

Impact of Immunological and Biochemical Parameters of Intake of *Agaricus Blazei Murill* (ABM) on Patients after Esophageal or Gastric Cancer Surgery

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ABSTRACT

Introduction: While many cancer patients are using complementary and alternative medicine, few clinical trials have evaluated its effectiveness. In this study, we aimed to evaluate the clinical significance of *Agaricus Blazei Murill* (ABM) on patients after radical surgery.

Methods: A total of 30 patients with esophageal cancer or gastric cancer were enrolled. ABM were taken orally 50 ml per pack twice a day for one month. Changes of Natural Killer cell (NK cell) activity, neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), Onodera's prognostic nutritional index (PNI), and various blood biochemistry were compared before and after ABM intake. Adverse events were assessed by Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Results: Red blood cell count and hematocrit decreased before and after intake of ABM, and potassium and CRP increased. No statistical differences were observed in NK cell activity, NLR, PLR, PNI before and after ABM intake. No severe adverse event was observed by ABM intake.

Conclusions: These results suggest that one month ABM intake on patients after radical surgery for esophageal cancer and gastric cancer does not affect immunological nor biochemical parameters.

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KEYWORDS: complementary and alternative medicine, *Agaricus Blazei Murill*, esophageal cancer, gastric cancer

Introduction

The number of patients using complementary and alternative medicine (CAM) is increasing. CAM refers to any medical system, practice, or product that is not thought of as standard care in the United States.¹⁾ National scale survey was conducted by the research group of Ministry of

Health, Labor and Welfare to analyze practical use of CAM in Japan, in 02001. As a result, 45% of cancer patients used CAM, and the most frequently used CAM product was mushrooms, *Agaricus blazei Murill* (ABM).²⁾

Frost M reviewed clinical trials on popular medicinal mushroom supplement.³⁾ They concluded that the outcome of those studies was variable and caution was recom-

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mended when extrapolating the results. They also claimed that many factors, such as poor study design, small sample sizes, lack of replication, mushroom variability, and problematic statistical methods, made it difficult to rely on the results of any individual study. Uebaba et al. demonstrated the safety and effectiveness of ABM for healthy subjects.⁴⁾ Ohno et al. showed the safety of ABM in various cancer, and they assessed quality of life of cancer patients.^{5,6)} However, there have been no reports focusing on patients with esophageal cancer and gastric cancer.

ABM has been reported to possess immunostimulatory action and antitumor effects by increasing Natural Killer cell (NK) activity in mice.⁷⁻⁹⁾ There are only a few reports in the human studies and the conclusions remain controversial.^{9,10)} Ahn WS et al. reported that ABM did not increase NK activity in gynecological cancer patients.⁹⁾ On the other hand, Ying Liu et al. reported that *Agaricus brasiliensis* KA21, one of an *Agaricus* mushroom, increased NK cell activity in healthy volunteers.¹⁰⁾ There were no studies on the patients with gastrointestinal cancers.

Therefore, we evaluated the safety and effectiveness of ABM in the patients with esophageal cancer and gastric cancer. We investigated the influence of ingestion of ABM on blood biochemical examination in patients after esophageal cancer and gastric cancer surgery. We also examined changes in NK activity and changes in immune index before and after the intake of ABM.

Materials and Methods

Patient selection

We conducted prospective open label study on a total of 30 patients who were surgically treated for esophageal or gastric cancer between January and June of 2015. Eligibility criteria were aged 20-80 years, those who were performed curative surgery for esophageal cancer or gastric cancer at Toho University Omori Medical Center (Tokyo, Japan), and those were cases with no signs of recurrence in 2 years or more after surgery. Eligibility criteria also included patients who have adequate organ function [white blood cell count, $>4,000/\text{mm}^3$ and $<12,000/\text{mm}^3$; hemoglobin, $>10.0 \text{ g/dl}$; platelet count, $>100,000/\text{mm}^3$; serum aspartate aminotransferase and alanine aminotransferase: less than 2.5 times the facility reference value; total bilirubin, $<1.5 \text{ mg/dl}$; and creatinine, $<2.0 \text{ mg/dl}$].

