

Dietary Administration of Mushroom Mycelium Extracts in Patients with Early Stage Prostate Cancers Managed Expectantly: A Phase II Study

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Objective: To assess the efficacy and safety of dietary supplements in patients with early stage prostate cancers who are managed expectantly.

Methods: Seventy-four patients with early prostate cancer, who were treated with expectant management, enrolled in the study. A mushroom mycelium extract was given at a dose of 4.5 g/day for 6 months. The primary endpoint was the proportion of patients in which the prostate specific antigen level decreased by 50% or more following treatment. The adverse events, change of prostate specific antigen value and quality of life were also evaluated.

Results: In only one of 74 patients (1.4%), the prostate specific antigen value decreased more than 50%. Grade 2 diarrhea and grade 1 itching were observed in one patient, and patient ingestion compliance was maintained near 100%. The alternation of prostate specific antigen values was stable before and after treatment. In subjects with strong anxiety prior to supplement ingestion, these feelings were significantly alleviated (state anxiety, $P = 0.0018$; trait anxiety, $P = 0.0099$).

Conclusions: In this phase II study of early prostate cancer patients who were managed expectantly, a mushroom mycelium extract was an ineffective treatment for reducing 50% or more the patient prostate specific antigen values.

Key words: dietary supplement – prostate cancer – expectant management

INTRODUCTION

Owing to an aging population, the westernization of dietary habits, and the widespread use of prostate specific antigen (PSA) screening and systematic prostate biopsy, there has been a marked increase in the incidence of prostate cancer patients. Moreover, most prostate cancers are discovered at an extremely early stage. For this reason, expectant management has been adopted as a treatment method for prostate cancer. An alternative to active treatment, expectant management involves closely monitoring the disease and intervening at any sign of progression. Prospective studies have

suggested that some patients with early stages prostate cancer may benefit from this treatment by avoiding treatment-related complications and significant prostate cancer progression. Expectant management for early stage prostate cancer has been adopted in various guidelines, such as the National Comprehensive Cancer Network guidelines (1), as a standard treatment method for prostate cancer. In Japan, the standards for determining cases in which this treatment method can be used have been recommended by a study group supported by a grant-in-aid for cancer research

from the Ministry of Health, Labour and Welfare, and this treatment method has been adopted in clinical practice (2).

It has become clear that cancer patients are expressing interest in and using complementary and alternative medicine (CAM). In the USA, the number of CAM users is increasing every year and is reported to include ~50% of all cancer patients (3). In addition, CAM is used by 30–43% of prostate cancer patients, who primarily use vitamin preparations (4). In Japan, Hyodo et al. conducted a large-scale nationwide investigation of over 3000 subjects and revealed that ~45% of cancer patients use some type of CAM (5). Approximately 97% of CAM treatments were dietary supplements, of which mushrooms were the most common. According to studies by Yoshimura et al. (6,7) and Sumiyoshi et al. (8), the rate of CAM use by prostate cancer patients is 20–30%, and the use of mushrooms was frequent. However, the information that patients using CAM most require (such as information regarding efficacy, the prevention of recurrence, survival benefits and side effects) is currently scarce, and there is no scientifically validated information. Few clinical trials have been performed, and there is an urgent need for CAM clinical trials in Japan.

Clinical trials for some kinds of dietary supplements have been performed in western countries. Green tea is the most widely used herbal product in the USA. A phase I study of green tea in lung cancer patients and a phase II study in prostate cancer patients showed that green tea supplementation had no antitumor activity (9,10). Shark cartilage is purported to have anti-angiogenesis effects that might inhibit malignant growth. However, two published clinical studies failed to show any evidence of antitumor activity (11,12). Lycopene belongs to the carotenoid family and may be important for the prevention of prostate cancer. Ansari et al. reported that lycopene is effective for the treatment of hormone refractory prostate cancer (13), but Jatori et al. reported that lycopene did not appear effective (14). Clinical trials are indispensable for scientific verification, but in Japan, few clinical trials examining CAM efficacy have been conducted.

