of the present communication. In the previous study, in which both groups of patients received the same MFC therapy, we were unable to see the effect of the maintenance chemotherapy with MFC. This time, therefore, the study was designed to determine whether the maintenance therapy requires MFC in addition to OK-432 or whether immunotherapy alone is adequate. It was thought that long-term administration of MFC might induce hematologic toxicities, suppress immunologic competence and, as a result, adversely affect the survival rate of patients on such therapy. In addition, our attention was focused on the possible association of carcinoma histology with the prognosis of patients as modified by a given treatment. While hematologic parameters such as WBC, platelets, and lymphocytes were also studied, the ultimate focus of our evaluation was the survival rates.

Materials and Methods

Drugs. A single dose of MFC consisted of 0.08 mg mitomycin C/kg, 10 mg 5-fluorouracil/kg, and 0.8 mg cytosine arabinoside/kg. OK-432 (Picibanil, Chugai Pharmaceutical Co. Ltd, Tokyo, Japan) is a lyophilized preparation of penicillin G-treated Su strain *Streptococcus pyogenes* [1]. The unit used is the klinische Einheit (KE), which corresponds to 0.1 mg dried streptococci. The standard quality of antitumor potency and safety is controlled by the manufacturer.

Patients. Each patients selected for this study underwent palliative gastrectomy for previously untreated advanced stomach cancer between July 1976 and September 1978 at one of our 20 institutions. Patients 75 years of age or older were excluded. Other exclusion criteria were leukopenia (less than 4,000/mm^3), thrombocytopenia (less than 100,000/mm^3), and severe malnutrition (less than 6.0 g/dl serum total protein). Palliative gastrectomy was defined as an operation which would remove major tumor masses including metastasized foci but leave certain tumor loads unresected.

Protocol. A total of 106 patients were used in the study. The therapeutic schema is shown in Fig. 1.

In the induction phase, all patients received the same chemoimmunotherapy with MFC and OK-432, beginning 1 week after gastrectomy. MFC was administered IV once weekly for a total of six times. OK-432 was administered IM on alternate days, the dose starting at 0.2 KE and increasing to 2 KE in 2 weeks by small increments, and then maintained at 2–5 KE. During the induction phase 11 patients were dropped from the study due to leukopenia (4), high fever (4), liver dysfunction (2), and general fatigue (1).

The remaining 95 patients were randomized to two groups to be maintained according to either regimen A or regimen B. Regimen A was chemoimmunotherapy with MFC and OK-432, and regimen B was immunotherapy with OK-432 alone. Randomization was by the sealed-envelope method.

In the maintenance phase, MFC was given bi-weekly, and 2–5 KE OK-432 was administered on alternate days while patients were hospitalized and once weekly after they were discharged until death. When such definite toxicities as leukopenia (3,000/mm^3 or less), thrombocytopenia (50,000/mm^3 or less), or liver dysfunction (GPT: 100 units or more) became manifest the administration of MFC was temporarily interrupted until the patient's recovery.

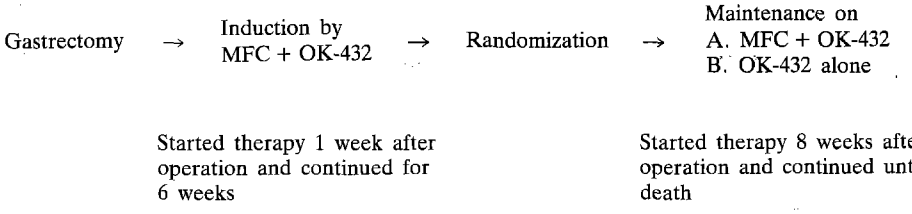

Fig. 1. Therapeutic schema

Statistical Methods. 'χ^2-test was used for comparison of patients' background factors in both groups. The survival rate was calculated by the method of Kaplan and Meier [7] and the differences in survival rates between the two regimens were tested by either the method of Cox and Mantel [2] or the calculation of standard errors given by the formula of Kaplan and Meier [7].

Results

Patient Exclusion

During the maintenance period, 6 of the 45 patients assigned to regimen A (group A) were excluded from the study: two showed side-effects of MFC, in three drug administration was inadequate, and one died within only 3 months. Similarly, 6 of the 50 patients assigned to regimen B (group B) were dropped: one had a high fever, in four drug administration was inadequate, and one died within only 3 months. Thus, 39 patients in group A and 44 patients in group B provided the basis for our observations.