Agaricus

ABM is one of the mushrooms contained in *Agaricus* genus. The mushrooms used for cooking are also one of the

mushrooms contained in *Agaricus* genus. ABM grew up in the mountains of the Piedate region of Sao Paulo, Brazil, and was collected as food for residents there. We selected "Sen-Sei-Ro S-S-G+ (extract) (SSI Co., Ltd., Tokyo, Japan)" as ABM products. This product obtained by adding 360 mg of ABMK-22 extracted from the extract of ABM and extracting only the low molecular weight component having a molecular weight of 10000 or less from the extract solution.

Blood sampling and evaluated parameters

Patients orally administered ABM 50 ml after meals twice a day for one month. Peripheral blood samples were obtained before ABM intake and after ABM intake. The following laboratory parameters were measured: white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell differentiation, creatinine, sodium, potassium, chlorine, total protein, albumin, total bilirubin, direct bilirubin, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, gamma-glutamyl transpeptidase, amylase, C-reactive protein, and NK cell activity. From the measured values, neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), Onodera's prognostic nutritional index (PNI) were calculated. Changes before and after ingestion of *Agaricus* were examined for measured value of blood biochemical test and index calculated as immune index.

Adverse events

Adverse events were assessed by Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Statistical analysis

In the statistical analysis, the Wilcoxon rank sum test was used to compare various parameters before and after intake of ABM. The statistical significance level was set at $P < 0.05$. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan, Version 1.11),¹¹⁾ which is based on R (The R Foundation for Statistical Computing, Vienna, Austria) and R commander.

Ethical consideration

This study was conducted with the approval of Toho University Medical School Ethics Committee. Approval number: 26047 "Phase II clinical trial analyzing the immunological effect of *Agaricus blazei* (*Agaricus*) in patients with esophageal cancer and gastric cancer."

Table 1 Patients' characteristics

	Number of patients (%)
Age	
≤65 years/>65 years	9 (33%) / 18 (67%)
Gender	
Male/Female	17 (63%) / 10 (37%)
Type of cancer	
Gastric cancer/Esophageal cancer	25 (93%) / 2 (7%)
Progress of cancer	
Early cancer/Advanced cancer	18 (67%) / 9 (33%)
Lymph node metastasis	
No/Yes	20 (74%) / 7 (26%)
Distant metastasis	
No/Yes	27 (100%) / 0 (0%)
Pathological stage	
I/II/III/IV	20 (74%) / 5 (19%) / 22 (7%) 00 (0%)

Table 2 Comparison between blood cell count before and after *Agaricus blazei* Murill intake.

		Before (mean ± SD)	After (mean ± SD)	P-value *
WBC	(/μl)	5288 ± 1376	5118 ± 1093	0.44
RBC	(10 ⁴ /μl)	420 ± 47.7	410 ± 45.7	<0.05
Hb	(g/dl)	13.1 ± 1.5	12.8 ± 1.3	<0.05
Ht	(%)	39.3 ± 4.1	38.1 ± 3.9	<0.05
Plt	(10 ³ /μl)	242 ± 114	229 ± 81.6	0.12
NEUT	(%)	58 ± 8.5	55.4 ± 11	0.18
LYMPH	(%)	33 ± 7.3	34.3 ± 8.5	0.38

SD: standard deviation

* Wilcoxon rank sum test

Results

Patients background

Among the total of 30 patients agreed to this study, three patients were excluded because blood samples were not available after intake of ABM (Table 1). Characteristics of the other 27 patients were shown in Table 1. The average age is 69 years old (range 55 to 82 years old), including 17 male (63%) and 10 female (37%). A total of 25 gastric cancer patients and 2 esophageal cancer patients were included. 18 patients (67%) were pathologically classified as early cancers and 9 patients (33%) were classified as advanced cancers.

Comparisons of blood parameters and laboratory data between before intake and after intake of ABM

Red blood cell count, hemoglobin, and hematocrit decreased significantly after intake of ABM (Table 2). Potas-

sium and CRP increased significantly after intake of ABM (Table 3). On the other hand, albumin decreased significantly.

Comparison between immunomodulatory parameters before and after intake of ABM.

There was no major change in NK cell activity and immunomodulatory parameters such as neutrophil lymphocyte ratio, platelet lymphocyte ratio and Onodera's prognostic nutritional index (Table 4).

