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Preoperative administration of polysaccharide Kureha and reduced plasma transforming growth factor-β in patients with advanced gastric cancer: A randomized clinical trial

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Abstract. Systemic abrogation of TGF-β signaling results in tumor reduction through cytotoxic T lymphocytes activity in a mouse model. The administration of polysaccharide-Kureha (PSK) into tumor-bearing mice also showed tumor regression with reduced TGF-β. However, there have been no studies regarding the PSK administration to cancer patients and the association with plasma TGF-β. PSK (3 g/day) was administered as a neoadjuvant therapy for 2 weeks before surgery. In total, 31 advanced gastric cancer (AGC) patients were randomly assigned to group A (no neoadjuvant PSK; n=14) or B (neoadjuvant PSK therapy; n=17). Plasma TGF-β was measured pre- and postoperatively. The allocation factors were clinical stage (cStage) and gender. Plasma TGF-β ranged from 1.85-43.5 ng/ml (average, 9.50 ng/ml) in AGC, and 12 patients (38.7%) had a high value, >7.0 ng/ml. These patients were largely composed of poorly-differentiated adenocarcinoma with pathological stage III/IV. All the six elevated cases in group B showed a significant reduction of plasma TGF-β (from 21.6 to 4.5 ng/ml, on average), whereas this was not exhibited in group A. The cases within the normal limits of TGF-β remained unchanged irrespective of PSK treatment. Analysis of variance showed a statistically significant reduction in the difference of plasma TGF-β between groups A and B (P=0.019). PSK reduced the plasma TGF-β in AGC patients when the levels were initially high. The clinical advantage of PSK may, however, be restricted to specific histological types of AGC. Perioperative suppression of TGF-β by PSK may antagonize cancer immune evasion and improve patient prognosis in cases of AGC.

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Introduction

Transforming growth factor-β (TGF-β), a member of the TGF-β superfamily of proteins, is known to regulate an extensive range of cellular processes, including wound healing, immune response, apoptosis, cell differentiation and cellular senescence (1,2). TGF-β signaling induces growth and development during early embryogenesis. However, in mature tissues a number of cells react to TGF-β with a cytostatic or apoptotic response. TGF-β has a role as a growth inhibitor and a tumor suppressor and can also induce tumor metastasis during the late stages of tumor development. Inactivation in TGF-β signaling frequently occurs in human cancers either by mutation or downregulation of the expression of any of the signaling components (3,4).

By contrast, the TGF-β plasma concentration has been reported to increase in a wide variety of advanced stages of human cancer, such as esophageal (5), gastric (6), colorectal (7-10), hepatocellular (11-17), lung (18-20) and breast cancer (21-28). These findings suggest that systemic elevation of TGF-β may be involved in tumor progression. Previously, systemic, but not local, abrogation of TGF-β signaling resulted in a dramatic reduction of tumors through the cytotoxic T lymphocytes (CTLs) activity in a murine model (29). In this model, TGF-β specifically inhibited the expression of the cytolytic gene products of perforin, granzyme A, granzyme B, Fas ligand and interferon-γ by acting on the CTLs. Together, these gene products are responsible for CTL-mediated tumor cytotoxicity. Notably, neutralization of systemic TGF-β in mice facilitates tumor clearance with restoration of cytotoxic gene expression in antigen-specific CTLs *in vivo*. These results suggest that systemic regulation of TGF-β has a clinical therapeutic potential for cancer through modification of tumor immunity.

Polysaccharide Kreha (PSK, also known as Krestin; Kureha Chemical Industry Co., Tokyo, Japan) is a unique protein-bound polysaccharide, which has been used as a chemoimmunotherapy agent in the treatment of cancer for over three decades in Japan. PSK is derived from the CM-101 strains of the fungus *Coriolus versicolor*, which is notably perceived to be a specific antidote for cancer. PSK administration in tumor-bearing mice also showed tumor regression with reduced TGF-β through CTL induction (30,31). In cancer clinics, PSK is considered to be well-suited for concurrent use with cytotoxic agents as a postoperative adjuvant treatment in Japan, as an oral formulation with a low incidence of adverse reactions will enable treatment for outpatient facilities (32,33). The study by Nakazato *et al* (32) demonstrated that supplementing adjuvant chemotherapy, mitomycin C and oral fluorouracil, with PSK significantly prolonged the survival rate following curative gastrectomy in a large prospective trial of patients with gastric cancer. In addition, simultaneous postoperative adjuvant PSK treatment with tegafur and uracil (UFT) has been shown to be effective against colorectal cancer (33).

