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Immunotherapy and combined assay of serum levels of carcinoembryonic antigen and acute-phase reactants

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Abstract Our previous studies have revealed that gastric and esophageal cancer patients with abnormal sialic acid levels had a better response than those with normal levels if they received polysaccharide K (PSK), a nonspecific immunomodulator. Serum levels of carcinoembryonic antigen (CEA) and acute-phase reactants (APR) such as immunosuppressive acidic protein, acid-soluble glycoproteins, α1-antichymotrypsin, and sialic acid were analyzed in 872 gastric cancer patients who had undergone resection from March 1979 to September 1993 at the Department of Surgery of Tokai University. The patients were categorized into four groups according to the preoperative serum levels: group A had normal levels of both CEA and APR, group B had abnormal CEA and normal APR levels, group C had a normal CEA level and normal levels of one or more APR, and group D had abnormal levels of both CEA and of one or more APR. Patients in group D who received PSK showed significantly better survival than those without PSK (29.3% versus 6.9%; log-rank test, $P = 0.0015$; Breslow test, $P = 0.0042$). CEA-positive patients receiving PSK therapy exhibited a significantly better survival rate than those without PSK (38.1% versus 18.6%; log-rank test, $P = 0.0136$; Breslow test, $P = 0.0125$). Cox's regression analysis showed that PSK therapy was significantly related to survival in group D, but not in the other groups. We conclude that the combined assay of tumor-associated factors (such as CEA) and various nonspecific reactants to the presence of cancer (such as immunosuppressive acidic protein, α1-antichymotrypsin, acid-soluble glycoproteins and sialic acid) provides a good set of preoperative indicators on which to base the selection of treatment for individual gastric cancer patients.

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Introduction

There is now evidence that high preoperative levels of tumor-derived products such as carcinoembryonic antigen (CEA) and acute-phase reactants (APR) are associated with a shorter survival [12, 28, 37]. Although, a number of tumor markers are available as good monitors of tumor progression and the effectiveness of cancer therapy, they fail to detect early cancer and to predict the response to therapy. When we treat patients with cancer, it is important to predict their prognosis and the effectiveness of therapy before starting treatment in order to improve the quality of life. We have previously reported that gastric and esophageal cancer patients with abnormal sialic acid (SA) levels showed better results than those with normal sialic acid levels if they received polysaccharide K (PSK) [16, 22, 38], and that gastric cancer patients with abnormal immunosuppressive acidic protein (IAP) levels, who underwent total or proximal gastrectomy with splenectomy showed good results when they received PSK [23].

CEA is one of the first known tumor markers and abnormal values are common in a wide range of carcinomas, especially those of the gastrointestinal tract. We hypothesized that immunosuppressive parameters, such as oncofetal antigens like CEA and various nonspecific glycoproteins like SA, IAP, acid-soluble glycoproteins (ASP), and α1-antichymotrypsin (ACT), that are APR, may be able to predict the effectiveness of immunotherapy with PSK, since the antitumor activity of PSK is probably related to modulation of host immunity and an ability to reverse the immunosuppressed condition of cancer patients.

The aim of this study was to evaluate retrospectively gastric cancer patients who had received PSK therapy, in order to assess the clinical usefulness of the combined assay of CEA and APR with immunosuppressive activity, such as IAP, ASP, ACT, and SA.

Table 1 The characteristics of 872 patients in relation to the serum carcinoembryonic antigen (*CEA*) and acute-phase reactant (*APR*) levels according to the type of the therapy. Statistically significant differences were found in depht of cancer between CEA⁻APR⁻ patients with and without polysaccharide K (PSK) (χ^2 = 15.422, P = 0.009). pTNM staging was based on histological findings according to the UICC [41]. Statistically significant differences were found in pTNM stage between CEA⁻APR⁻ patients with and without PSK (χ^2 = 12.776, P = 0.026). Statistically significant differences in the age, the depth of tumor invasion, lymph node metastasis, and pTNM stage were found between patients in groups A, B, C, and D ($P < 0.0001$). *Differentiated* papillary adenocarcinoma, tubular adenocarcinoma well-differentiated type, and tubular adenocarcinoma moderately differentiated type; *Undifferentiated* poorly differentiated adenocarcinoma, mucinous adenocarcinoma, and signet-ring cell carcinoma. *M* tumor invades mucosa, *SM* tumor invades submucosa, *MP* tumor invades muscularis propria, *SS* tumor invades subserosa, *S* tumor penetrates the serosa, *SI* tumor invades adjacent structures

