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Immune-modulating Effect of Korean Red Ginseng by Balancing the Ratio of Peripheral T Lymphocytes in Bile Duct or Pancreatic Cancer Patients With Adjuvant Chemotherapy

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Abstract. *Background/Aim: We aimed to clarify the clinical effect of Korean Red ginseng administered with adjuvant chemotherapy on the immune function of patients with bile duct or pancreatic cancer. Patients and Methods: This was a prospective, randomized controlled trial conducted at a single tertiary center. Twenty-six consecutive patients who underwent curative resection for bile duct or pancreatic cancer followed by 5-fluorouracil/leucovorin or gemcitabine chemotherapy were included. They were randomized 1:1 to the ginseng and control groups. Immune and inflammatory markers were assayed in peripheral blood samples during and after chemotherapy. Results: Intergroup differences in immune-related parameters before and during chemotherapy were not significant. After chemotherapy, the percentage of $CD4^+$ T lymphocytes was significantly higher in the ginseng group than in the control group (42.01% vs. 33.69%, p=0.048). The ratio of $CD4^+/CD8^+$ T lymphocytes was also higher in the ginseng group (2.03 vs. 1.28, p=0.027). Neutropenia and liver dysfunction prevalence did not differ between the groups. Conclusion: The ginseng group, which received Korean Red ginseng daily during adjuvant chemotherapy, showed higher levels of $CD4^+$ T lymphocytes and $CD4^+/CD8^+$ T lymphocyte ratio after chemotherapy.*

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One of the strategies employed by cancer cells to develop treatment resistance is to suppress cellular antitumor immunity. Recent studies have shown that naturally occurring or tumor-induced regulatory T cells and immature myeloid cells including myeloid-derived suppressor cells down-regulate immune surveillance and antitumor immunity and create an immunosuppressive environment in the host (1-4). Therefore, to achieve a potent antitumor effect, such immunosuppressive factors need to be overcome.

Natural compounds derived from plants, such as ginsenosides, have been gaining interest as promising candidates for development as anticancer agents owing to their low toxicity and antiangiogenic properties. Korean Red ginseng is derived from Panax ginseng Meyer by steaming and is one of the most widely used medicinal herbs in Asia and North America (5). It is composed of saponins including ginsenosides and polysaccharides (6-8). Ginsenosides are known to have beneficial effects on cardiovascular and immune functions in addition to possible chemoprotective and therapeutic effects *in vitro* and *in vivo* (9-11). Korean Red ginseng is also known to enhance T cell proliferation and cytokine secretion by inhibiting the immunosuppressive activity of myeloid-derived suppressor cells (12). Given this background, our study aimed at clarifying the effect of Korean Red ginseng administered with adjuvant chemotherapy on immune function in patients with bile duct or pancreatic cancer.

Patients and Methods

Study design. This was a prospective, randomized controlled trial performed at a single tertiary hospital from January 2012 to January 2016. The trial was approved by the institutional review board of Gangnam Severance Hospital, Yonsei University College of Medicine, Korea (3-2011-0233). Written informed consent was

