poorly differentiated adenocarcinoma in Barrett's epithelium and microscopically proven metastatic lymph-nodes in the coeliac region at laparotomy. He refused surgical treatment after six courses of chemotherapy, and is now, 2½ years later, in perfect condition without clinically detectable tumour (endoscopy plus biopsies). The median survival time of all evaluable patients was 7 months (range 2–54) after start of treatment and 3.5 months after stopping chemotherapy. 3 patients are still alive, with a follow-up of 2, 3 and 24+ months, respectively, after stopping treatment.

DISCUSSION

Although 2 patients in this phase II study achieved a well documented major regression, ifosfamide seems to have minor activity in untreated patients with advanced adenocarcinoma of the oesophagus or oesophageal–gastric junction area. Such a lack of response has also been documented for epidermoid carcinoma of the oesophagus in two other trials [3, 4]. However, we could not confirm the severe toxicity, especially myelosuppression, described in these reports. Several factors could play a role in this discrepancy. For example, our patients had a better performance status than those described by Ansell *et al.* [3]. More than half of the patients in Nanus *et al.*'s report were pretreated with radiotherapy and/or chemotherapy [4]. Concerning the dose and schedule of ifosfamide, we administered 6 g/m^2 as a continuous infusion over 48 h instead of 7.5 g/m^2 over 5 days as daily short intravenous infusions. On the other hand, our data on bone marrow suppression are not different from those of Ansell *et al.*, and clearly less serious than those of Nanus *et al.*, who experienced 18 episodes of WBC count nadir <1000 in 59 cycles of therapy against 0 in our series of 63 cycles.

In conclusion, ifosfamide, given in a dose of 6 g/m^2 over 48 h, has a low activity as first-line treatment in patients with adenocarcinoma of the oesophagus. The application of a continuous administration over 48 h may result in a more favourable toxicity profile than observed in fractionated regimens using daily short intravenous infusions for several days.

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Clinical Outcome of Postoperative Adjuvant Immunochemotherapy with Sizofiran for Patients with Resectable Gastric Cancer: a Randomised Controlled Study

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Adjuvant immunochemotherapy using the antitumour polysaccharide sizofiran (SPG), an extract from the culture broth of *Schizophyllum commune* Fries, was prescribed randomly for 386 Japanese patients with resectable gastric cancer. Although the overall survival probability for 5 years did not differ between the SPG and control groups, in 264 patients with curatively resected cancer, the probability to 5 year survival and to recurrence in the sizofiran-administered patients was better than in the controls. In the multivariate analysis, four of six prognostic factors correlated with the prognosis of the 264 patients who underwent curative surgery, that is, nodal involvement (χ^2 = 21.426, P = < 0.0001), age distribution (χ^2 = 9.262, P = 0.010), sizofiran administration (χ^2 = 6.507, P = 0.011), and primary tumour size (χ^2 = 9.345, P = 0.025). Thus, patients with a curatively resected gastric cancer had a better prognosis when sizofiran was prescribed in combination with antitumour drugs.
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INTRODUCTION

WHILE AN early diagnosis of gastric cancer is now feasible, extensive resection has to be done for those in the advanced stage of the disease. The long-term survival of these patients depends on the extent of micrometastasis present at the time of surgery, that is, the micrometastasis responsible for the recurrence has to be given due consideration. For this purpose, adjuvant cancer chemotherapy has been prescribed [1–3], but since anticancer drugs have immunosuppressive effects, adjuvant immunotherapy is required to gain an extended time of survival.

Sizofiran (SPG), a glucan extracted from culture medium

of Basidiomycetes *Schizophyllum commune* Fries, has a mean molecular mass of 450 000 and consists of repeating units of β-1, 3-D-glycopyranosyl residues forming triple stranded helices [4]. In *in vivo* studies, sizofiran proved to be a modifier of the innate biological response to malignant tumours [5–9].

To evaluate the antitumour effects of sizofiran used in combination with adjuvant chemotherapy, a randomised controlled study was done on patients with a resectable gastric cancer and treated in 43 different hospitals throughout Japan. The 5-year survival probabilities are reported herein.

PATIENTS AND METHODS

411 Japanese patients with resectable gastric cancer were entered into the study. Patients meeting the following criteria were excluded from the study: lack of microscopic diagnosis; intramucosal cancer with no metastatic lymph-nodes (Tis, N0) [10]; age over 80; primary cancer of another organ; and cardiac, hepatocellular and/or renal dysfunctions.