Table 1. Comparison of background factors

Factor	Category	A	B	χ^2-test
1. Sex	Male	25	30	NS
	Female	14	14	
2. Age	≤ 59	24	23	NS
	≥ 60	15	21	
3. Gastric resection	Total	8	6	NS
	Partial	29	36	
	Unknown	2	2	
4. Lymphnode removal	R(0)	7	3	NS
	R(1)	12	17	
	R(2)	17	19	
	R(3)	0	1	
	Unknown	3	4	
5. Largest diameter (cm)	≤ 5	12	7	NS
	≤ 10	16	27	
	≥ 10.1	8	9	
6. Lymphnode metastasis	N(1)	4	9	NS
	N(2)	14	22	
	N(3)	14	8	
	N(4)	5	3	
	Unknown	2	2	
7. Serosal invasion	S(0)	2	3	NS
	S(1)	5	3	
	S(2)	22	26	
	S(3)	10	12	
8. Liver metastasis	H(0)	37	38	NS
	H(1–2)	0	1	
	Unknown	0	1	
9. Peritoneal metastasis	P(0)	17	19	NS
	P(1)	12	16	
	P(2)	4	7	
	P(3)	5	1	
	Unknown	1	1	
10. OW*	–	31	35	NS
	+	7	5	
	Unknown	1	4	
11. AW**	–	33	35	NS
	+	5	5	
	Unknown	1	4	
12. Borrmann	I	1	3	NS
	II	2	7	
	III	25	22	
	IV	9	6	
	Unclassified	1	4	
	Unknown	1	2	
13. Histology	pap	4	8	NS
	tub	12	13	
	por	16	15	
	muc	3	1	
	sig	2	5	
	unknown	2	2	
14. Hb (g/dl)	≤ 10.9	7	9	NS
	≤ 12.9	14	21	
	≥ 13.0	18	13	
	Unknown	0	1	
15. WBC (10^3/mm^3)	≤ 3.9	1	5	NS
	≤ 5.9	11	21	
	≤ 7.9	20	11	
	≤ 9.9	6	5	
	≥ 10	1	2	
16. Platelets (10^4/mm^3)	≤ 19	5	12	NS
	≤ 29	11	18	
	≤ 39	10	8	
	≥ 40	9	3	
	Unknown	4	3	
17. Lymphocytes (10^3/mm^3)	≤ 0.99	0	4	NS
	≤ 1.49	5	11	
	≤ 1.99	11	7	
	≥ 2.00	17	15	
	Unknown	6	7	
18. Total protein	≤ 6.9	25	32	NS
	≥ 7.0	13	11	
	Unknown	1	1	
19. GPT	≤ 19	33	35	NS
	≥ 20	5	9	
	Unknown	1	0	
20. Urinary protein	–	27	31	NS
	±	4	8	
	+	1	2	
	Unknown	7	3	

