# Korean Red Ginseng as a Postoperative Immune Modulator in Patients with Advanced Gastric Cancer

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**Abstract**

In this paper, we present evidence that the red ginseng from Panax ginseng C.A. Meyer inhibits the recurrence of advanced gastric cancer and shows immunomodulatory activities during postoperative chemotherapy. Flow cytometric analyses for peripheral T-lymphocyte subsets showed that the red ginseng powder restored CD4 levels to the initial preoperative values during postoperative chemotherapy. Depression of CD3 during postoperative chemotherapy was also inhibited by the red ginseng powder ingestion. This study demonstrated a 5-year disease free survival and overall survival rate that was significantly higher in patients taking the red ginseng powder during postoperative chemotherapy vs. control (68.2% vs. 33.3%, 76.4% vs. 38.5%, respectively, $p < 0.05$). The mean value of serum IL-10 of the ginseng group was reduced progressively during the postoperative chemotherapy. The values of the ginseng group were close to that of the control group on postoperative months 3. These studies suggest that the red ginseng may have some immunomodulatory properties associated with CD3 and CD4 activity and interleukin 10 during postoperative chemotherapy and some potential of improving prognosis in patients with advanced gastric cancer.

**Key words** : Gastric cancer, Interleukin, Lymphocyte subsets, *Panax ginseng*, Survival

## Introduction

The red ginseng has been reported to help increase physical endurance and stimulate physical and mental performance as an East Asian traditional herbal medicine.[1] The red ginseng and some extracts of Panax ginseng showed anticarcinogenic actions including inhibition of tumor angiogenesis and metastasis[2-4] and induction of apoptosis in tumor cells.[5] Another study has shown that an extract from Panax ginseng is able to activate multiple effector pathways of immunostim-

ulation for anti-tumor action.[6]

Gastric cancer is a leading cause of cancer related mortality in Korea. Despite varied treatment strategies, the control of this cancer at an advanced stage remains problematic. Furthermore the immunologic role of ginseng remains unclear in patients with gastric cancer who undergo gastrectomy. However the red ginseng has a potential to improve the anticancer immunity on patients with advanced gastric cancer. Therefore the authors have conducted two studies based on the postoperative immunological alteration of T-lymphocyte subsets and cytokines following the gastric resection with curative intent. The aims of these study were to prospectively evaluate on the postoperative host immunity and survival and the impact of the red ginseng extract on circulating interleukin (IL) 2 and 10 in advanced gastric cancer during chemotherapy after operative treatment.

## Subject and Methods

***Study I for T-lymphocyte subsets***

Forty-two patients who had undergone curative gastric resection with D2 lymph node dissection by the same surgeon for histologically proven AJCC stage III gastric adenocarcinoma were considered eligible for this study. Patients were identified preoperatively between July 1, 1995 and June 30, 1996. These patients were followed up regularly at our clinic between July 1, 1995 and Jun 30, 2000. All patients were treated with chemotherapy each month during the first six months after the operation. 5-FU was administered by continuous infusion at a dosage of 500 $mg/m^2$/day, on days 1 through 5. Bolus cisplatin was given at a dosage of 60 $mg/m^2$/day on day 1. All patients were randomly allocated into two groups before operation: patients designated to receive the red ginseng (RG group, n=22) and control group (non-RG group, n=20). The RG group took the red ginseng powder capsules (Korea Ginseng Corporation, Seoul. Korea) orally at a dosage of 4.5 g/day during the first six months after operation. T-lymphocyte subsets were evaluated at preoperative day 1 and postoperative months 1, 3 and 6 from peripheral venous blood draws. The distribution of T-lymphocyte subsets was evaluated using the FACScan flow cytometer (Beckton Dickinson, Mountain View, CA). Results were expressed as the total number and percentage of positive cells counted. This study was performed after informed consent was obtained.

***Study II for Interleukin(IL) 2 and 10***

Fifty patients who had undergone whatever curative gastric resection with D2 lymph node dissection or not for histologically proven advanced gastric adenocarcinoma were considered eligible for this study. Patients were identified preoperatively between May 1, 2001 and November 30, 2001. These patients were followed up regularly at our clinic between May 1, 1995 and March 31, 2002. All patients were treated with chemotherapy each month during the first six months after the operation. 5-FU was administered by continuous infusion at a dosage of 500 mg/m$^2$/day, on days 1 through 5. Bolus cisplatin was given at a dosage of 60 mg/m$^2$/day or heptaplatin (Sunpla®, SK chemical, Seoul, Korea) was given at a dosage of 400 mg/m$^2$/day on day 1. All patients were randomly allocated into two groups before operation: patients designated to receive the red ginseng extract (RGE group, n=24) and control group (non-RGE group, n=26). The RGE group took the red ginseng extract (Korea Ginseng Corporation, Seoul. Korea) orally at a dosage of 3 g/day during the first three months after operation. Circulating IL-2 and 10 were measured on venous blood by using ELISA and monoclonal antibodies at preoperative day 1, postoperative months 1, and 3 from peripheral venous blood draws. The healthy controls (n=25) without the gastric cancer also were measured on venous blood. This study was performed after informed consent was obtained.