Randomisation

Just after surgery, the patients were divided into two groups, the macroscopically curatively resected group and the macroscopically non-curatively resected group. Classification of the curatively and non-curatively resected patients was performed as follows. With regard to the non-curative resection, if hepatic and/or peritoneal metastases as well as unresectable cancerous extension to adjacent structures and/or unresectable metastatic lymph-nodes were macroscopically evident, that is, intra-abdominal residual cancer tissues remained postoperatively (R2) [10], the classification of non-curative resection applied.

To each group, the sizofiran group (sizofiran + chemotherapy) and the control group (chemotherapy only) were allocated randomly in the 43 hospitals according to instructions of an independent controller (N.O.), who was responsible for the randomisation.

Postoperative adjuvant therapy

All patients were given 0.4 mg/kg and 0.2 mg/kg of mitomycin on the day of surgery and the next day, respectively. Oral futraful, 12 to 16 mg/kg per day, was initiated on the 14th postoperative day and was continued for as long as possible. For the sizofiran group, sizofiran was administered intramuscularly 40 mg once a week or 20 mg twice a week concurrently with the start of oral futraful. This immunotherapy also was continued for as long as possible.

Classification of patients

Staging in these patients was performed according to TNM classification [10].

Statistical analysis

Survival curves were calculated using the Kaplan–Meier method [11] and the Cox–Mantel test was used to evaluate differences between the survival curves [12]. The multivariate analysis using Cox's proportional hazards model was applied to determine the independent significance of prognostic factors, including effects of sizofiran on survival time [13]. The χ^2 test and Wilcoxon's rank sum test were used to compare the following 7 prognostic factors (Tables 3–5): sex, age, primary tumour (T), lymph-node metastasis (N), distant metastasis (M), curability in surgery and sizofiran administration.

Table 1. Causes of ineligibility and dropout

	Curative		Non-curative		
Criteria	Sizofiran	Control	Sizofiran	Control	Total
Ineligibility	10	9	1	2	22
Benign disease	1	1	0	0	2
Malignant lymphoma of the stomach	1	1	0	0	2
Intramucosal cancer with no metastatic lymph-nodes	7	7	1	0	15
Synchronous double cancer	1	0	0	0	1
Gastrojejunostomy only	0	0	0	2	2
Dropout	0	3	0	0	3
Death within 4 weeks of curative resection	0	3	0	0	3
Total	10	12	1	2	25

RESULTS

From October 1979 to December 1982, 411 gastric cancer patients in 43 different hospitals were registered for this study. Of these patients, 22 had to be excluded: 11 in the sizofiran group and 11 in the control group. 3 dropouts excluded from evaluation belonged to the control group (Table 1). In the remaining 386 patients, the curatively resected patients in the control and sizofiran groups numbered 134 and 130, respectively. Non-curatively resected patients numbered 60 and 62, respectively.

Distribution of background factors

As shown in Table 2, background factors analysed included the sex, age, degree of serosal invasion, lymph-node metastasis, peritoneal or hepatic metastasis, histological stage, curability in surgery and surgical approaches. These background factors were not statistically significant between the control and sizofiran groups in case of the curative and non-curative groups (Table 2).

Doses of the two drugs, mitomycin and futraful, given to both groups were much the same, and the mean total dose of sizofiran ingested was 1134 mg.

Survival probabilities

The 5-year survival probabilities are summarised in Fig. 1. The survival of patients with curative resection in the sizofiran group was higher at $P = 0.073$ (Cox–Mantel test) than that of the control group, although there was no significant difference ($P = 0.589$) in survival in the non-curatively resected patients between the sizofiran and control groups. As shown in Fig. 2,

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Table 2. Clinical data

Background factors	Curative		Non-curative	
	Sizofiran	Control	Sizofiran	Control
No of patients	130	134	62	60
Sex				
Male	85	86	33	41
Female	45	48	29	19
Age at surgery				
Under 40	11	16	6	3
40–49	22	22	9	7
50–59	30	46	14	16
60–69	42	32	23	20
70–79	25	18	10	14
Peritoneal metastasis				
p(−)	129	133	37	33
p(+)	1	1	25	27
Hepatic metastasis				
H(−)	130	134	51	52
H(+)	0	0	11	8
Histological serosal invasion				
ps(−)	67	65	12	12
ps(+)	63	69	50	48
Histological lymph-node metastasis				
N(−)	52	54	3	2
N(+)	78	80	59	58
Histological stage				
I	39	43	1	0
II	32	32	2	3
III	49	49	8	11
IV	10	10	51	46
Curability in surgery				
Curative	120	122	5	8
Non-curative	10	12	57	52
Extent of resection				
Total gastrectomy	45	46	28	22
Distal gastrectomy	82	86	34	37
Proximal gastrectomy	3	2	0	1

ps = prognostic serosal invasion, n = lymph-node metastasis, H = hepatic metastasis, p = peritoneal metastasis.