Characteristics	CEA⁻GP⁻			CEA⁺GP⁻			CEA⁻GP⁺			CEA⁺GP⁺		
	PSK⁻	PSK⁺	Total	PSK⁻	PSK⁺	Total	PSK⁻	PSK⁺	Total	PSK⁻	PSK⁺	Total
No.	309	177	486	17	7	24	179	110	289	43	30	73
Sex												
Male	211	124	335	12	6	18	133	70	203	36	25	61
Female	98	53	151	5	1	6	46	40	86	7	5	12
Lymph node metastasis												
N0	224	120	344	8	3	11	89	43	132	7	9	16
N1	51	34	85	2	3	5	38	21	59	7	8	15
N2	24	16	40	6	0	6	30	29	59	6	5	11
N3	3	1	4	0	0	0	3	6	9	6	0	6
N4	7	6	13	1	1	2	19	11	30	17	8	25
Depth of invasion												
M	127	52	179	2	0	2	35	13	48	0	3	3
SM	87	49	136	2	3	5	38	16	54	5	1	6
MP	22	30	52	4	0	4	17	11	28	2	4	6
SS	36	25	61	4	3	7	31	28	59	11	8	19
SE	31	19	50	4	1	5	53	37	90	20	9	29
SI	6	2	8	1	0	1	5	5	10	5	5	10
pTNM stage												
1A	196	90	286	4	2	6	66	24	90	4	4	8
1B	36	35	71	4	2	6	24	16	40	3	2	5
2	26	22	48	1	1	2	16	15	31	2	7	9
3A	16	11	27	3	1	4	16	13	29	2	2	4
3B	6	7	13	2	0	2	11	13	24	2	0	2
4	29	12	41	3	1	4	46	29	75	30	15	45
Histological type												
Differentiated	165	79	244	10	4	14	87	50	137	26	19	45
Undifferentiated	144	98	242	7	3	10	92	60	152	17	11	28
Therapy												
Gastrectomy alone	190	77	267	5	2	7	83	18	101	14	5	19
Gastrectomy + chemotherapy	119	100	219	12	5	17	96	92	188	29	25	54

Materials and methods

Preoperative CEA, IAP, ACT, ASP, and SA levels were analyzed in serum from 872 resected gastric cancer patients with histologically confirmed adenocarcinoma from March 1979 to September 1993 at the Department of Surgery of Tokai University. CEA and APR were assayed with the following commercial kits. CEA was determined with a Dainabott double monoclonal kit (Dainabot Co. Ltd. Tokyo, Japan); the sensitivity of this kit is 0.08 ng/ml and it recognizes both CEA and NCA-2 (non-specific cross-reacting antigen). ACT was determined by single radial immunodiffusion (SRID) using antisera and standards obtained from the Department of Biochemistry of our university and the sensitivity of this SRID method is 70 μg/ml. IAP [34], which shows a close correlation with α1-acid glycoprotein, was determined with a commercial kit (IP plate; Sanko Junyaku Co. Ltd., Tokyo, Japan) and the sensitivity of this kit is 50 μg/ml. ASP which is a perchloric-acid-soluble glycoprotein, was determined by Coomassie brilliant blue G-250 (ASPRO-GP kit; Otsuka Assay Laboratories Co. Ltd. Tokushima, Japan; the sensitivity of this kit is 0.4 mg/ml): it is almost identical to the seromucoid determined by Winzler's method, and contains 60% IAP, but it is not well known that these markers are identical to the gene product known as α1-acid glycoprotein. SA was measured by enzymatic assay with a commercial kit using neuraminidase (Kyokuto Sialic Acid Test, Kyokuto Pharmaceutical Co. Ltd., Tokyo, Japan) and the sensitivity of this test is 0 mg/ml. In this study, the upper limits of the normal ranges for these proteins were defined as: CEA 7.0 ng/ml; IAP 558 μg/ml; ASP 1.48 mg/ml; ACT 280 μg/ml and SA 0.858 mg/ml [15, 17–20].