A mushroom mycelium extract [active hexose correlated compound (AHCC)] is a generic term used to describe a plant polysaccharide extracted from a liquid culture of basidiomycetous mycelia of *Lentinula edodes*. In basic studies on AHCC, it has been reported that AHCC has immunostimulating activity, anticancer activity, cancer-preventive actions and can prevent side effects during cancer chemotherapy, among other functions (15,16). Regarding clinical applications, Matsui et al. compared cases that were administered AHCC with cases that were not administered AHCC after a hepatectomy for liver cancer, and reported that the survival rate was significantly better in the group administered with AHCC (17). Moreover, White et al. reported that administering AHCC to prostate cancer patients may impede cancer progression (18).

According to this background, we conducted a clinical trial in which AHCC was administered to patients with early stage prostate cancer who were expectantly managed, while

the usefulness of such an administration were examined and the results reported.

PATIENTS AND METHODS

The clinical trial was an open trial conducted as a multicenter clinical study. The patients had been histopathologically diagnosed with prostate cancer, and 40 patients were undergoing expectant management and 34 patients had already undergone expectant management for 6 months or more (Table 1). The mean age of all of the patients was 73.5 years of age (range: 59–91 years of age), while the mean age of patients for whom expectant management was started was 70.8 years of age and for patients for whom expectant management was being continued was 76.8 years of age.

In this trial, we administered AHCC as a dietary supplement. AHCC, which was a commercially available dietary supplement, was purchased from Amino Up Chemical Co., Ltd. (Sapporo, Japan) and produced by the extraction from culture broth of Basidiomycetes (*Lentinula edodes*) mycelia. The component characteristics included abundant carbohydrate components (70% or more), including mainly polysaccharides, and a high number of alpha-glucans (15). AHCC was chosen as the dietary supplement for this trial for several reasons as follows: (1) it is derived from a mushroom health food product that is commonly used in Japan; (2) there are reports in which survival rates were improved after post-operative AHCC adjuvant therapy for liver cancer (17); (3) its efficacy for prostate cancer has been confirmed in basic studies, and there are clinical studies indicating its direct therapeutic effects and trial results indicating that it may inhibit PSA elevations (18); and (4) it has been used for over 20 years in 60 countries without any serious side effects, and the quality control for the finished product is satisfactory (19). The AHCC safety has been confirmed in animal experiments and with healthy volunteers, and no severe adverse events were observed, even when 9 g were administered per day (19).

Each patient in the present study was treated with 4.5 g of AHCC per day for six consecutive months. Moreover, for willing subjects, the period was extended by another 6 months and administration continued for a total of 12 months. Patients who were registered in this trial received no specific medication, dietary supplement or regular food. The

Table 1. Patient characteristics at baseline

	Total	Onset	Ongoing
No. pts.	74	40	34
Mean age (years of age)	73.5	70.8	76.8
Mean PSA (ng/ml)	7.486	7.087	8.012

Onset, patients were undergoing expectant management; Ongoing, patients had already undergone expectant management for 6 months or more; No. pts., number of patients; PSA, prostate specific antigen.

patients visited the hospital and underwent an examination every 2 months. During these examinations, a digital rectal examination, a PSA test and a biochemical blood examination were performed. In addition, immune parameter examinations [T helper 1/T helper 2 (Th1/Th2) and natural killer (NK) cell activity] and a questionnaire survey of the state-trait anxiety inventory (STAI) both before administration and 6 months after the start of administration were conducted. The STAI is the definitive test for measuring anxiety in adults. It clearly differentiates between the temporary condition of state anxiety and the more general and long-standing quality of trait anxiety.

We defined the primary endpoint as the proportion of cases in which the PSA level decreased by 50% or more from the baseline levels. A decrease in the PSA level of 50% or more is used to determine the effectiveness of medication for prostate cancer.