The current study presents a randomized clinical trial for the validation of the therapeutic potential of PSK. The primary endpoint of PSK treatment is the effect on plasma TGF-β in advanced gastric cancer (AGC), and the secondary endpoint is its prognostic effect.

Materials and methods

End points. The primary objective of the study was to evaluate whether the preoperative addition of PSK modifies the systemic TGF-β concentration. The study was approved by the ethics committees of Kitasato University (Sagamihara, Kanagawa, Japan).

Resources. The study received grants from the Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMTC) and the Kureha Chemical Industry Co. (Tokyo, Japan). The costs of the preoperative PSK administration was not covered by National Health Insurance as PSK must be administered to cancer patients in combination with any chemotherapeutic drugs and the Kureha Pharmacoceutical Inc. (Tokyo, Japan) supported the costs. By contrast, the plasma values of TGF-β during the perioperative course were assessed by SLR Laboratories (Tokyo, Japan) and as this cost was not covered by the grants of the National Health Insurance, it was funded by the JFMTC grant.

Plasma TGF-β quantification. Enzyme-linked immunosorbent assay (ELISA) was used to measure plasma TGF-β1. The blood samples were stored at 4˚C following collection, and the platelet-poor plasma was obtained by centrifugation at 1,000 x g for 15 min followed by 10,000 x g for 10 min. The plasma samples were maintained at -80˚C until assayed. Prior to being assayed, all the samples were activated by 1.0 N hydride chloride at a volume of one-fifth of the plasma, followed by 1.2 N NaOH/0.5 M HEPES, according to the manufacturer's instructions (Quantikine Human TGF-β ELISA kit; R&D Systems, Minneapolis, MN, USA). This assessment kit was used in a previous study that showed the distribution of the TGF-β1 values in the healthy volunteer (5). The kit cannot differentiate between active and inactive TGF-β as the samples were all activated by acid as previously described.

Eligibility criteria. The resectable gastric cancer patients, as assessed preoperatively, with curative intent that satisfied the inclusion criteria and did not meet the exclusion criteria as described were recruited as subjects. The inclusion criteria were as follows: i) Histologically proven, resectable advanced gastric adenocarcinoma with clinical stage (cStage) IB to III (as assessed using the 13th edition, Japanese Gastric Cancer Association Stage (34); ii) age between 20-80 years; iii) no preoperative cancer treatment, such as chemotherapy, immunotherapy and radiotherapy; iv) no synchronous or metachronous cancers; v) sufficient organ functions; vi) preoperative Eastern Cooperative Oncology Group performance status, 0-2; and vii) provided written informed consent. Exclusion criteria included: i) Fresh gastrointestinal bleeding or patients who underwent transfusion; ii) ascites or pleural effusion; iii) serious infectious disease; iv) intestinal palsy or occlusion; v) females who were pregnant or planned to become pregnant during the study period; and vi) psychological disease requiring treatment.

Registration. The eligible patients, ≥14 days before surgery, were centrally registered and randomly assigned to treatment by the Registration Center, located at the Department of Clinical Research Center, School of Medicine, Kitasato University. Randomization was performed by the minimization technique. The patients were allocated according to two factors: Clinical disease stage (cStage IB/II/III) and gender. patients were accrued between May, 2009 and June, 2011.

Treatment methods. The enrolled patients were randomly assigned to surgery alone (group A) or to preoperative 2-week administration of PSK (group B) by the Registration Center. The medication was started 14 days before surgery and PSK (3 g/day) was administered as a neoadjuvant therapy. Plasma TGF-β was measured preoperatively (1, 7 and 14 days) and postoperatively (1, 3 and 7 days).

Follow-up. During the treatment, patients underwent physical and laboratory examinations simultaneously with TGF-β assessment (1, 7 and 14 days preoperatively, and 1, 3 and 7 days postoperatively). Chest-abdominal CT scans were obtained every 6 months for 3 years.