## Results

***Study I for T-lymphocyte subsets***

No adverse effect was observed in both groups during the observation period. The recurrence rate was greater in the non-RG group than in the RG group ($p<0.05$). Mean duration of disease free survival was significantly longer in the RG group ($p<0.05$). The overall 5-year survival rate and 5-year disease free survival rate is illustrated in Fig. 1. The overall 5-year survival rate was significantly higher in the RG group than in the non-RG group (76.4% vs. 38.5%, $p<0.05$). The 5-year disease free survival rate of the RG group and non-RG group also showed a significant difference (68.2% vs. 33.3%, $p<0.05$). Total leukocyte counts in the RG and non-RG groups progressively decreased after operation from preoperative values and there was no statistical difference between the two groups, except the values at postoperative month 6 ($p<0.05$). CD3 was consistently higher in the RG group during the observation period and it sharply declined at postoperative month 1, when compared to CD 3 at preoperative day 1. CD3 in the RG group was

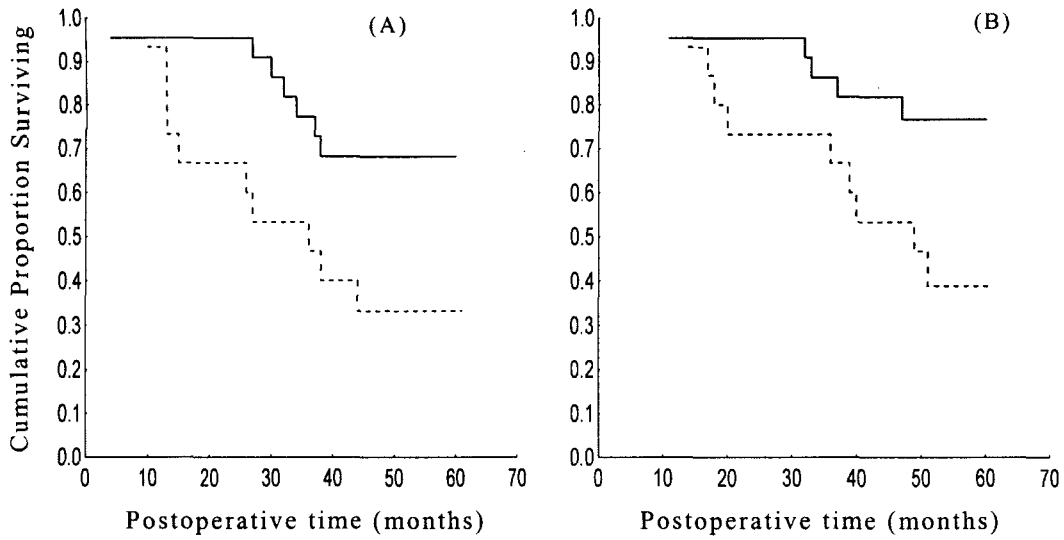


**Fig. 1.** Cumulative proportion curves of disease free survival (A; $p<0.05$) and overall survival (B; $p<0.05$) by the Kaplan-Meier Method in patients with AJCC stage III gastric cancer following a curative D2 resection. Solid line represents patients taking the red ginseng powder during chemotherapy; dotted line represents patients not taking the red ginseng powder.

restored close to the preoperative value at postoperative month 3 ($p<0.05$) but CD3 in the non-RG group was not restored at any point throughout the observation period (Fig. 2A). CD4 was not found to be different between the RG and non-RG groups at preoperative day 1. However, CD4 was consistently higher in the RG group after operation. CD4 was significantly different between the two groups at postoperative months 1, 3 and 6 ($p<0.05$). CD4 in both groups sharply decreased at postoperative month 1 as did CD3. At postoperative month 3, CD4 was restored close to the preoperative values in the RG group but not in the non-RG group (Fig. 2B). CD8 was consistently higher in the RG group than in the non-RG group after operation when compared with the preoperative values, however there was no significant difference between the two groups. All CD4/CD8 ratios except at postoperative month 3 ($p<0.05$) showed no significant difference between the RG and non-RG groups.