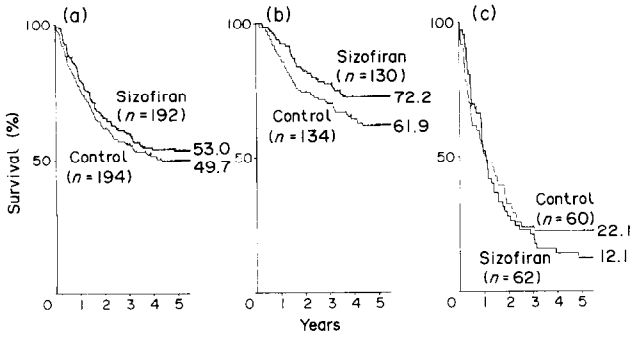

Fig. 1. 5-year survival possibilities in patients treated by curative or non-curative resection for gastric cancer. (a) All patients, $P = 0.4039$; (b) curative patients, $P = 0.0731$; (c) non-curative patients, $P = 0.5889$ (Cox–Mantel test).

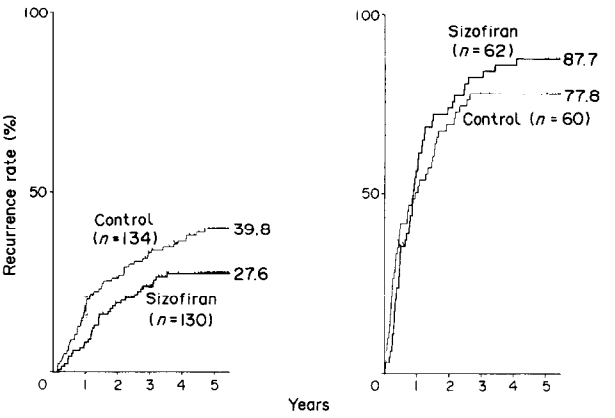

Fig. 2. Probability of recurrence in patients treated by curative (left, $P = 0.0407$) or non-curative resection (right, $P = 0.5181$) for gastric cancer.

the time to recurrence in patients curatively resected was significantly longer ($P = 0.041$, Cox–Mantel test) than that of the control group. In the non-curatively resected patients, no difference was observed between the sizofiran and control groups.

Multivariate analysis using Cox's proportional hazards model

For the 264 patients resected curatively, the survival time for the sizofiran group tended to be longer compared to that for the

Table 3. Multivariate analysis using Cox's proportional hazards model in all patients

Variable	n	Regression coefficients	χ^2	P
Macroscopic curability				
Curative	264	0		
Non-curative	122	0.5771	7.6168	0.006
Sex				
Male	245	0		
Female	141	0.0037	0.0005	0.981
Age (years)				
≤ 49	96	0		
50–69	223	−0.0451	4.6391	0.098
≥ 70	67	0.3639		
Primary tumour				
T1	40	0		
T2	116	1.1872	17.6132	0.0005
T3	177	1.6591		
T4	53	1.9801		
Lymph-node metastasis				
N0	112	0		
N1	107	0.5761	13.8859	0.001
N2	167	0.9871		
Distant metastasis				
M0	289	0	11.8530	0.0006
M1	97	0.7328		
Sizofiran treatment				
Not given	194	0		
Given	192	−0.1310	0.7603	0.383

control group; however, with respect to the survival time of all the patients and of 122 patients resected non-curatively, there was no difference between the sizofiran and control groups. Accordingly, further analysis was focused on these three groups.

As summarised in Table 3, the multivariate analysis in all the patients was performed combining sizofiran treatment and other prognostic factors including sex, age distribution, primary tumour size, lymph-node metastasis, distant metastatis and macroscopic curability in surgery (Table 3). Of these 7 variables, primary tumour and distant metastasis were the most important factor for predicting survival ($P < 0.001$ for both) and sizofiran treatment was not a significant factor ($P = 0.383$).

Table 4 shows the multivariate analysis in 264 patients given curative resection. Of the 6 variables, nodal metastasis, age distribution, sizofiran treatment, and primary tumour size were important factors for predicting survival with $P < 0.0001$, $P = 0.010$, $P = 0.0011$ and $P = 0.025$, respectively.