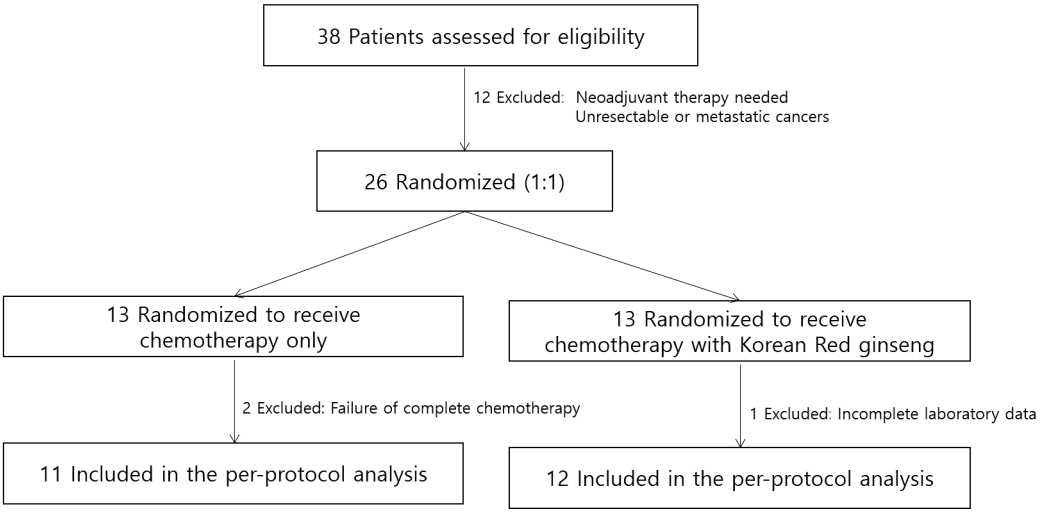

Figure 1. *Flow diagram of patient enrollment. Three patients were excluded from the data analysis due to failure to maintain chemotherapy or incomplete laboratory data.*

obtained from all participants. In all, 26 consecutive patients who underwent curative resection for bile duct or pancreatic cancer followed by adjuvant chemotherapy were included. The enrolled patients were categorized into the ginseng or control groups in a 1:1 ratio (Figure 1). Patients were excluded from the trial under specific conditions: 1) preoperative chemotherapy or radiotherapy, 2) palliative resection, 3) failure to take the Korean Red ginseng, 4) failure to visit regularly after operation.

Intervention. A regimen comprising 5-fluorouracil/leucovorin or gemcitabine alone was used as adjuvant chemotherapy for bile duct or pancreatic cancer. Folinic acid (20 mg/m^2) was administered as an intravenous bolus followed by an intravenous bolus of fluorouracil (425 mg/m^2) on 3 consecutive days every 21 days. Gemcitabine (1,000 mg/m^2) was infused over 30 min once a week for 3 out of 4 weeks. Each regimen was administered to the patients for 6 cycles.

The ginseng group received 3 g of Korean Red ginseng (Korea Ginseng Corporation, Seoul, Republic of Korea) daily as a pill. The dosage of 3 g/day was decided based on the safety dose from previous reports (13, 14). Peripheral blood sampling was performed thrice during the study period: before the initiation of adjuvant chemotherapy, during chemotherapy, and after the end of chemotherapy (Figure 2). Immune-related markers including CD4$^+$ T lymphocytes; CD8$^+$ T lymphocytes; immunoglobulins G, A, and M; absolute neutrophil count; and total lymphocyte count were evaluated. To assess the toxic effects of Korean Red ginseng, the prevalence of adverse events was investigated using the Common Terminology Criteria for Adverse Events v4.0.

Statistical analysis. The target sample size was calculated to have 80% power with a type I error rate of 0.05 and a dropout rate of 10%. Incremental differences between the two groups were based on a previous study, reporting 1.5 fold higher levels of anti-inflammatory cytokines in the ginseng group in colorectal cancer (13). All analyses were conducted in the per-protocol population. Statistical analyses were performed using SPSS software, version 21.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed using Chi-square tests or Fisher's exact tests, and continuous variables were analyzed using Student's *t*-tests. A *p*-value of <0.05 was considered statistically significant.

Results

Patient demographics. Baseline characteristics of the enrolled patients are listed in Table I. Intergroup differences regarding sex, age, body surface area, location of cancer, and intravenous chemotherapy regimen were not significant.

Immune and inflammatory parameters in peripheral blood samples. Comparison of immune-related parameters revealed no difference between the two groups before and during the period of adjuvant chemotherapy. However, after chemotherapy, the percentage of CD4$^+$ T lymphocytes was higher in the ginseng group (ginseng *vs*. control=42.0% *vs*. 33.7%, p=0.048) (Table II). Further, the ratio of CD4$^+$/CD8$^+$ T lymphocytes was not significantly different before and after chemotherapy between the groups. Nevertheless, the ratio of CD4$^+$/CD8$^+$ T lymphocytes showed an increasing trend and a decline after chemotherapy in the ginseng and control groups, respectively. Moreover, after chemotherapy, the ratio of CD4$^+$/CD8$^+$ T lymphocytes was higher in the ginseng group (ginseng *vs*. control=2.0 *vs*. 1.3, p=0.027) (Figure 3).