The following 53 factors were examined at 6 specific time-points (1, 7 and 14 days preoperatively and 1, 3 and 7 days postoperatively) in the clinical study: White blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin (MCH), MCH concentration, platelet count (PLT), neutrophil count, eosinophil count, lymphocyte count, monocyte count, basophil count, large unstained cell count, total protein concentration (TP), albumin concentration (Alb), total bilirubin, direct bilirubin, aspartate aminotransferase, alanine transaminase, alkaline phosphatase, cholinesterase, γ-glutamyl transpeptidase, lactate dehydrogenase, creatine phosphokinase (CPK), amylase, glucose, total cholesterol, triglyceride, blood urea nitrogen (BUN), creatinine, uric acid, sodium (Na), potassium, chlorine, calcium (Ca), phosphorus and C-reactive protein. The factors examined at the first point (preoperative) were pro-thrombin

time (PT)-%, PT-international normalized ratio, activated partial thromboplastin time (APTT), APTT-%, control T (time), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), CA125, CA72-4, *Helicobacter Pylori* antibody (Ab), Hepatitis C virus Ab, Hepatitis B (HBs) surface antigen, Treponema pallidum Ab and human immunodeficiency virus antigen-Ab.

Statistics. Continuous variables were evaluated by Student's t-test; categorical variables were evaluated by Fisher's exact test or the χ^2 test, as appropriate. Data were assessed using analysis of variance (ANOVA) and $P<0.05$ was considered to indicate a statistically significant difference.

Umin registration of the study. The study was registered to the Infrastructure for Academic Activities of the University Hospital Medical Information Network (identifier UMIN000006025). The details are available at the following address: https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000007129&language=J.

Table I. Characteristics of the patients with advanced gastric cancer.

	Group A n=14	Group B n=17	P-value
cStage			NS
cStage IB	3	4	
cStage II	7	8	
cStage III	4	5	
Gender			NS
Male	9	11	
Female	5	6	
R0 resection			NS
Yes	10	14	
No	4	3	

cStage, clinical stage; NS, not significant.

Results

Elevated level of plasma TGF-β is significantly reduced by 2-week PSK administration in AGC. The plasma TGF-β concentration was previously reported in a normal volunteer, and the average (± standard deviation) was 4.6±2.3 ng/ml (5). Therefore, the high level of TGF-β was defined as ≥7.0 ng/ml. The 31 AGC patients allocated by cStage and gender were distributed into groups A (no PSK administration, n=14) and B (PSK administration, n=17). The patient characteristics are shown in Table I. As a result, 12 preoperative patients (38.7%) showed a high level of TGF-β in AGC, and groups A and B included six cases designated as those with high values in the study, respectively.

Notably, the AGC patients with elevated levels of TGF-β had significantly suppressed levels by the 2-week administration of PSK (group B), and its reduction was statistically significant (Wilcoxon signed-rank test: P=0.028 1-week before; and P=0.028 1-day before compared to the baseline TGF-β 2-weeks before) (Fig. 1A). By contrast, the TGF-β levels for the patients within a normal limit of TGF-β did not change in group B (Fig. 1C). The AGC patients with elevated levels of TGF-β were only slightly reduced for group A patients who were not administered PSK, and its reduction was not statistically significant (Fig. 1B). Such a mild reduction of the plasma TGF-β may be due to a stressful psychotic effect of the preoperative condition. The group A patients within the normal limit for the TGF-β value did not exhibit a similar change to group B (Fig. 1D). The representative individual cases are shown as examples from patients that represent the effect on TGF-β by PSK administration (Fig. 1E and F). The high initial TGF-β levels were significantly suppressed in patients following preoperative administration (Fig. 1E), and the effect was persistent during the postoperative term. By contrast, the high TGF-β values of patients were occasionally accompanied by a mild reduction of TGF-β (Fig. 1F), but notably, the majority of TGF-β reduction during the postoperative term was accompanied by primary tumor resection (resection of the primary cancer could not be performed in case 3, whereas R0 resection was performed in case 2).