Adverse events of ABM intake

Adverse events were shown in Table 5. Although several minor adverse events were observed, there were no severe adverse events. Grade 1 hypoalbuminemia was observed in 5 patients. Grade 1 Hyper potassium was observed in 4 patients and Grade 2 Hyper potassium was observed in 1 patient.

Table 3 Comparison between blood chemistry before and after intake of *Agaricus blazei* Murill.

		Before (mean \pm SD)	After (mean \pm SD)	P-value *
C-reactive protein	(mg/dl)	0.0 \pm 0.1	0.2 \pm 0.4	<0.05
Total Protein	(g/dl)	7.5 \pm 0.5	7.3 \pm 0.5	0.07
Albumin	(g/dl)	4.1 \pm 0.3	4.0 \pm 0.3	<0.05
Sodium	(mM)	140 \pm 2	140 \pm 2	0.83
Potassium	(mM)	4.1 \pm 0.3	4.2 \pm 0.5	<0.05
Chlorine	(mM)	106 \pm 2.7	106 \pm 1.7	0.98
Blood urea nitrogen	(mg/dl)	14 \pm 4.1	14 \pm 4.5	0.37
Creatinine	(mg/dl)	0.8 \pm 0.2	0.8 \pm 0.2	0.53
Total bilirubin	(mg/dl)	0.8 \pm 0.3	0.7 \pm 0.3	0.07
Direct bilirubin	(mg/dl)	0.2 \pm 0.1	0.2 \pm 0.1	0.72
Aspartate aminotransferase	(IU/l)	28 \pm 16	28 \pm 21	0.47
Alanine aminotransferase	(IU/l)	18 \pm 10	19 \pm 16	0.63
Lactate dehydrogenase	(U/l)	196 \pm 26	196 \pm 31	0.76
Alkaline phosphatase	(IU/l)	251 \pm 76	248 \pm 78	0.49
gamma-glutamyl transpeptidase	(U/l)	30 \pm 33	31 \pm 38	0.68
amylase	(IU/l)	86 \pm 27	81 \pm 26	0.21

SD: standard deviation

*Wilcoxon rank sum test

Table 4 Comparison between immunomodulatory parameters before and after intake of *Agaricus blazei*.

	Before (mean \pm SD)	After (mean \pm SD)	P-value *
NK cell activity (%)	42.7 \pm 10.3	41.1 \pm 11.9	0.57
NLR	1.93 \pm 0.85	1.8 \pm 0.8	0.31
PLR	0.14 \pm 0.05	0.14 \pm 0.04	0.53
PNI	49.2 \pm 3.9	48.4 \pm 4.6	0.25

SD, standard deviation

NK cell, natural killer cell

NLR, neutrophil lymphocyte ratio

PLR, platelet lymphocyte ratio

PNI, Onodera's prognostic nutrition index

*Wilcoxon rank sum test

Table 5 Adverse events of *Agaricus blazei* intake.

	Grade1 *	Grade2 *
Hypoalbuminemia	5	0
Hyper potassium	4	1
Abnormal GOT	2	0
Abnormal GPT	1	0
Abnormal ALP	4	0
Diarrhea	1	0

*Common Terminology Criteria for Adverse Events v4.0

Discussion

In this prospective study, although ABM has no severe adverse effects, we did not find any effects on immunological parameters. While some of the blood parameters changed, no immunological parameters improved after one month intake of ABM.

Although some of the previous reports showed improvements of immunological parameters in other type of solid tumors, in our present study, we could not confirm such tendency. Three possible explanations were raised as follows: (i) One month intake of ABM was not enough to have effects on immunological parameters, (ii) Potential ef-

fects of ABM was useful only for the patients with poor immunological conditions, (iii) Potential malabsorption after reconstruction of upper gastrointestinal tract might affect immunological conditions. Actually, previous reports used ABM for three months or more. In this present study, only the patients with good general condition were enrolled. Therefore, the potential effects of ABM to recover poor immunological parameters to be normal conditions were hardly observed.

This study has limitations that warrant mention. First, there might be only a few subjects to confirm the changes of immunological parameters. Second, since it is a single-arm, single-dose study, the statistical power was not enough to assess any effects on immunological and biochemical parameters.

In conclusion, these results suggest that one month ABM intake on the patients after radical surgery for esophageal cancer and gastric cancer does not affect immunological nor biochemical parameters.

Conflicts of interest: None declared.

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