The secondary endpoints were in compliance with AHCC administration, adverse events, and changes in Th1/Th2, NK activity and STAI before and after administration. In addition, for the patients for whom expectant management was being continued, we compared the PSA doubling time (PSADT) before and after administration. The PSADT was calculated as the natural log of 2 divided by the slope, as PSA values were distributed on the *y*-axis of a scatter plot and time on the *x*-axis. A line function fitted the PSA values over time and the PSA slope was calculated using a least-squared regression. This clinical trial was approved by the Institutional Review Board. The trial began after obtaining a written consent from all patients enrolled in the study.

All adverse events were graded using the version 3.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events. The χ^2 -test, a Student's paired *t*-test and a Mann-Whitney's *U* test were used to assess the relationship between pre- and post-treatment parameters. Differences in means with *P*-values less than 0.05 were considered to be statistically significant. All the statistical analyses were conducted using the SPSS 16.0J statistical software package (SPSS, Tokyo, Japan).

RESULTS

Seventy-four patients were registered in this phase II trial. During the course of treatment, three patients discontinued treatment due to disease progression (rapid elevations in PSA levels), rupturing of an abdominal aortic aneurysm (determined to be an incidental event by the Data Monitoring Committee) and diarrhea (an adverse event). After the 6-month trial period was completed, more than half of the patients requested that administration be continued.

PRIMARY ENDPOINT

Only one out of 74 patients (1.4%) had a PSA decrease greater than 50%. The case being a 69-year-old patient with

stage T1cN0M0 prostate cancer. In the histopathological analyses of the biopsy specimen, 1 out of 12 specimens was positive for cancer and the Gleason score was 3 + 3 = 6. In this patient, the PSA decreased by a maximum of 54%, and the PSA changes were almost stable. AHCC was administered for 12 months, and over 2 years have passed but expectant management is still being continued till today.

SECONDARY ENDPOINTS

The changes in the PSA levels during the trial period are shown in Fig. 1. The PSA baseline values after 6 months' administration of AHCC were 7.49 and 7.52 ng/ml, respectively. The changes in PSA levels were stable. Even when the subjects were divided between patients for which expectant management was started and continued in patients or between those with an administration period of 6 months and those with an administration period of 12 months, the results were similar and the changes in PSA levels were stable.

Patient compliance with AHCC administration was very good, nearing 100%. Adverse events included grade 2 diarrhea that was observed in one patient, and grade 1 itching that was observed in one patient. The treatment was discontinued for the former patient, but administration of the full amount was possible in the latter patient.

Although there was a mild decrease in the NK activity after administration, it was not statistically significant. Conversely, a mild increase in Th1/Th2 levels was observed, but was not statistically significant (Fig. 2).

The STAI results are shown in Table 2. The patients whose state anxiety score was 42 or above, or the trait anxiety score was 44 or more, were defined as patients with strong anxiety. The former considered 19 patients, and the latter consisted of 15 patients. State anxiety in patients was significantly lower after administration, and improvement noted. Similarly, for trait anxiety, significantly lower values were observed after administration and trait anxiety was improved. In other words, in subjects with strong feelings of

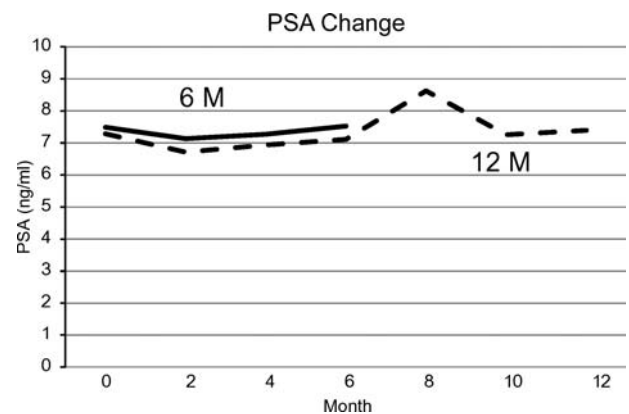


Figure 1. Prostate specific antigen (PSA) levels after treatment. The changes in the PSA levels were stable. 6 M, administration for 6 months (71 patients); 12 M, administration for 12 months (39 patients).