Adverse events during adjuvant chemotherapy. To evaluate the toxicity of ginseng administered during adjuvant chemotherapy, the prevalence of adverse events during chemotherapy was determined. The number of patients with neutropenia of a grade higher than 3, granulocyte colony-

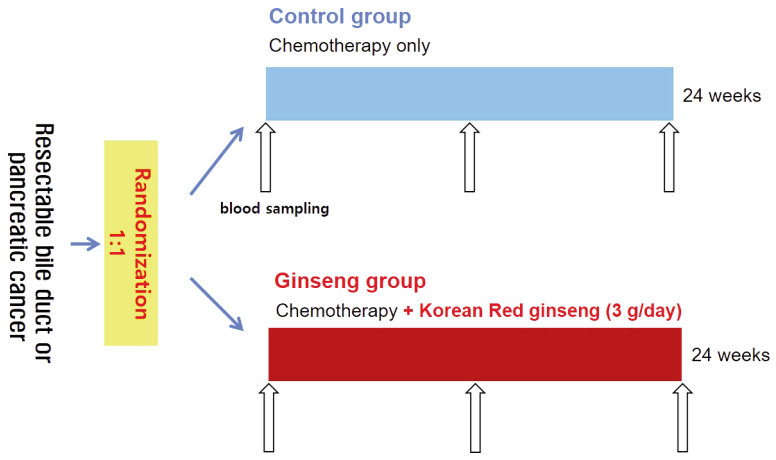

Figure 2. *Study scheme*.

Table I. *Patient demographics*.

	Ginseng group n (%)	Control group n (%)	*p*-Value
Gender			
Male	8 (61.5)	8 (61.5)	1.000
Female	5 (38.5)	5 (38.5)	
Age (years)			
Mean (SD)	62.2 (11.2)	62.8 (9.2)	0.880
BSA (kg/m^2)			
Mean (SD)	1.70 (0.19)	1.67 (0.21)	0.650
Location of cancer			
Pancreas	7 (53.8)	6 (46.2)	1.000
Bile duct	6 (46.2)	7 (53.8)	
Chemotherapy regimen			
Gemcitabine	10 (76.9)	8 (61.5)	0.673
FL chemotherapy	3 (23.1)	5 (38.5)	

BSA: Body surface area; FL: 5-fluorouracil/leucovorin.

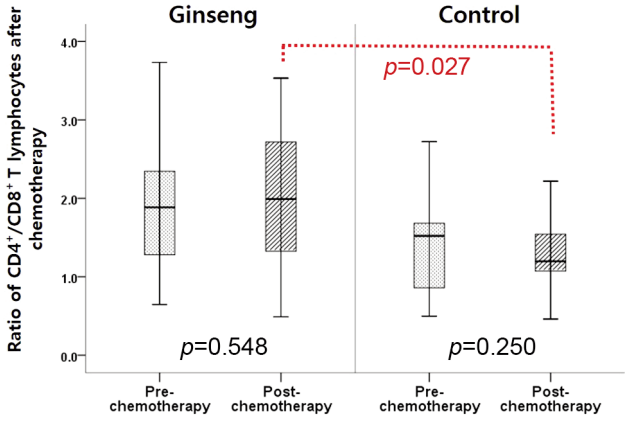

Figure 3. *Comparison of the ratio of CD4$^+$/CD8$^+$ T lymphocytes between the two groups. This figure shows the ratio of CD4$^+$/CD8$^+$ T lymphocytes before and after chemotherapy in the two groups. The Ginseng group had a significantly higher ratio of CD4$^+$/CD8$^+$ T lymphocytes after chemotherapy compared to the control group.*

stimulating factor use, or elevations in aspartate aminotransferase or alanine aminotransferase of a grade higher than 3 were not different between the two groups. Moreover, no difference in the number of neutropenic episodes or granulocyte colony-stimulating factor injections was observed between the two groups (Table III).

