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Clinical Experiences of AHCC

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Introduction

Numerous basic research studies and clinical trials have been performed to find a way to prolong the life of advanced cancer patients. In reality, however, any rational, scientific, treatment for advanced cancer patients without any side effects has not been established due to pathological conditions and complicated varying circumstances of each individual case. Therefore, the best treatment for each patient should be based on the clear understanding of the patient's social, economical, physical and mental condition, accordingly. While there are many folk remedies used in the treatment of cancer, our clinical trial uses the functional food, Active Hexose Correlated Compound (AHCC) for cancer patients. In addition to the basic research reports of AHCC, we would like to explain our experiences of using AHCC in clinical settings.

I. Basic Information (Background) of AHCC

A. Production and Property of AHCC

In 1989, AHCC was jointly researched and developed by Okamoto from the College of Pharmacy, Tokyo University, and Yamazaki from Teikyo University and Amino Up Chemical Co., Ltd. AHCC is an extract of mycelium, obtained through the long-term cultivation of several types of basidiomycetes in a medium containing substrate of a certain concentration. After undergoing enzymatic decomposition, concentration, and freeze-drying, the functional food AHCC is obtained from the cultured liquid. The germ-free equipment used in the manufacturing of AHCC, such as the large-scale culture tanks (maximum 15 tons), centrifugal thin membrane vacuum evaporator, and the vacuum freeze-dryer, follows GMP standards for the quality control of medical products. Currently, the manufacturer, Amino Up Chemical, is acquiring ISO 9002 status and HACCP certification, the international standards in quality control. (Certified in 2001)

AHCC is a tan powder with a slight unique odor. It is highly hygroscopic, deliquescent, and water-soluble. AHCC is stable for 2 years under cool and dark storage.

One of the active components of AHCC is an oligosaccharide, having a molecular weight of 5,000 daltons. The oligomer of glucose in AHCC has an alpha 1,4 linkage structure while the glucans in PSK or Lentinan have different linkage structures. The safety of AHCC is

demonstrated in toxicological studies conducted in compliance with GLP standards and guidelines for toxicological experiments.

Figure 1. AHCC Manufacturing Process

Mycelium obtained from basidiomycetes
↓
Precultivation in liquid medium
↓
Main cultivation in large-scale tanks
↓
Enzyme reaction
↓
Decomposition and Concentration
↓
Freeze-drying
↓
Secondary Processing

B. Basic Studies in Animal Models

1. The protective effect of AHCC against liver injury

Male ICR mice were treated with AHCC orally at a dose of 1g/kg/day for 3 days, and 0.4ml CCl_4 (diluted with olive oil 20%(w/v)) was administered by peritoneal injection on the fourth day, for 4 days. Serum investigation found that the pre-treatment of AHCC caused a biochemical and morphological effect in preventing liver injury induced by CCl4.In particular, the pre-treatment of AHCC prevented the decrease of cytochrome P-450 in the liver microsome fraction induced by CCl4. Also in the pathological tissue investigation, AHCC was found to reduce the necrosis of the cells in liver parenchyma, which widely spread around the central vein by CCl4.

2. The protection effect of AHCC on the bone marrow inhibition induced by anti-cancer agent

Male ddY 8-week-old mice were treated with either 5-FU(50mg/kg),CY(100mg/kg) or both 5-FU and CY for 14 days. The effect of oral co-administration of AHCC was investigated. The result found that AHCC inhibited side effects such as weight loss or a decrease of unripe erythrocyte/mature erythrocyte ratio in bone marrow, that is caused by anti-cancer drugs.

3. The protective effect of AHCC on liver injury induced by anti-cancer agents

Male ddY 8 week-old-mice were divided into 4 groups; the control group, the AHCC-treated group, the anti-cancer drug-treated group (6-MP 2.5 mg/kg and MTX 30mg/kg), and AHCC + anti-cancer drug co-treated group. At the end of the experimental trial, body weight, blood cells, serum GOT, GPT, ALP, albumin and total protein were measured. In the AHCC-treated group, the weight loss induced by the anti-cancer drug was significantly inhibited. Also in AHCC-treated group, the decrease of erythrocyte and leukocyte was prevented. Anti-cancer drugs commonly cause a 50% decrease in erythrocytes and leukocytes. Isolated liver enzymes, which usually increases to double its normal range due to anti-cancer drugs, was prevented by AHCC. Serum albumin also decreased as a result of the AHCC. These improvements of biochemical parameters were observed from pathological histology.