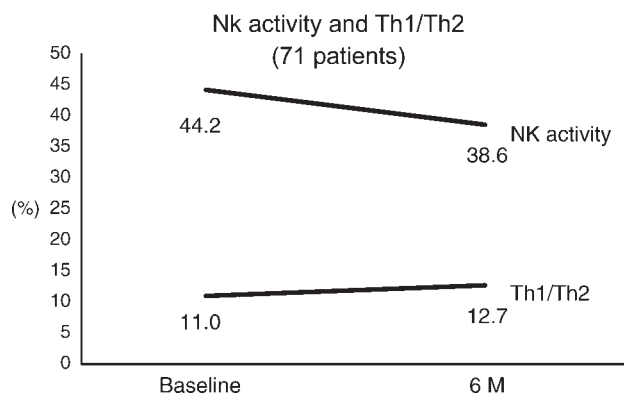


Figure 2. Natural killer (NK) cell activity and T helper 1/T helper 2 (Th1/Th2) at baseline and 6 months. No significant difference was observed.

Table 2. State–trait anxiety inventory at baseline and 6 months

Anxiety	No. pts.	Baseline	6 M	P
State	19	51 ± 9	44 ± 8	0.0018
Trait	15	53 ± 8	46 ± 10	0.0099

No. pts., number of patients; Baseline, before treatment; 6 M, 6 months after treatment.

Table 3. Prostate specific antigen doubling time at baseline and 6 months (31 patients)

	Less than 24 months	Between 24 and 120 months	120 months or above
Before	12 Pts.	7 Pts.	12 Pts.
After	9 Pts.	5 Pts.	17 Pts.

Pts., patients; Before, before treatment; After, after treatment.

anxiety at the beginning of the trial, there were statistically significant reductions in these feelings after 6 months of AHCC administration ($P < 0.01$).

PSADT was examined for the 31 subjects who underwent expectant management. Although the PSADT after administration was prolonged compared with PSADT prior to administration, no statistically significant difference was observed (Table 3).

DISCUSSION

In Japan, ~20–30% of prostate cancer patients using CAM (6–8), and this proportion is similar to the proportions reported in the USA. However, the types of CAM differ from those used in the USA; almost all of the patients use dietary supplements, with mushrooms being the most common. In addition, the purposes of usage included curing

cancer and prolonging survival. Prostate cancer patients in Japan have been using dietary supplements as anticancer agents.

Although many patients are using CAM as dietary supplements, the efficacy and side effects have not yet been scientifically verified. In this study, we conducted an intervention trial targeting patients with early stage prostate cancer who were managed expectantly to verify the efficacy of health food products on reducing PSA levels. This trial seems the first official CAM trial in Japan (study supported by a grant-in-aid for cancer research from the Ministry of Health, Labour and Welfare).

The reasons for targeting patients with early stage prostate cancer managed expectantly include the following: the incidence of patients has been increasing in recent years in Japan; lifestyle interventions through diet and exercise may delay cancer progression; and PSA is a suitable tumor marker for determining efficacy. In particular, lifestyle intervention trials have been reported by Ornish et al. In the results of this trial, PSA elevations were significantly more controlled and conventional treatment was avoided or delayed in the intervention group, for which a low-fat, plant-based diet and exercise were implemented and supplements such as vitamin E were provided, in comparison to the control group (20).

Of the 74 patients who entered this trial, there was only 1 patient who exhibited a decrease in PSA levels of 50% or more compared with PSA levels prior to treatment. In this patient, the PSA decreased by a maximum of 54%. AHCC was administered for over 1 year and expectant management is being continued, and 2 years have passed since the start of the trial. White et al. conducted an interventional trial using AHCC for patients with various stages of prostate cancer (18). In their results, including seven patients undergoing expectant management, there were no cases in which the PSA level decreased by 50% or more. As in the present trial, the primary endpoint was defined as the proportion of patients in which the PSA level decreased by 50% or more. When conducting a clinical trial using CAM treatments, the primary endpoint definition is an important issue. The present method used determined the efficacy of medication for prostate cancer. Dietary supplement users in Japan hope to obtain antitumor effects, and some dietary supplements and anticancer agents are considered to overlap. Based on these reasons, the primary endpoint was defined herein as the proportion of cases in which the PSA level decreased by 50% or more. It will be necessary in future to examine the efficacy of this primary endpoint when conducting CAM clinical trials targeting prostate cancer.