The patients were categorized into four groups according to the preoperative serum levels. Group A had normal levels of both CEA (less than 7.0 ng/ml) and APR (less than 558 μg/ml IAP, 1.48 mg/ml ASP, 280 μg/ml ACT, and 0.858 mg/ml SA), the median and range of their CEA, IAP, ASP, ACT, and SA being 1.9 ng/ml (0.1–6.8 ng/ml), 345 μg/ml (50–558 μg/ml), 1.08 mg/ml (0.317–1.48 mg/ml), 205.3 μg/ml (85.3–280 μg/ml), and 0.55 mg/ml (0.189–0.82 mg/ml) respectively. Group B had abnormal CEA (more than 7.0 ng/ml) and normal APR levels, the median and range of their CEA, IAP, ASP, ACT, and SA being 12.2 ng/ml (7.2–181.1 ng/ml), 365 μg/ml (102–523 μg/ml), 1.056 mg/ml (0.247–1.462 mg/ml), 208.0 μg/ml (132.0–280 μg/ml), and 0.58 mg/ml (0.394–0.81 mg/ml) respectively. Group C had a normal CEA level and abnormal APR (one or more abnormal levels of IAP, ASP, ACT and SA: more than 558 μg/ml IAP, 1.48 mg/ml ASP, 280 μg/ml ACT, or 0.858 mg/ml SA), the median and range of their CEA, IAP, ASP, ACT, and SA being 2.5 ng/ml (0–7.0 ng/ml), 555 μg/ml (210–1654 μg/ml), 1.638 mg/ml (0.411–6.0 mg/ml), 297.0 μg/ml (149.3–884 μg/ml), and 0.715 mg/ml (0.432–1.405 mg/ml) respectively. Group D had abnormal levels of both CEA and APR, the median and range of their CEA, IAP, ASP, ACT, and SA being 18.0 ng/ml (7.1–727 ng/ml), 675 μg/ml (300–1543 μg/ml), 2.03 mg/ml (1.073–

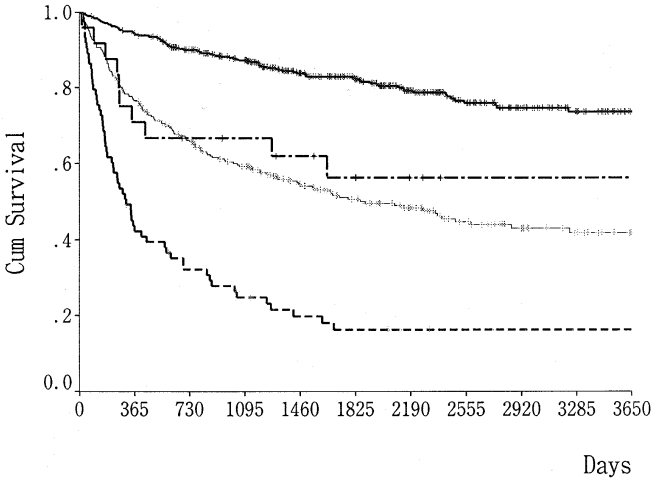

Fig. 1 Survival according to the preoperative carcinoembryonic antigen (CEA) and acute-phase reactant (APR) levels. —— Group A (n = 486), —·— group B (n = 24), —— group C (n = 289), and – – – group D (n = 73). *Cum* cumulative