4. Protective effect on metastasis of breast cancer by AHCC and UFT combination

Matsushita and his colleagues inoculated SST-3 (transplantable adenocarcinoma) into T-cell-depressed SHR rats for the purpose of observing the effect of UFT (tegafur and uracil, 4:1) and AHCC. The average tumor size in the AHCC and UFT co-administered group was significantly smaller when compared to the control group. The metastasis to lymph nodes was also reduced significantly. Furthermore, the decrease of NK cell activity by UFT was restored by the AHCC combination.

5. Effects of AHCC on opportunistic infection

Ishibashi reported the preventive effect of AHCC against *Candida albicans* and *Pseudmonas aeruginose*. The immune suppression model was prepared by cyclophosphamide, in which AHCC was administered for 4 days before *Candida albicans* and *Pseudmonas aeruginosa* inoculation. After the infection, AHCC treatment continued for 2-4 weeks. The AHCC group showed a prolonged survival period as compared to the control group.

Although the experimental data is limited, these reports have suggested that oral AHCC treatment can suppress the side effects of anticancer agents, change the immune system in order to prolong the survival period of cancer patients, and prevent infection. Furthermore, some studies reported that AHCC could prevent diabetes in rats, caused as a result of streptozotocin infection, and alopecia as a result of anticancer agents.

II. The Clinical Trial of AHCC

A. Change of the Immunity by AHCC in Man

Uno and his colleagues measured NK activity, INF-alpha and IL-12 of Th1 related cytokines in peripheral blood monocytes, as the immunological parameters in 38 AHCC-treated solid cancer patients. 6 grams of AHCC was administered each day as 2 grams, three times daily after meals. Consequently, NK activity was increased clearly by the AHCC treatment, confirming INF-alpha and IL-12 production in monocytes is a response to the AHCC treatment. It should be mentioned that AHCC administration improves the performance status (PS) significantly when compared with before AHCC administration, showing a positive correlation between the increases of immunology-parameters and the improvement of PS.

B. AHCC trials in cancer patient

We administered 464 patients orally with AHCC (3~6g/day) before meals from April 1994 to December 1999 as shown in Table 1. The AHCC used for this clinical trial was micro-coated AHCC with hardened oil. The administration period of AHCC was 2 to 70 months, with an average of 20 months. The classification of the patient was expressed in Table 1. The main case was Hepatocellular carcinoma (HCC), with a man-to-woman ratio of 1:0.7. The age distribution was 28 years old to 81 years old, with an average of 59 years old. Children were not included in this trial. Out of the participants, 70 patients started to take AHCC after HCC surgery, others were diagnosed with HCC (checked twice) but did not have surgery, came from other hospitals, clinics or other departments of our hospital. Other cancer patients (not HCC) received AHCC treatment because other therapies, such as surgery or chemotherapy, would not expect to prolong their survival period. Therefore, almost all of these patients had metastasis or existing cancer tissue. Although some patients were suffering from the same cancer, such as gastric cancer, the conditions of the patients differed from each other, but with different metastases. Except HCC, the other cancers could not be analyzed in detail because of the limited number of cases, with the prognosis of gastrointestinal cancers the worst, and pancreatic cancers slightly below.

1. Prognosis of postoperative hepatocellular carcinoma patients treated with AHCC

We conducted this study from February 1992 to September 1999. All of the patients underwent curative resection of liver tumors at the First Department of Surgery, Kansai Medical University. The patients were histologically diagnosed with hepatocellular carcinoma. 175 patients were recruited for this trial during this period. Of these patients, a total of 23 cases were excluded, 2 cases of operative death, 7 cases of hospital death, 10 cases, in which the cancer doubled and 4 cases dropped out. As a result, 152 patients were enrolled in the study. Of the 152 patients, 70 patients were given AHCC (3-6g/day) and 82 patients did not take AHCC. These two groups were analyzed retrospectively. We examined the patients clinical backgrounds including

age, sex, liver function, preoperative tumor markers (AFP or PIVKA-Ⅱ), hepatitis virus (hepatitis B, hepatitis C), preoperative therapy, illness term, tumor size, number of tumors, histological differentiation, amount of intra-operative bleeding, operation time, postoperative hospitalization period and postoperative complication. As a result, the balance between the two groups was kept. In the postoperative period, the AHCC group had a low value tumor marker in the first year making the probability of survival in AHCC group very good. Furthermore, after analyzing the AHCC non-treated group and checking the recurrence of hepatocellular carcinoma, the treated group after a recurrence had a higher probability of survival than the AHCC non- treated group after a recurrence. Although the period was not long and the analysis was a retrospective one, we concluded that the oral administration of AHCC was effective on the improvement of the prognosis of hepatocellular carcinoma.