The multivariate analysis in 122 patients resected non-curatively is shown in Table 5. Distant metastasis was the only one important factor ($P < 0.001$), whereas sizofiran treatment had no statistical significance ($P = 0.388$).

With regard to the time to recurrence in the patients treated by curative resection, the multivariate analysis led to similar conclusion (data not shown).

Side-effects

Side-effects attributable to sizofiran became evident in 5 patients (3%): mild and temporary redness, swelling, induration and/or rash at the area of injection. These symptoms were mild and were not serious enough to discontinue the treatments.

Table 4. Multivariate analysis using Cox's proportional hazards model in 264 patients undergoing curative resection

Variables	*n*	Regression coefficients	χ^2	*P*
Sex				
Male	171	0		
Female	93	−0.0629	0.0703	0.791
Age (years)				
≤ 49	71	0		
50–69	150	−0.4494	9.2622	0.010
≥ 70	43	0.4594		
Primary tumour				
T1	39	0		
T2	93	1.0283	9.3448	0.025
T3	114	1.4613		
T4	18	1.7804		
Lymph-node metastasis				
N0	106	0		
N1	88	0.6583	21.4246	< 0.0001
N2	70	1.4405		
Distant metastasis				
M0	256	0	1.1132	0.291
M1	8	−0.5763		
Sizofiran treatment				
Not given	134	0		
Given	130	−0.5831	6.5071	0.011

Table 5. Multivariate analysis using Cox's proportional hazards model in 12 patients resected non-curatively

Sex	*n*	Regression coefficients	χ^2	*P*
Sex				
Male	74	0		
Female	48	−0.0761	0.1125	0.737
Age (years)				
≤ 49	25	0		
50–69	73	0.1987	2.8525	0.240
≥ 70	24	0.5331		
Primary tumour				
T1–T2	24	0		
T3	63	0.5550	5.9009	0.052
T4	35	0.8458		
Lymph-node metastasis				
N0	6	0		
N1	19	0.0005	0.1684	0.919
N2	97	0.1168		
Distant metastasis				
M0	33	0	13.0371	0.0003
M1	89	1.0088		
Sizofiran treatment				
Not given	60	0		
Given	62	0.1834	0.7442	0.388

DISCUSSION

The data in the current study show that the prognosis for patients with a curatively resectable gastric cancer depends on four factors. Nodal involvement is of urgent clinical importance in the prognosis, as shown in Table 4, and is entirely dependent on surgical procedures. On the other hand, in the 122 patients resected non-curatively, distant metastasis alone is an important prognostic factor (Table 5).

While adjuvant cancer chemotherapy is effective for many patients with gastric cancer, it is much less effective for those in the advanced stage of the disease [1, 2]. Some degree of immunological incompetence is induced by major surgery [14] and adjuvant chemotherapy begun immediately following surgery, particularly a bolus administration of mitomycin, has untoward effects on the depressed immunological status [15]. For this reason, adjuvant immunotherapy was given strong consideration. Sizofiran proved effective for the curatively resected patients, as shown in Table 4.

Okamura *et al.* [16, 17] reported clinical data on a randomised controlled study in patients with stage II or III cervical cancer, treated with irradiation plus sizofiran. At 48 and at 60 months after start of the study, the overall survival of stage II and III cancer patients in the sizofiran group was significantly longer than in the control group.

As immunological parameters, Okamura *et al.* [16] and our study group [18] evaluated the number of peripheral lymphocytes, the number of T-cells, lymphoproliferation induced by phytohemaglutinin, etc. The number of lymphocytes decreased from the pretreated value due to irradiation, surgery and cancer chemotherapy in patients of both the sizofiran and control groups. However, comparing the lymphocyte counts in the groups at 1, 3 and 6 months after treatment, the sizofiran group

tended to have a more rapid recovery, compared with the recovery of the control group.

These observations suggest that the immunological depression in those with cervical cancer or gastric cancer, due to radiation, major surgery and adjuvant chemotherapy, was overcome immunotherapeutically, by sizofiran.

Some investigators observed that sizofiran *in vivo* enhances the immune system, including activation of macrophages and T lymphocytes, induction of natural killer cells and augmentation of humoral factors, such as interleukins 1, 2 and 3, interferon and macrophage-activating factor [5–9, 19–21]. Another basidiomycetes glucan, lentinan, purified from edible mushrooms, has a chemical structure very similar to that of sizofiran, and it seems to have remarkable antitumour activity, at least in experimental murine models [22, 23].

All these data show that sizofiran warrants further attention, when prescribed in combination with anticancer drugs to treat patients with curatively resected gastric cancer.

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