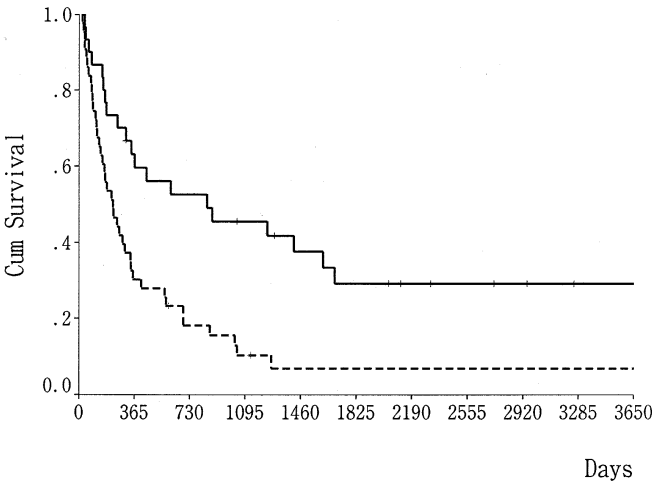

Fig. 2 Survival of patients with abnormal levels of CEA and one or more APR (group D) according to polysaccharide K (PSK) therapy. ——. Patients receiving PSK, and – – – patients without PSK

6.5 mg/ml), 340 μg/ml (102.7–648 μg/ml), and 0.81 mg/ml (0.513–1.32 mg/ml) respectively. All patients gave informed consent to the study. In the chemotherapy group, patients with macroscopic stage 1B to 4 disease underwent gastrectomy with concomitant intravenous injection of mitomycin C (Kyowa Hakko Co. Ltd., Tokyo, Japan) at a dose of 0.4 mg/kg and another dose of 0.2 mg/kg was also given on postoperative day 1. This was followed by oral administration of various fluoropyrimidines, such as N^1-(2′-tetrahydrofuryl)-5-fluorouracil (Futraful; Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) at 600 mg/day, 5-fluorouracil (5-FU; Kyowa Hakko Kogyo Co. Ltd., Tokyo, Japan) at 150 mg/day, 1-hexylcarbamoyl-5-fluorouracil (Mitsui Pharmaceutical Co. Ltd., Tokyo, Japan) at 400 mg/day, or UFT (a 1:4 mixture of tegafur and uracil; Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) at 300 mg/day from day 14 after surgery. Alternatively, oral administration of a fluoropyrimidine alone was started from day 14. In the immunotherapy group, PSK (Krestin; Kureha Chemical Industry Co., Ltd., Tokyo, Japan) was administered orally from day 14 after gastrectomy at a dose of 3.0 g/day. Use of fluoropyrimidines was left to the judgment of the attending doctor. Postoperative adjuvant therapy was continued for at least 3 months unless there was tumor progression. Subjects took turns receiving chemotherapy with or without immunotherapy using PSK, and patients at macroscopic stage 1A received gastrectomy alone with PSK or without PSK. Many of the patients refused postoperative therapy or their doctors did not consider postoperative adjuvant therapy to be indicated, so they underwent gastrectomy alone without postoperative adjuvant therapy.

In a Cox multivariate regression analysis of factors related to survival, the variables entered were serum levels of CEA, IAP, ASP, ACT and SA, and PSK therapy, age, histological type, and pTNM stage [41].

Table 2 Results of univariate analysis of factors related to survival. *Parameter* the estimated coefficient, *SE* the standard error of the estimated coefficient, *Wald* the Wald statistic, *Sig* the significance level for the Wald statistic, *RR* relative risk, *CI* confidence interval, *SA* sialic acid, *IAP* immunosuppressive acidic protein, *ASP* acid-soluble glycoproteins, *ACT* α1-antichymotrypsin