Elevated plasma TGF-β is restricted to diffuse-type gastric cancer. The association of the histological type of the patients with elevated plasma TGF-β was investigated. Twelve AGC patients with elevated plasma TGF-β were composed of 10 patients with diffuse-type gastric carcinoma and two patients with papillary adenocarcinoma. In order to confirm the specificity of the elevated plasma TGF-β to poorly-differentiated adenocarcinoma, 19 additional gastric cancer patients were included, such as early gastric cancer, for the examination of the preoperative TGF-β value. Notably, the patients with elevated plasma TGF-β levels were again restricted to diffuse-type gastric carcinoma (11/27; 41%) and papillary adenocarcinoma (3/3; 100%), whereas any of the 20 intestinal-type gastric carcinoma, except papillary adenocarcinoma, showed no increase of plasma TGF-β for the gastric cancer patients (0/20; 0%) (Fig. 2A). The difference of the plasma TGF-β value between diffuse- and intestinal-type (excluding papillary) was statistically significant ($P<0.0001$). Systemic elevation of the TGF-β value in diffuse-type gastric cancer may be derived from the tumors, as they increased in quantity as the stage progressed (Fig. 2B).

TGF-β immunohistochemistry and plasma level in AGC. Immunohistochemistry of TGF-β was performed in AGC. TGF-β was strongly immunostained for normal mucosal cells, including parietal and chief cells, and mucosal cells in the fundus, body or antrum of the stomach (Fig. 2C), as well as cancer cells with varying degrees of differentiation and infiltrating tumor stromal cells. Furthermore, the muscle cells in normal tissues were intensely immunostained for TGF-β (data not shown). As a result, there was no correlation of TGF-β immunohistochemical staining with the plasma TGF-β level.

Persistent suppression of plasma TGF-β during the perioperative course by preoperative PSK administration. Preoperative