* Macroscopic infiltration at oral cut margin of resected stomach

** Macroscopic infiltration at anal cut margin of resected stomach

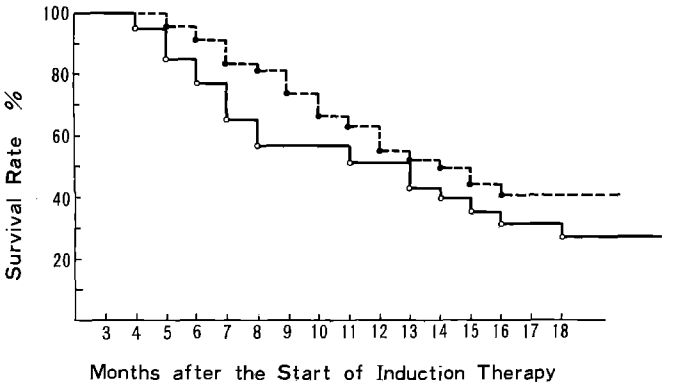

Fig. 2

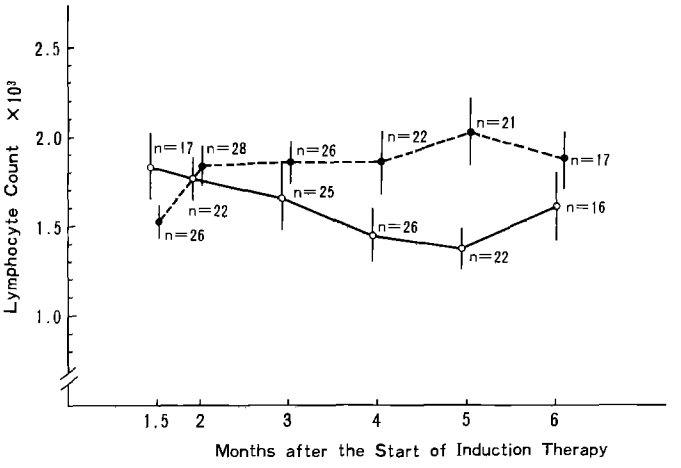

Fig. 3

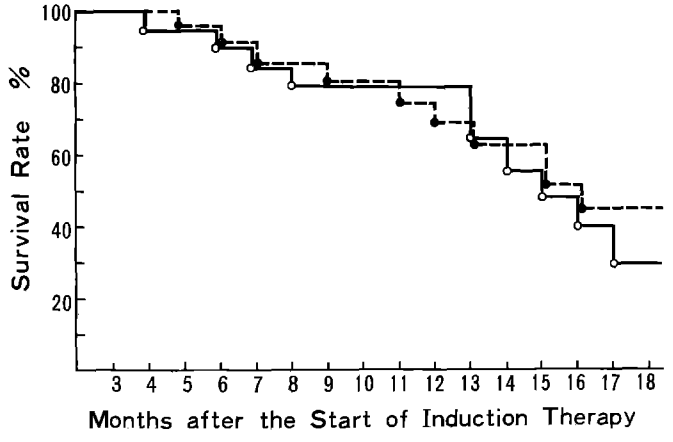

Fig. 4

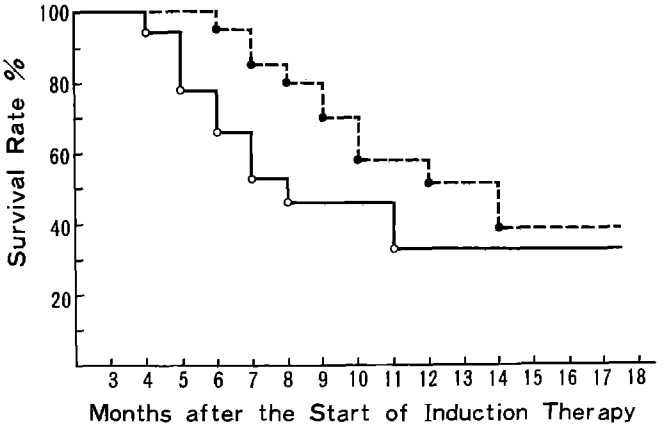

Fig. 5

Fig. 2. Comparison of estimated survival rates between patients receiving maintenance chemoimmunotherapy with MFC plus OK-432 (group A) and maintenance immunotherapy with OK-432 alone (group B). (O———O) A (n = 39); (●– – –●) B (n = 44)

Fig. 3. Comparison of lymphocyte counts between groups. (O———O) A; (●———●) B

Fig. 4. Estimated survival rates of patients with *differentiated* carcinoma histology (papillary, tubular and mucinous adenocarcinomas). Note that the survival curves are similar in groups A and B. (O———O) A (n = 19); (●– – –●) B (n = 22)

Fig. 5. Estimated survival rates of patients with *undifferentiated* carcinoma histology (poorly differentiated adenocarcinoma and signet-ring cell carcinoma). The survival curves differ markedly between groups in this category of patients. Also note that patients receiving OK-432 alone (group B) show significantly higher survival rates than those receiving additional MFC therapy (group A) for an extended period of time. (O———O) A (n = 18); (●———●) B (n = 20)

Comparison of Patients' Backgrounds

A comparison of the two study groups on the basis of 20 factors at the time of admission into induction therapy is summarized in Table 1. No categorical difference was observed between the two regimens in any of 20 factors. Factors 3–13 are categorized according to the General Rules for Gastric Cancer Study in Surgery and Pathology [5], the major part of which has been adopted in the System for Registration and Classification of the Stomach Cancer for WHO International Reference Center [13].

Survival Rate

The estimates of survivorship function, S(t), calculated according to the method of Kaplan and Meier [7], are plotted in Fig. 2, with numerical data given in Table 2. The estimated survival rates were higher in

Table 2. Labels for ordered survival months and survival rates, S(t), as estimated by the method of Kaplan and Meier [7]