This trial is ongoing and as the patients increase, the observation period will be extended. Chronic hepatitis or hepatic cirrhosis could be thought to be the cause of hepatocellular carcinoma for most patients on this trial. The long-term intake of AHCC does not result in any liver function problems. In fact, many cases shown the serum bilirubin, liver enzymes, and gamma-GTP improve. We feel that it is necessary to observe the effects of the long-term intake of AHCC on liver function. Also, the hepatocellular carcinoma cases resulted from hepatitis C and hepatic cirrhosis, it was found that HCV-RNA deceased as a result of AHCC treatment through retrospective investigation. The data of both AHCC and control group is collected for further analysis.

In four patients who have hyperbilirubinmia (over 3.0mg/dl), obvious ascites and increased tumor markers caused by hepatocellular carcinoma, oral AHCC administration (6 grams/day) decreased ascites, serum bilirubin and tumor marker levels significantly. I suggest that AHCC be considered a useful therapy for ascites when diuretic drugs, ascitic puncture, and albumin are not effective.

2. Unresectable pancreatic carcinoma

The prognosis of non-excision was quite poor. In a case of pancreatic carcinoma, when abdominal incision was impossible, the prognosis was six months. For non-excision pancreatic carcinoma, we confirmed tissue diagnosis during the operation, carried out selective thermocoagulation and mass reduction. As a postoperative therapy, we conducted low dose radiation and chemotherapy, namely, low dose F-P (5-FU 250mg/day, 4 weeks) and CDDP (5mg/day, 5days per week for 4weeks) or low dose CPT-11 (CPT-11: (8mg/day) 4weeks). Along with the radiation and chemotherapy, AHCC was administered. During the treatment, 4 patients

survived more than10 months. In 1 case, the pancreatic cancerous tumor disappeared on CT, and the patient has survived for 3 years.

Since the number of the cases were limited, even a retrospective comparative investigation between the AHCC-treated group and untreated group was impossible. However, although a definite therapy to prolong the survival rate of progressive pancreatic cancer patients has not been found, alternative medicines, including AHCC should be used when observing any side effects.

3. Side effect of AHCC in cancer patients

A blood test is conducted on all patients every 1 to 2 months. The test markers are shown in Table 2. Any changes or abnormal data in the blood test and the biochemical data was not found as a result of AHCC treatment. The average investigation period is about 20 months and therefore, further long-term investigation is needed.

One postoperative case on hepatocellular carcinoma associated with chronic hepatitis, taking AHCC for a long period of time, suffered from ITP. However, it is not clear if there is any causal relationship between its long-term AHCC intake and the ITP. The hepatocellular carcinoma did not recur. In another case, a patient suffered from the recurrence of the upper-part cholangioma after operation, was taking AHCC for 3 months and underwent IVH, but unfortunately committed suicide.

While case numbers are few, closer investigations and further discussion of AHCC is warranted.

The higher bioactive substance should be noted to have more various side effects. Therefore, although a food, it might not be safe for patients, especially for progressive cancer patients.

4. Change of subjective symptoms after AHCC treatment

We have had many patients taking AHCC experience recovered appetite, awaken in a good mood, gain weight, and become cheerful, although these phenomenon cannot be shown as objective, reproductive data. Additionally in some cases, less side effects of chemotherapy were shown after AHCC treatment as compared to before AHCC treatment. We theorize that AHCC might have a psychotropic effect. Further research is needed.

Conclusion

Health and functional foods are used by progressive cancer patients who hope increased survival time regardless of ambiguous information that includes phrases used to describe these foods, such as "might be effective against cancer". However, we fear that non evidence-based foods might shorten the lifetime of patients, whose life has already been shortened by cancer.

Although our data is retrospective, AHCC does not increase the risk of shortening the lifetime of cancer patients, at least in the case of hepatocellular carcinoma.

Clinical doctors should neither deny alternative medicine without studying, nor accept alternative medicine easily without critical investigation. Based on scientific, rational data, alternative medicine should be applied.

Table1 Case Classification

hepatocellular carcinoma	187 cases
pancreatic carcinoma	64 cases
breast cancer	43 cases
colon cancer or rectum cancer	36 cases
gastric cancer	34 cases
gallbladder cancer	12 cases
other cancers and a disease	88 cases
Total	464 cases

Table2 Blood Chemicals

Whole blood
- Blood count ; WBC, RBC, Hb, Ht, number of platelet, etc.
- Leukocyte image

Serum
- Electrolyte ; Na^+, K^+, Cl^-
- Blood glucose level
- UN, CRTN
- TP, Alb, A/G
- AST(GOT), ALT(GPT), Ch-E
- T-Bil, D-Bil
- ALP, GGT

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