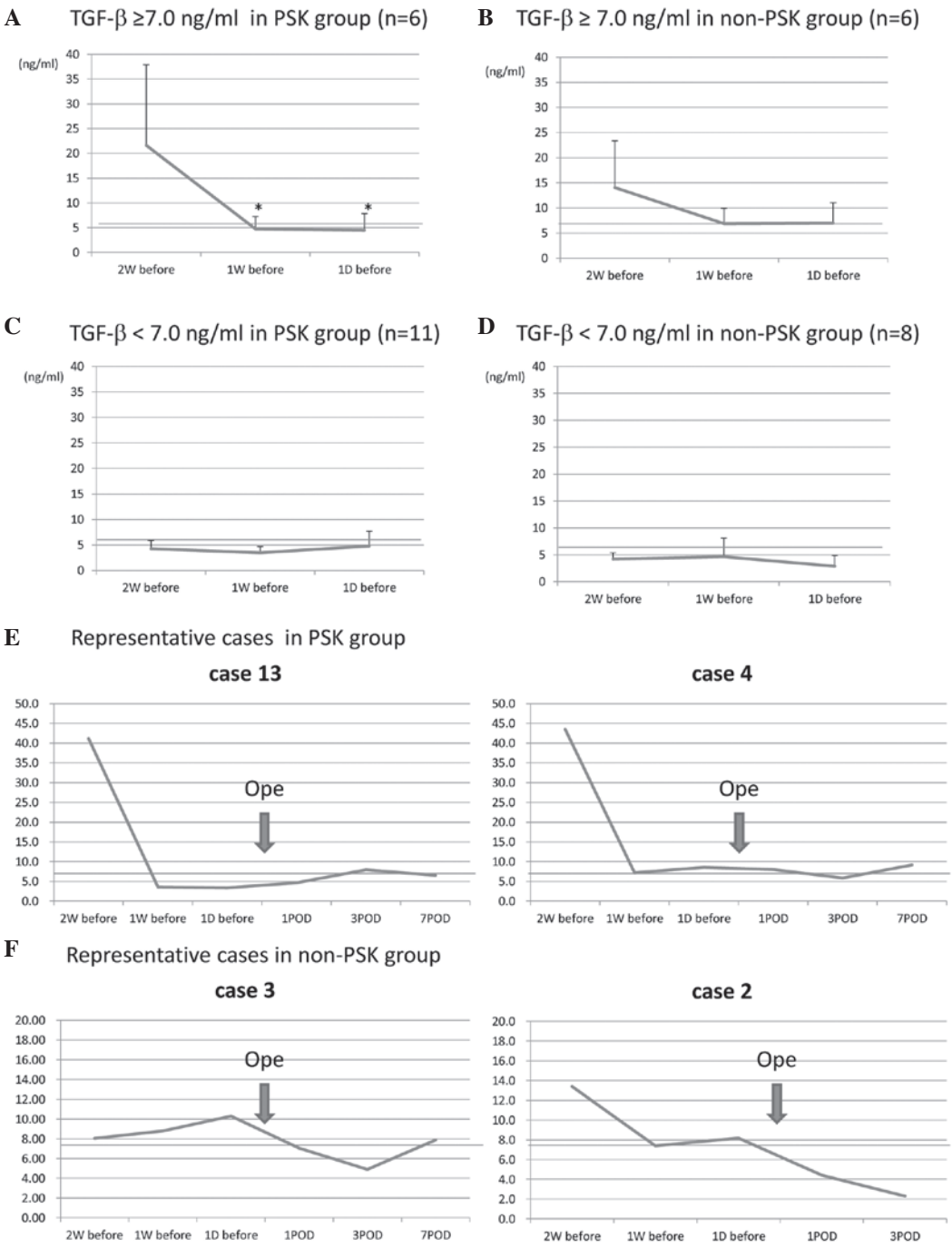

Figure 1. Plasma TGF-β concentration in groups A (no PSK administration) and B (PSK administration). Plasma TGF-β concentration in (A) group B and (B) group A patients who exhibited a high preoperative TGF-β value (≥7.0 ng/ml). Plasma TGF-β significantly decreased 7 and 14 days after PSK administration for group B, but not for group A. *Statistical difference (P=0.028 for the asterisks). Plasma TGF-β concentration in (C) group B and (D) group A patients who exhibited a low preoperative TGF-β value (<7.0 ng/ml). Plasma TGF-β was constant prior and subsequent to PSK administration for group B, and during preoperative terms for group A. (E and F) Perioperative measurement of plasma TGF-β concentration shown in representative cases (cases 4 and 13 for group B and cases 2 and 3 for group A) who exhibited a high preoperative TGF-β value (≥7.0 ng/ml). Plasma TGF-β was significantly reduced at 7 and 14 days after starting PSK administration (group B) and was occasionally reduced at 7 and 14 days, despite no administration of PSK (group A), however a high value (~7 ng/ml) was still shown. TGF-β, transforming growth factor-β; PSK, polysaccharide-Kreha; W, week; D, day; POD, postoperative day.

PSK administration can sustain a suppressed level of TGF-β during the perioperative course, even though PSK was not administered during the postoperative term. The difference from the baseline (2-weeks before) to each time-point was further assessed between groups A (n=14) and B (n=17) by ANOVA (Fig. 3). The PSK-administration group (group B) exhibited a significant reduction from the baseline as compared to the no PSK-administration group (group A) (P=0.019). These findings also supported that PSK has the ability to reduce the plasma TGF-β level in cancer patients.

Multivariate analysis for plasma TGF-β concentration, irrespective of PSK administration in AGC. Significant side-effects of preoperative PSK administration were not experienced in the study, as no symptoms of nausea, vomiting, diarrhea and fatigue, as well as any hematological toxicity,