***Study II for Interleukin 2 and 10***

Twenty-five patients as the control group, twenty-six patients as the non-ginseng group, and twenty-four patients as the ginseng group were eligible in this study. The mean value of serum IL-2 of the control group was 0.216±0.263 pg/ml. The mean value of serum IL-2 of the non-gin-

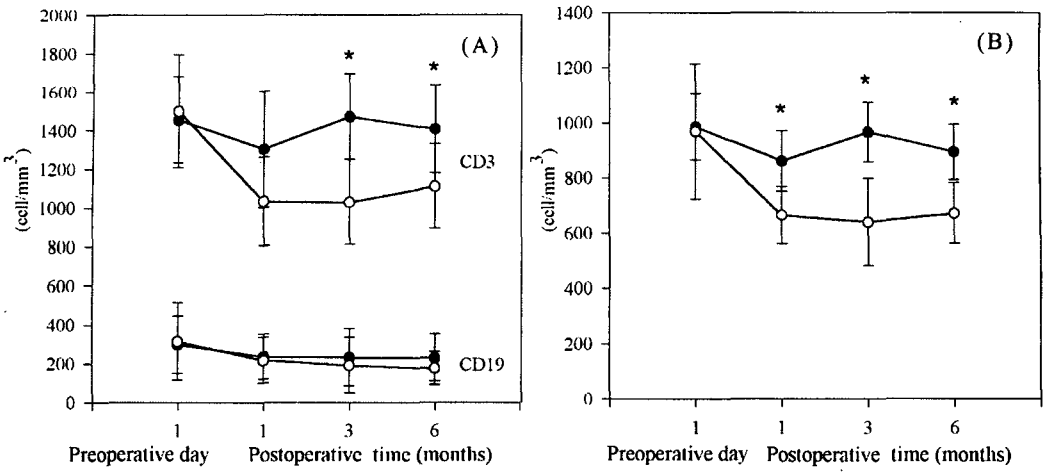


**Fig. 2.** Changes of CD3, CD19 (A) and CD4 (B) in patients with AJCC stage III gastric cancer following a curative D2 resection. All patients were treated with chemotherapy during the first 6 months after operation. Asterisk indicates $p < 0.05$. Solid circles represent patients taking the red ginseng powder during chemotherapy; open circles represent patients not taking the red ginseng powder.

seng group was 0.146±0.091 pg/ml on preoperative day 1, 0.176±0.133 pg/ml on postoperative month 1 and 0.175±0.079 pg/ml on postoperative months 3. The mean value of serum IL-2 of the ginseng group was 0.111±0.202 pg/ml on preoperative day 1, 0.192±0.129 pg/ml on postoperative month 1, and 0.186±0.126 pg/ml on postoperative months 3. The mean value of serum IL-2 of the control group was lower than that of the non-ginseng and ginseng groups on preoperative day 1, there was a significant statistical difference. These values of the ginseng group were more increased than these of the non-ginseng group during the postoperative chemotherapy (Fig. 3A). The mean value of serum IL-10 of the control group was 0.608±0.372 pg/ml. The mean value of serum IL-10 of the non-ginseng group was 12.015±23.863 pg/ml on preoperative day 1, 6.365± 7.501 pg/ml on postoperative month 1 and 4.558±4.134 pg/ml on postoperative months 3. The mean value of serum IL-2 of the ginseng group was 9.409±10.82 pg/ml on preoperative day 1, 4.001±4.475 pg/ml on postoperative month 1, and 1.105±0.543 pg/ml on postoperative months 3. The mean value of serum IL-10 of the control group was lower than that of the advanced gastric cancer patients including the non-ginseng and ginseng groups (Fig. 3B; $p<0.001$). These values of the ginseng group were reduced progressively during the postoperative chemotherapy. The values of the ginseng group were close to that of the control group on postoperative months 3 (Fig. 3B; $p<0.003$). There was no significant statistical difference in IL-2 and 10 between the

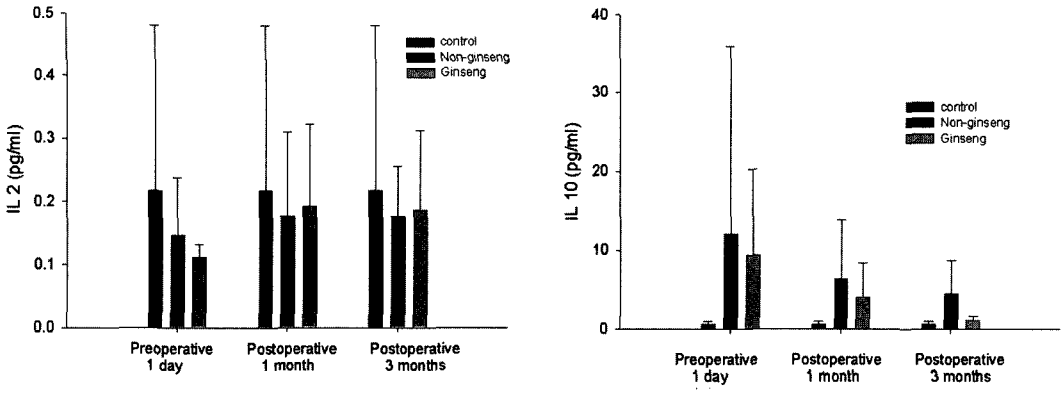


**Fig. 3.** Mean values of Interleukin 2 (A; pg/ml) and 10 (B; pg/ml) from peripheral venous blood during chemotherapy. A black box represents the healthy control group; a red box represents the non-ginseng group; a green box represents the ginseng extract group; the p-values of control vs. non-ginseng and control vs. ginseng at preoperative 1 day were <0.05, respectively.

patients with stage 3 and 4.