Group A		Group B	
Survival months, t	S(t)	Survival months, t	S(t)
4, 4	0.949		
5, 5, 5, 5+	0.846	5, 5	0.955
6, 6, 6, 6+	0.769	6, 6, 6+, 6+, 6+	0.909
7, 7, 7	0.648	7, 7, 7	0.835
8, 8, 8+	0.567	8	0.811
9+, 9+		9, 9, 9, 9+, 9+	0.737
		10, 10, 10+, 10+	0.658
11, 11, 11+	0.513	11	0.631
		12, 12	0.549
13, 13, 13, 13+, 13+	0.427	13	0.521
14, 14+, 14+	0.395	14, 14	0.494
15	0.355	15, 15, 15+, 15+	0.439
16	0.316	16	0.408
17+		17+	
18, 18+	0.271	18+	
		21, 21+, 21+, 21+	0.371
23+			
24+		24+, 24+, 24+, 24+	
25	0.180	25+	
26+			
		27+	
28+			
		29+	

+, alive

group B (maintenance with immunotherapy alone) than in group A (maintenance with MFC and immunotherapy) throughout the 18-months period. The differences between the two study groups were statistically significant up to 9 months after the start of induction therapy. At 8 months, the difference in survival rate reached its maximum of 24.4%, with survival of 56.7% in group A and of 81.1% in group B.

Hematologic Parameters

Statistical comparisons between the two study groups showed no significant difference in WBC and platelet counts. As shown in Fig. 3, however, the lymphocyte counts of group A tended to gradually decline 3 months after the start of induction therapy, and the difference became largest at 5 months, when it was statistically significant, with 1387 ± 122 (SE) and 2035 ± 193 in groups A and B, respectively.

Histology and Survival Rate

The five histologic types listed in Table 1 were grouped into two categories according to the degree of cell differentiation. The differentiated category consisted of papillary adenocarcinoma, tubular adenocarcinoma, and mucinous adenocarcinoma. The undifferentiated category included the rest, i.e., poorly differentiated adenocarcinoma and signet-ring cell carcinoma. This division roughly corresponded to that of Lauren [9], our differentiated category corresponding to his intestinal type and our undifferentiated category to his diffuse type.

When so divided, there were 41 patients with a differentiated histology and 38 patients with an undifferentiated histology. Survival curves of these patients are separately shown in Figs. 4 and 5. In patients with differentiated carcinoma the survival curve did not differ at all in the two study groups (Fig. 4). Interestingly, however, the two groups showed a statistically significant difference in the survival distribution of the patients with undifferentiated histology (Fig. 5). Thus, the survival rate of group B patients was consistently higher than that of group A patients in the undifferentiated category. That this was not due to an imbalance in the patients' backgrounds has been confirmed by a comparison of the two study groups in the undifferentiated category by χ^2-tests.

Discussion

The results of the present study show that maintenance immunotherapy with OK-432 alone gives a significantly better survival curve than maintenance chemoimmunotherapy with MFC and OK-432. The effect of immunotherapy in prolonging the life of gastric cancer patients at a high risk of recurrence has been suggested by Edynak et al. [3]. The results of our previous study [12] in patients undergoing palliative gastrectomy and those obtained by Uchida and Hoshino [15] in inoperable gastric cancer patients, both utilizing a randomized patient allocation schema, have shown certain beneficial effects of immunotherapy with OK-432 that are not obtained with chemotherapy alone. The potentiation of cell-mediated immunity by OK-432 in animals has been well documented [4, 6, 8, 14]. It is likely that the maintenance administration of MFC in the present study concealed the immunopotentiating effect of OK-432 to some extent. While our study protocol did not permit us to evaluate the effect of OK-432 therapy per se, a sign of such an effect was seen in the increase of lymphocyte counts in the group of patients treated with OK-432 alone (Fig. 3).

A characteristic association of carcinoma histology with the effects of the two different treatment

regimens was noted in this study. Patients with undifferentiated carcinoma experienced more markedly deleterious effects following the administration of MFC than those with differentiated carcinoma (compare Fig. 5 with Fig. 4). It is of interest to determine whether gastric cancer patients with carcinoma histology of lower degrees of differentiation are relatively non-responsive to chemotherapy but responsive to immunotherpy. Such a study would require at least three randomized arms of treatment, i.e., no adjuvant therapy, immunotherapy only, and chemotherapy only. This type of study with an arm of no adjuvant therapy can be conducted only in patients undergoing curative resection. Alternatively, in patients undergoing palliative resection, a study comparing chemotherapy only, immunotherapy only, and chemoimmunotherapy would provide partial answers to the same question. Both types of trials are in progress in our cooperative study group. In the study of the latter type we are using tegafur instead of MFC, and OK-432 is again being used for immunotherapy. This third study has so far involved a total of 98 patients and will be the subject of a later communication.

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Received February 5/Accepted August 31, 1981