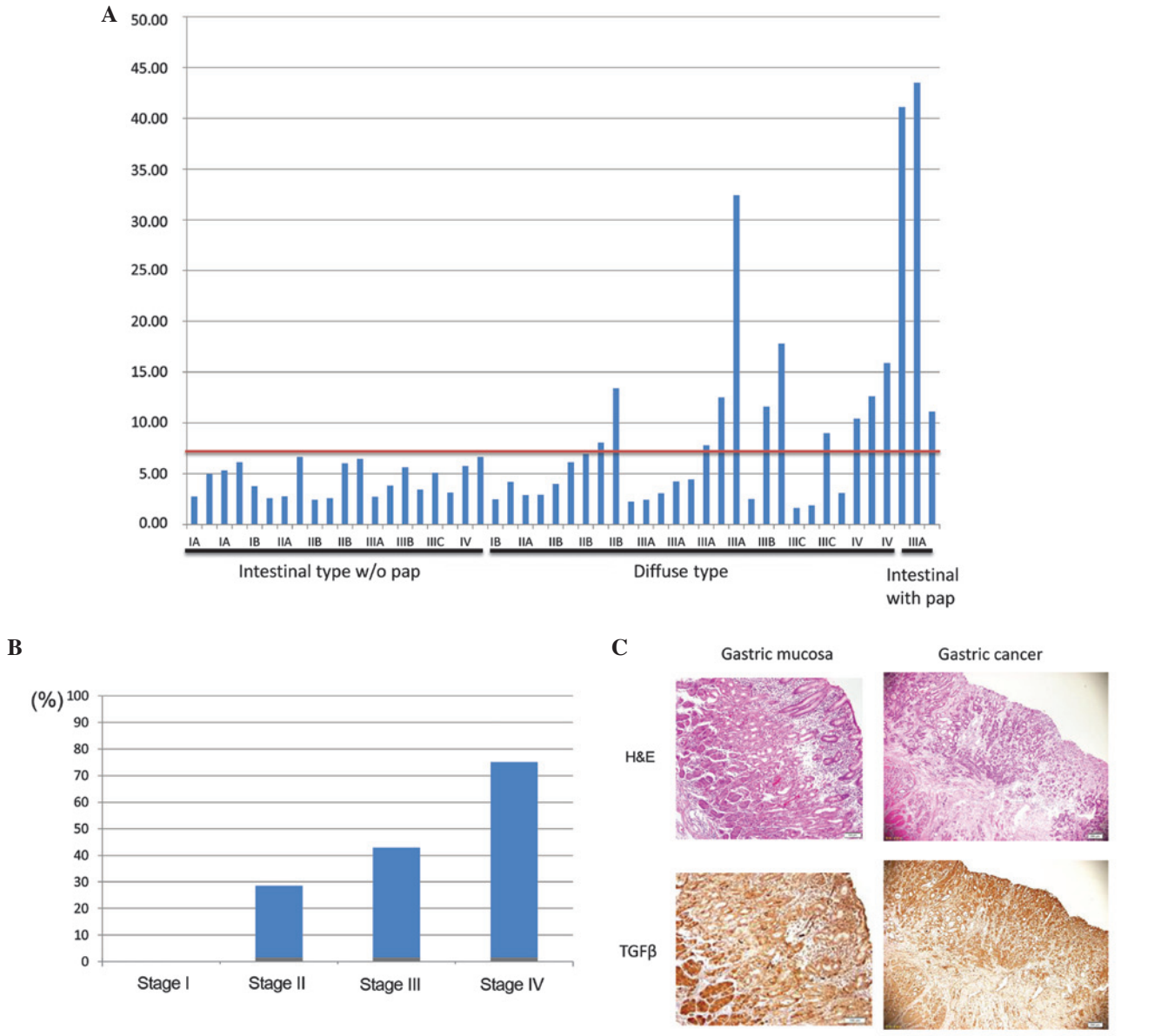

Figure 2. Preoperative TGF-β plasma concentration in gastric cancer is specific to diffuse-type or papillary gastric cancer, and is not associated with local expression in tumor tissues. (A) Plasma TGF-β concentration was examined, and a high concentration was recognized in diffuse-type advanced gastric cancer or papillary adenocarcinoma. (B) Plasma TGF-β concentration was significantly correlated with stage progression in advanced gastric cancer. (C) Immunohistochemistry was performed in gastric mucosa and gastric cancer. TGF-β was constitutively expressed in normal mucosa, as well as cancer cells in almost all the tested tumors. There is no clear correlation between local expression and plasma TGF-β level. TGF-β, transforming growth factor-β; PSK, polysaccharide-Kreha; pap, papillary adenocarcinoma; H&E, hematoxylin and eosin.

were not observed. In order to reveal the effect on various clinical factors against the plasma TGF-β concentration in AGC, 11 variables (PLT, control T, TP, Alb, CPK, BUN, Na, Ca, CEA, CA72-4 and quantitative HBs antigen) were obtained with a significant correlation coefficient from the results of the clinical blood tests (assessing 53 factors) using single regression analysis regarding TGF-β (Table II).