## Discussion

Although we do not completely understand the mechanisms that underlie the specific immunologic alterations, it is clear that both functional and quantitative defects in immunity develop with cancer, especially in advanced stages.[7,8] Although it is still unknown which components of ginseng are able to reduce the risk of cancers, the preventive effect of ginseng against cancers was observed in almost all types of ginseng products, which included fresh ginseng extract, white ginseng extract and powder, and red ginseng products.[9] Panax ginseng has been reported to have immunomodulating activity in immunosuppressed mice.[10,11] However, the mechanisms of antitumor effects of ginsenosides are yet to be understood completely. Our study showed that the depression of CD3 was inhibited by the red ginseng powder ingestion during chemotherapy. Panax ginseng was shown to enhance cellular immune function of peripheral blood mononuclear cells in both normal individuals and patients with depressed cellular immunity. Ginsenoside $Rg_1$ from Panax ginseng increased CD4 with respect to the whole T-cell number. Ginsenoside $Rg_1$ also partly restored the impaired immune reactivity by cyclophosphamide.[12] In our study, CD4 was significantly higher in patients taking the red ginseng powder, most notably during chemotherapy. CD4 was restored during chemotherapy to levels similar to preoperative values in

patients taking the red ginseng powder but were not restored in patients not taking the red ginseng powder. CD3 and CD4 among T-lymphocyte subsets were only significantly higher in patients taking the red ginseng powder during postoperative chemotherapy with the exception of the effects of multiple time points by the repeated measure ANOVA. Therefore, these results suggest that the red ginseng powder may have some potential in facilitating the recovery of immune function during chemotherapy after operation. This study showed that the 5-year overall survival and disease free survival rate was significantly higher in patients taking the red ginseng powder during chemotherapy after the curative resection when compared with controls. Furthermore, this study showed that the immunosuppression associated with chemotherapy resulted in a worse prognosis after curative gastric resection based on survival times. It suggests that the red ginseng powder may help to improve the postoperative survival in patients with AJCC stage III gastric cancer.

The extract of Panax ginseng (ginsan) inhibited pulmonary metastasis of melanoma cells, induced macrophage cytokines, and generated LAK (lymphokine-activated killer) cells in synergy with IL-2.[13] However, the antitumor cytotoxicity of the red ginseng remains unclear in gastric cancer. Furthermore, the cell-mediated cytotoxicity was depressed in patients with advanced gastric cancer, especially stage IV gastric cancer. It was induced by the decreased production of serum Interleukin-2 (IL-2) that was recognized as a T-cell growth factor.[14,15] The gastric cancer cells produced serum immunosuppressive factors that suppressed antitumor cytotoxicity of IL-2-induced lymphocytes.[16] Furthermore, the incidence of lymph node metastasis was increased by the functional deficit of T-lymphocytes and the elevated CD8. These were also induced by the reduced production of serum IL-2 in patients with advanced gastric cancer.[17] Serum IL-10 is often elevated in patients with advanced gastric cancer. The elevated serum IL-10 plays an important role of a suppression of host anti-cancer immunity.[18,19] In our study, the mean value of IL2 was more increased in RGE group than in non-RGE group during the postoperative chemotherapy, although there was no statistical significance. However, the values of IL-10 were more sharply depressed in RGE group than in non-RGE group during the postoperative chemotherapy, there were statistical significances. Therefore, these results suggest that the red ginseng extract has some immunomodulatory properties for improving anti-cancer immunity and preventing the immune suppression during the chemotherapy.

## Conclusion

The present study is the first clinical prospective study evaluating the effects of the red ginseng for advanced gastric cancer, although the number of patients who were enrolled in this study was small to fully evaluate the therapeutic effects of ginseng on postoperative host immunity and survival. However, in spite of this limitation, these results suggest that the red ginseng may help to improve the postoperative survival impacted on the numerical changes of T-lymphocyte subsets in patients with advanced gastric cancer. Additionally, the results of these studies suggest that the red ginseng may have some immunomodulatory properties associated with CD3 and CD4 activity and interleukin 10 in patients with advanced gastric cancer during postoperative chemotherapy. The author is evaluating now the effect of the red ginseng extract on interleukin with a larger sample size in patients with advanced gastric cancer.

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