In the present trial, the changes in PSA levels were substantially stable. This was observed regardless of whether the administration period was 6 months (0.03 ng/ml elevation) or 12 months (0.1 ng/ml elevation). The PSA levels in prostate cancer patients with expectant management are elevated gradually. It is unclear whether the stable PSA levels were due to AHCC because we did not define a control.

In the results, the PSADT was very long at 399 months with a 6-month treatment and 99 months with a 12-month treatment. The distribution of patients for whom expectant management was started according to PSADT, the PSADT was as follows: the PSADT was below 24 months in 25% of the patients, was between 24 and 120 months in 20% of the patients and was 120 months or above in 55% of the patients. In Japan, Kakehi et al. (2) reported a similar distribution of 108 cases for which expectant management was started according to PSADT. According to that distribution, the corresponding values were 21%, 24% and 55%, respectively. Based on these results, it is believed that the PSADT of patients for whom expectant management was started had no effect after AHCC treatment. Next, we compared the PSADT before and after the trial for patients for which expectant management had been continued for 6 months or more prior to the start of the trial. In the distribution according to the pre-trial PSADT, the PSADT was below 24 months in 39% of the patients, between 24 and 120 months in 22% of the patients and 120 months or above in 39% of patients. In the distribution after starting treatment, the corresponding values were 29%, 16% and 55%, respectively. Although the proportion of patients with extended PSADTs increased after starting the trial, these differences were not statistically significant. These results suggested that dietary uptake of AHCC contributes to the stabilization of the disease status in patients with early stage prostate cancers who are expectantly managed.

In this interventional trial, we examined the changes in the anxiety states after AHCC treatment. In patients exhibiting strong anxiety before the start of the trial, the anxiety significantly decreased after 6 months of treatment. In addition, similar results were obtained when anxiety was categorized into state and trait anxiety. In prostate cancer patients who were managed expectantly, some patients had strong anxiety despite having chosen expectant management, rather than active treatment. In addition to patients with strong anxiety, it is believed that patients with low anxiety will also proactively accept some type of intervention. Based on the fact that the compliance for AHCC was very high in this trial, it is understood that these patients constitute a cohort that will proactively accept some type of intervention. In this trial, patient anxiety was significantly reduced, but it is not clear whether this is an effect of AHCC treatment or if similar results would be obtained with other CAMs. It is necessary to conduct randomized comparative trials of AHCC and a placebo or another CAM.

Dietary supplements, particularly mushroom-derived plant polysaccharides such as AHCC, are used with the expectation that they will have immunostimulating actions (21). It has been confirmed in basic and clinical studies that AHCC affects NK activity. In this trial, there were no effects on NK activity or Th1/Th2 before and after AHCC administration.

One of the limitations of this study includes its small number of subjects. However, few clinical trials as to CAM have been carried out in Japan. We therefore designed the

present study as a feasibility study. The findings obtained here may warrant further comparative studies of a larger sample size.

CONCLUSION

We conducted an interventional study using a mushroom mycelium extract (AHCC) targeting early stage prostate cancer patients with expectant management. Only 1.4% of patients displayed PSA levels that were decreased by 50% or more after AHCC treatment. Changes in PSA levels before and after treatment were substantially stable. In patients exhibiting strong anxiety before the start of the trial, the anxiety significantly decreased after 6 months of treatment. There were no complications related to the safety of AHCC, and only 1 out of the 74 patients discontinued AHCC due to side effects (diarrhea). Moreover, the patient compliance with AHCC treatment was very high. We believe that in the future, these results should be considered when conducting randomized comparative trials.

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Conflict of interest statement

None declared.

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