A multiple linear regression analysis was performed using 5 or 10 variables among the 11 variables, with a smaller significant level of the correlation coefficient in an ascending order. The result showed that the obtained multiple correlation coefficients were relatively high values of 0.693 or 0.923, for the case of using 5 or 10 variables, respectively. However, each partial correlation coefficient obtained by a multiple linear regression analysis was not significant, except for quantitative

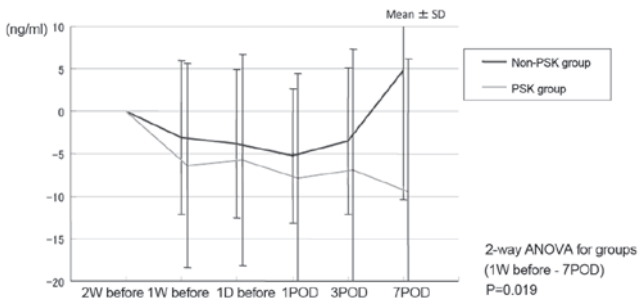

Figure 3. Transition of perioperative plasma concentration of TGF-β in groups A and B. Plasma concentration of TGF-β was significantly reduced in group A during perioperative terms as compared to those in group B. ANOVA analysis revealed that there was a statistically significant difference between groups A and B (P=0.019). TGF-β, transforming growth factor-β; PSK, polysaccharide-Kreha; W, week; D, day; POD, postoperative day; ANOVA, analysis of variance; SD, standard deviation.

HBs antigen only, P=0.022. This finding is consistent with a previous study of TGF-β, which has been demonstrated to be responsible for fibrotic disease, including liver cirrhosis (35).

The non-significant level of partial correlation coefficients in multiple linear regression, despite the significant level in the single regression, may be due to the high correlation of variables with each other, which negate a section of the overprediction of the other variables. As a multiple linear regression analysis calculates multiple correlations in parallel, there is the potential that an independent variable has no use in the prediction of the dependent variable when another independent variable was included in the model.

Table II. Factors associated with the plasma TGF-β level in advanced gastric cancer.

Variable	R	P-value	Coefficient
Platelet count	0.174	0.039	0.276
Control T for APTT	0.547	<0.001	0.05882
Total protein	0.284	0.001	0.04396
Albumin	0.280	0.001	0.0278
Creatine phosphokinase	0.192	0.041	-6.687
Blood urea nitrogen	0.181	0.035	0.128
Sodium	0.202	0.018	0.09018
Calcium	0.297	0.002	0.03622
CEA	0.391	0.022	0.368
CA72-4	0.492	0.011	0.303
Quantitative hepatitis B surface antigen	0.535	0.002	0.000315

TGF-β, transforming growth factor-β; APTT, activated partial thromboplastin time; CEA, carcinoembryonic antigen; CA72-4, carbohydrate antigen 72-4.

Discussion

The plasma TGF-β level has been reported to increase in a wide variety of advanced human cancer stages (5-28), suggesting that the systemic elevation of TGF-β may be involved in tumor progression. Previously, systemic, but not local, abrogation of TGF-β signaling results in significant reduction of tumors through CTL activity in a murine model (29), suggesting that the systemic regulation of TGF-β has a clinical therapeutic potential through the modification of tumor immunity. PSK is derived from the CM-101 strains of the Fungus *Coriolus versicolor*, which is widely perceived to be a specific antidote for cancer, and its administration in tumor-bearing mice also showed tumor regression with reduced TGF-β through CTL induction (30,31). To the best of our knowledge, the present clinical study confirmed for the first time that the systemic reduction of TGF-β was clinically accomplished by PSK administration in advanced human cancers.

This finding may reflect the direct action of TGF-β, as TGF-β was demonstrated to directly bind with PSK and such an immune complex has the potential to promote the excretion of TGF-β in the urine (36). The reduction of TGF-β is clinically favorable, as it accomplished normalization of the TGF-β value, but never eliminated plasma TGF-β. In mature tissues, numerous cells respond to TGF-β with either a cytostatic or apoptotic response, so therefore, complete elimination of TGF-β may deteriorate cancer, as a previous animal model has suggested (1). Notably, the inactivation in TGF-β signaling frequently occurs in human cancer cells either by mutation or by downregulation of the expression of any of the signaling components. Therefore, such a negative effect of the TGF-β signaling defect would not be considered as much in advanced cancer, and the positive effect of the normalization of systemic TGF-β value is regarded rather than the negative effect in late-phase cancer treatment.