Variable	Parameter	SE	Wald	Sig.	RR	95% CI	
						Lower	Upper
Female	0.0000				1.0000		
Male	–0.0194	0.1239	0.0244	0.8759	0.9808	0.7693	1.2505
Age (years)							
<60	0.0000				1.0000		
≥60	0.9129	0.1168	61.1262	<0.0001	2.4916	1.9819	3.1323
pTNM 1A–2	0.0000				1.0000		
pTNM 3A–4	2.3082	0.1238	347.5022	<0.0001	10.0567	7.8897	12.8190
Differentiated	0.0000				1.0000		
Undifferentiated	0.2706	0.1130	5.7312	0.0167	1.3107	1.0503	1.6358
SA–	0.0000				1.0000		
SA+	1.3119	0.1392	88.8456	<0.0001	3.7131	2.8266	4.8775
CEA–	0.0000				1.0000		
CEA+	1.2574	0.1371	84.1300	<0.0001	3.5161	2.6877	4.5999
IAP–	0.0000				1.0000		
IAP+	1.3235	0.1149	132.6880	<0.0001	3.7565	2.9991	4.7053
ASP–	0.0000				1.0000		
ASP+	1.3236	0.1138	135.1836	<0.0001	3.7568	3.0055	4.6959
ACT–	0.0000				1.0000		
ACT+	1.2010	0.1131	112.8068	<0.0001	3.3234	2.6628	4.1480
PSK+	0.0000				1.0000		
PSK–	0.0303	0.1158	0.0684	0.7936	1.0308	0.8215	1.2934

Table 3 Multivariate analysis of serum levels of CEA and APR relative to survival

Variable	Parameter	SE	Wald	Sig.	RR	95% CI	
						Lower	Upper
CEA	0.0061	0.0009	42.8872	<0.0001	1.0061	1.0043	1.0080
IAP	0.0019	0.0004	17.6332	<0.0001	1.0019	1.0010	1.0027
ASP	0.0020	0.0001	4.1156	0.0425	1.0020	1.0001	1.0040
SA	0.0064	0.0048	1.7778	0.1824	1.0064	0.9970	1.0158
ACT	0.0000	0.0004	0.0150	0.9027	1.0001	0.9992	1.0009

Table 4 Cox multivariate regression analysis of factors relative to survival in group D

Variable	Parameter	SE	Wald	Sig.	RR	95% CI	
						Lower	Upper
PSK+	0.0000				1.0000		
PSK–	0.6328	0.2906	4.7413	0.0294	1.8829	1.0652	3.3281
pTNM 1A-2	0.0000				1.0000		
pTNM 3A-4	1.5017	0.3626	17.1470	<0.0001	4.4892	2.2054	9.1381
Age (years)							
<60	0.0000				1.0000		
≥60	0.5744	0.2985	3.7040	0.0543	1.7761	0.9895	3.1882
Differentiated type	0.0000				1.0000		
Undifferentiated type	0.1974	0.2709	0.5310	0.4662	1.2182	0.7164	2.0714

The χ^2 test with Yates' correction and Fisher's exact test were used for statistical evaluation of the data. Survival curves were calculated using the Kaplan-Meier product-limit estimate and differences in survival were assessed by the log-rank test and the Breslow test. *P* values of less than 0.05 were considered to be significant. All statistical analyses were carried out using SPSS 7.5 software (SPSS Inc., Chicago, USA).

Results

Table 1 shows the clinical characteristics of the 872 patients stratified according to PSK therapy. Their ages ranged from 21 to 93 years (median: 59 years), and 70.8% were men. Within group A, there were significant differences in the depth of tumor invasion and pTNM stage between the patients who had and had not received PSK therapy (depth: $\chi^2 = 15.422$, $P = 0.009$, pTNM stage: $\chi^2 = 12.776$, $P = 0.026$). Within groups B, C, and D, and among CEA-positive patients, there were no significant differences in sex, pTNM stage, and histological types between the patients who had and had not received PSK therapy. There were significant differences in the age, the depth of tumor invasion, lymph node metastasis, and pTNM stage among patients in groups A, B, C, and D ($P<0.0001$). Patients in group D showed more tumor aggressiveness than those in other groups.