Discussion

In this study, we aimed to determine the clinical effect of Korean Red ginseng as an immune-modulating agent in patients undergoing adjuvant chemotherapy for bile duct or pancreatic cancer. Compared to the control group, the ginseng group showed a higher percentage of CD4$^+$ T lymphocytes after chemotherapy. Furthermore, the ratio of CD4$^+$/CD8$^+$ T lymphocytes after chemotherapy was higher in the ginseng group.

Genetic or epigenetic disarrangements because of inflammation are known to cause angiogenesis, metastasis, and remodeling to malignant features, which leads to cancer progression (15-17). Korean Red ginseng is heat-processed ginseng prepared by the repeated processes of steaming and drying of fresh ginseng (18). It has been known to undergo changes in its types and concentrations of chemical

Table II. *Comparison of immune-related parameters between the two groups.*

	Ginseng group (n=12) (mean, SD)	Control group (n=11) (mean, SD)	*p*-Value
Before chemotherapy			
Absolute neutrophil count (10^3/μl)	3.5 (1.4)	3.0 (1.8)	0.445
C-reactive protein (mg/l)	5.5 (11.6)	5.2 (7.7)	0.939
Total lymphocyte count (10^3/μl)	2.1 (0.5)	1.0 (0.6)	0.625
AST (IU/l)	24.8 (8.0)	33.8 (22.2)	0.185
ALT (IU/l)	20.2 (15.2)	31.2 (25.1)	0.186
IgG (mg/dl)	1,274.9 (254.6)	1,396.9 (459.3)	0.370
IgA (mg/dl)	246.0 (56.2)	264.9 (88.3)	0.521
IgM (mg/dl)	113.4 (71.9)	96.1 (45.3)	0.471
$CD4^+$ T lymphocytes (%)	43.0 (7.9)	36.1 (11.6)	0.125
$CD8^+$ T lymphocytes (%)	25.9 (8.4)	28.8 (12.4)	0.509
$CD4^+/CD8^+$ T lymphocyte ratio	1.9 (0.9)	1.5 (0.8)	0.225
During chemotherapy			
Absolute neutrophil count (10^3/μl)	3.1 (1.8)	3.0 (1.0)	0.822
C-reactive protein (mg/l)	1.3 (1.5)	2.6 (3.7)	0.318
Total lymphocyte count (10^3/μl)	2.0 (0.6)	1.8 (0.6)	0.723
AST (IU/l)	26.9 (10.5)	28.6 (15.1)	0.743
ALT (IU/l)	23.6 (18.6)	29.5 (23.6)	0.490
IgG (mg/dl)	1,289.0 (217.3)	1,362.8 (210.9)	0.388
IgA (mg/dl)	250.0 (66.4)	246.6 (61.0)	0.891
IgM (mg/dl)	120.4 (65.3)	89.1 (42.6)	0.161
$CD4^+$ T lymphocytes (%)	40.9 (8.2)	34.6 (8.8)	0.090
$CD8^+$ T lymphocytes (%)	25.8 (9.5)	28.9 (8.9)	0.433
$CD4^+/CD8^+$ T lymphocyte ratio	1.8 (0.8)	1.3 (0.6)	0.101
After chemotherapy			
Absolute neutrophil count (10^3/μl)	3.9 (1.2)	3.6 (1.7)	0.670
C-reactive protein (mg/l)	3.1 (5.9)	5.9 (10.2)	0.432
Total lymphocyte count (10^3/μl)	2.0 (0.6)	1.8 (0.6)	0.828
AST (IU/l)	29.1 (12.)	29.2 (11.5)	0.987
ALT (IU/l)	25.3 (18.7)	28.8 (16.6)	0.622
IgG (mg/dl)	1,222.3 (221.6)	1,334.9 (221.4)	0.217
IgA (mg/dl)	293.4 (100.7)	342.0 (120.9)	0.446
IgM (mg/dl)	263.4 (58.1)	245.3 (58.3)	0.333
$CD4^+$ T lymphocytes (%)	42.0 (9.6)	33.7 (9.4)	**0.048**
$CD8^+$ T lymphocytes (%)	24.1 (9.0)	29.3 (11.3)	0.233
$CD4^+/CD8^+$ T lymphocyte ratio	2.0(0.9)	1.3(0.5)	**0.027**