The mechanism to increase plasma TGF-β in human cancer remains to be elucidated, and it is known that plasma TGF-β does not reflect the TGF-β in cancer cells of the primary site (6). The immunohistochemistry results of the present study also supported the findings. TGF-β is localized to almost all cells, such as peptic, parietal, gastric gland and muscle cells of the normal tissues, as well as gastric cancer cells, irrespective of differentiation or tumor infiltrating cells (Fig. 2C). Additionally, plasma TGF-β is increased as the stage progresses in diffuse-type gastric cancer, so its elevation may be derived from tumor-host interaction. The proposed mechanism of the recent study suggested that abrogation of TGF-β signaling in carcinomas recruits myeloid-derived suppressor cells (MDSCs) that promote metastasis through immune evasion (37). Notably, the animals that abrogate TGF-β signaling exhibit in a clear elevation of TGF-β1 from the carcinoma tissues, as well as the spleen. The hypothesis that MDSCs may be one of the most important sources for the elevation of plasma TGF-β in human cancer should be confirmed in a future study, however, the rationale for explaining the systemic elevation of TGF-β is noteworthy (38).

PSK is considered to be well-suited for concurrent use with cytotoxic agents as postoperative adjuvant treatment in Japan, as an oral formulation with a low incidence of adverse reactions will enable treatment for outpatient facilities. The study by Nakazato *et al* (32) demonstrated that supplementing adjuvant chemotherapy, mitomycin C and oral fluorouracil, with PSK significantly prolonged the survival rate following curative gastrectomy in a large prospective trial of patients with gastric cancer. In addition, simultaneous postoperative adjuvant PSK treatment in combination with UFT is effective against colorectal cancer (33). Recently, Maehara *et al* described a detailed history and the prospects of the clinical potential of PSK in human cancers, in which PSK has been proved to be effective in specific conditions (39). These clinical trials have suggested that PSK is effective in improving the prognosis for cancer patients, provided it is administered in the highly-specific conditions. In terms of the optimal specific conditions, perioperative administration appears to be the most optimal as the minimal residual disease status was achieved following surgical resection. The present study showed that the postoperative sustained level of TGF-β was achieved by preoperative PSK administration, using ANOVA (Fig. 3).

PSK is not marketed in the USA. However, Bastyr University (Kenmore, WA, USA) has initiated a focus on the efficacy of PSK treatment for prostate and breast cancer, and are currently conducting a PSK study under the National Institute of Health grant from the National Center for Complementary

and Alternative Medicine (40). The principal results of the study have already revealed notable aspects of PSK, including the demonstration of PSK as a selective Toll-like receptor 2 (TLR2) agonist. The activation of dendritic cells and T cells, which are the crucial factors involved in tumor immunity, by PSK is TLR2-dependent (41). In addition, PSK treatment in neu transgenic mice significantly inhibited breast cancer growth. Selective depletion of specific cell populations indicates that the PSK antitumor effect is dependent on cluster of differentiation 8 (CD8)(+) T cells and natural killer (NK) cells, but not CD4(+) T cells. As PSK does not inhibit tumor growth in TLR2(-/-) mice, this indicates that the antitumor effect is regulated by TLR2 (42). Additionally, human NK cells were activated by PSK to produce interferon-γ and to lyse K562-target cells. PSK also increased trastuzumab-mediated antibody-dependent cell-mediated cytotoxicity against SKBR3 and MDA-MB-231 breast cancer cells. The direct and interleukin 12-dependent indirect effects appear to be involved in the outcomes of PSK on NK cells. The oral administration of PSK significantly enhanced the antitumor effect of anti-HER2/neu mAb therapy in neu transgenic mice. These fundamental results are notable as anti-human epidermal growth factor type 2 (HER2) monoclonal-antibody therapy has been proved to be extremely effective in combination with classical chemotherapeutic disease in the Trastuzumab for Gastric Cancer trial (treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer), and PSK was shown to prevent apoptosis of circulating T cells induced by anti-cancer drugs, S1, for gastric cancer (43).

In conclusion, to the best of our knowledge, PSK was shown to normalize plasma TGF-β in advanced gastric cancer for the first time, if the initial levels were high. The clinical advantage of PSK may, however, be restricted to specific histological types of gastric cancer. The perioperative suppression of TGF-β by PSK may antagonize cancer immune evasion and improve patient prognosis in gastric cancer with specific condition.

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