Among groups C and D, the numbers of patients who were positive for IAP, ASP, ACT, and SA were 142 (49.1%) and 54 (74.0%), 213 (73.7%) and 63 (86.3%), 188 (65.1%) and 50 (68.5%), and 58 (20.1%) and 31 (42.5%) respectively.

Figure 1 shows the ten-year survival rates of groups A, B, C, and D, which were 73.6%, 56.3%, 41.9%, and 16.1% respectively. There were significant differences in survival between groups A and B, A and C, A and D, B and D, and C and D. There was no significant difference in survival between groups B and C. The 10-year survival rates of groups A, B, C, and D without PSK were 72.6%, 47.9%, 47.6%, and 6.9% respectively, while, those of patients receiving PSK were 74.9%, 71.4%, 33.3%, and 29.3% respectively. Patients in group D who received PSK had a significantly better survival rate than those without PSK (log-rank test, $P = 0.0015$; Breslow test, $P = 0.0042$; Fig. 2). Within groups A, B, and C, there were no significant differences in survival between patients with or without PSK.

The 10-year survival rates of CEA-negative patients with and without PSK therapy were 58.7% and 63.2% respectively, while CEA-positive patients with and without PSK had survival rates of 38.1% and 18.6% respectively. CEA-positive patients receiving PSK therapy exhibited significantly better survival than those without it (Fig. 3; log-rank test, $P = 0.0136$; Breslow test, $P = 0.0125$).

In univariate analysis, age, pTNM stage, histological type, CEA, IAP, ASP, ACT, and SA were significantly related to survival, but sex and PSK therapy were not (Table 2). Table 3 shows the results of a Cox multivariate regression analysis of serum levels of CEA, IAP, ASP, ACT, and SA related to survival. CEA, IAP, and ASP were significantly related to survival, but ACT and SA were not.

Table 4 shows the results of a Cox multivariate regression analysis of factors related to survival in group D patients. PSK therapy was the most significant factor related to survival in group D, but in the other groups as well as in CEA-positive-patients, PSK therapy was not significantly related to survival, according to the result of a Cox multivariate analysis.

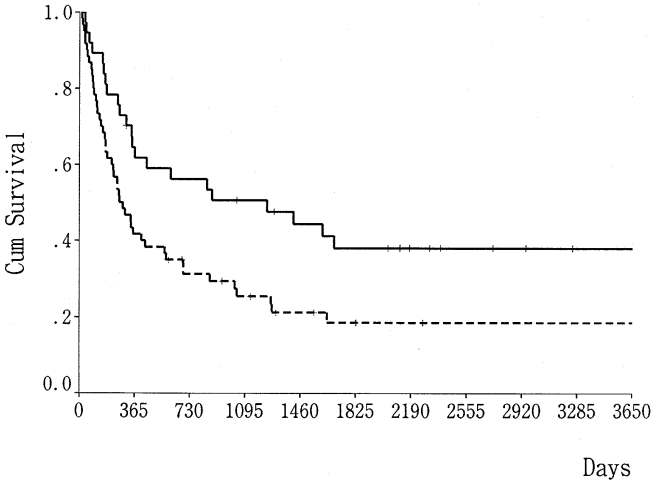

Fig. 3 Survival of patients with abnormal CEA levels according to PSK therapy. —— Patients receiving PSK; and – – – patients without PSK