AST: Aspartate aminotransferase; ALT: alanine aminotransferase; Ig: immunoglobulin. Significant *p*-Values are shown in bold.

constituents such as ginsenosides during the steaming process (19). Many researchers have attempted to identify the clinical benefits of Korean Red ginseng in terms of antitumor activity, neuroprotective effect, and management of immune system and cardiovascular disorders (20-23). Korean Red ginseng has been reported to have immune-modulating properties, whereby it could enhance T-cell proliferation, suggesting it can regulate cellular immune responses (24, 25).

A dynamic balance in the $CD4^+/CD8^+$ ratio is crucial for maintaining stable immune function (26). $CD3^+$ T cells play a central role in the cellular immune response of the host and are divided into $CD4^+$ helper T cells and $CD8^+$ cytotoxic T cells. These cells boost immune responses via the secretion of lymphatic factors by $CD4^+$ helper T cells and induce other lymphatic cells crucial for an antitumor effect. Therefore, a decrease in the number of $CD4^+$ T cells is associated with a weakened immune function, whereas a decrease in the number of $CD8^+$ cytotoxic T cells, which inhibit $CD4^+$ and B cell function, enhances antibody formation and cellular immune responses (27).

A decreased $CD4^+/CD8^+$ ratio has been reported to be correlated with decreased immune function (28, 29). Wang et al. showed that patients with non-small cell lung cancer had a significantly lower $CD4^+/CD8^+$ ratio than healthy controls and patients with advanced-stage cancer had a significantly lower $CD4^+/CD8^+$ ratio than those with early-stage cancer (27). In the present study, the ginseng group

Table III. *Prevalence of chemotherapy-related adverse events.*

	Ginseng group n (%)	Control group n (%)	*p*-Value
No. of patents with neutropenia of grade ≥3†	5 (41.6)	3 (27.2)	0.453
No. of episodes of neutropenia of grade ≥3†	1 (0-9)	0 (0-3)	0.210*
No. of patients with G-CSF use	4 (33.3)	3 (27.2)	0.428
No. of episodes with injection of G-CSF	1 (0-6)	0 (0-2)	0.092*
No. of patients with elevated AST or ALT of grade ≥3†	0 (0)	0 (0)	NS

No.: Numbers; G-CSF: granulocyte colony-stimulating factor; AST: aspartate aminotransferase; ALT: alanine aminotransferase; *Mann-Whitney *U*-test; †grades according to the CTCAE.

showed a significantly higher number of $CD4^+$ T lymphocytes after chemotherapy along with a higher ratio of $CD4^+/CD8^+$ T lymphocytes. This finding demonstrates that Korean Red ginseng may have an immune-modulating effect and could be beneficial for patients who underwent cytotoxic chemotherapy.

Although this was a prospective trial, the data obtained are preliminary and should be interpreted very carefully due to the small number of patients enrolled and the relatively heterogeneous baseline characteristics of the sample. Nevertheless, to our knowledge, this is the first randomized clinical trial investigating the effects of Korean Red ginseng in real-world hepatobiliary or pancreatic cancer patients undergoing adjuvant chemotherapy. We found that simultaneous administration of Korean Red ginseng with adjuvant chemotherapy resulted in a higher number of $CD4^+$ lymphocytes as well as a higher ratio of $CD4^+/CD8^+$ T lymphocytes after chemotherapy in patients with bile duct or pancreatic cancer. Thus, the findings of this study are noteworthy and suggest that Korean Red ginseng is a safe alternative immune-modulating agent for use during chemotherapy in patients with bile duct or pancreatic cancer.

Conflicts of Interest

The Authors have no conflicts of interest in relation to this study.

Authors' Contributions

Research design: Lee KY, Park JS and Jeong J; Statistical analysis: Kim I-k; Article writing: Kim I-k; Supervision: Kang J; Review and revision: Lee KY, Park JS and Jeong J.

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