Discussion

If we could predict rational or effective forms of therapy for individual cancer patients before treatment, then patients should gain both an improved quality of life and a better outcome. Tumor-associated markers may aid in assessing the extent of disease and provide a tool for following the response of patients to therapy. In addition, they may help the monitoring of patients for the early detection of recurrence [1, 29]. Acute-phase reactants in colon cancer, estrogen and progesterone receptors, the multidrug-resistance phenotype, pS2 protein and INT-2 amplification in breast cancer, and Ki-S5 immunoreactivity scores in renal cell cancer have all been reported to be useful predictors of the clinical outcome [3, 4, 30, 33, 35, 36], but these markers did not assist in selecting individual patients for specific therapy. Johnston et al. reported that thymidylate synthase protein and thymidylate synthase mRNA expression were correlated with the response to chemotherapy based on 5-FU plus leucovorin in patients with colorectal and gastric cancer [8]. Regarding correlations with the response to immunotherapy, Lacombe et al. reported on the *p53* gene and bacillus Calmette-Guérin therapy in superficial bladder carcinoma [11], and Tartour et al. reported the association between the elevation of serum cross-reacting protein levels and poor response to interleukin-2 (IL-2) therapy in melanoma [39]. This report may differ from our findings, because of different mechanisms for fighting tumors: IL-2 and PSK may affect the tumors directly and indirectly respectively. However, from these reports and our findings suggest that it may be important that gastric cancer patients with both positive CEA and APR show good responses to PSK therapy.

It has been generally accepted that ACT production is promoted by cytokines such as IL-6 and leukemia-inhibitory factor, while α,1-acid glycoprotein is increased by IL-1 and tumor necrosis factor [2]. Increased serum levels of APR are due to an acute reaction [6] that is controlled by cytokines [10], and their activities are potentiated by PSK [5, 7, 9, 42]. PSK is an antitumor drug prepared from *Coriolus vesicolor* (Fr.) Quel, a member of the Basidiomycetes. It is composed of proteins and polysaccharides and has a molecular mass of approximately 100 kDa. PSK has been shown to exert a beneficial therapeutic effect in various experimental studies of tumor therapy [40]. We have also reported on the effectiveness of nonspecific immunotherapy with PSK in gastric cancer, as determined by a retrospective study of gastric cancer [24]. The antitumor activity of this nonspecific immunopotentiator is considered to be based on its regulation of host immunity and it is widely administered in Japan by the oral route, since it has the ability to normalize the immunosuppressed state of cancer patients. In Japanese clinical trials of PSK therapy in patients with gastric cancer [14], colon cancer [13], and esophageal cancer [25–27], this agent was effective when combined with chemotherapy. Moreover, PSK may decrease the serum levels of immunosuppressive acute-phase reactants in gastric cancer patients [21]. Our previous study showed that SA is a good predictor of the response to PSK therapy, but determination of SA does not allow precise individualization of treatment. The present study shows that it is possible to predict the response to PSK therapy in gastric cancer patients, and that the combined preoperative assay of both tumor-associated factors (such as CEA) and various nonspecific reactions to the presence of a cancer (such as IAP, ACT, ASP, and SA) provide a useful set of indicators on which to base the choice of PSK therapy for individual gastric cancer patients.

Prado et al. reported that CEA expression by colorectal carcinoma cells was protective against natural-killer(NK)-mediated lysis, and pointed out that CEA may act as a cross-reacting antigen for class-I major histocompatibility complex molecules, since the presence of both molecules on tumor cells seemed to hamper interaction with NK cells [31]. They also suggested that CEA molecules, often present at high concentrations in the blood of patients with malignant tumors, might act as a suppressive factor for host immunocompetent cells. Rivoltini et al. reported the inhibition of lymphokine-activated killer (LAK) cell lytic activity by addition of CEA, and suggested that it could bind to a ligand on the LAK cell surface, thus blocking effector/target-cell adhesion [32]. Our results suggest that the response to PSK may be related to the effectiveness of the immune system and that PSK inhibits the interference of CEA with interactions between NK cells and tumor and/or between LAK cells and tumor, possibly directly or by modulating cytokine production.

We conclude that the combination of preoperative tumor-associated factors (such as CEA) with nonspecific responses to the presence of cancer (such as IAP, ACT, ASP, and SA) provides a good set of indicators for the appropriate treatment for individual cancer patients. Further evaluation of the association between the production of tumor antigens and nonspecific reactants and the effects of immunomodulating agents should be undertaken in the future.

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