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Improved Survival of Patients with Gastric Cancer or Colon Cancer when treated with Active Hexose Correlated Compound (AHCC): Effect of AHCC on digestive system cancer

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Abstract

Background/Aim: Active hexose correlated compound (AHCC) is a functional food extracted from Basidiomycete mushrooms. AHCC has demonstrated immune stimulating activity in vitro and in vivo and may be a potent biological response modifier in cancer therapy. AHCC has been shown to improve the prognosis of patients with hepatocellular carcinoma. We investigated the effect of AHCC on the survival rate of patients with gastric cancer or colon cancer.

Study Design: From April 1995 to April 2002 we conducted a prospective cohort study.

Methods: 245 patients with a histopathological diagnosis of gastric or colon cancer were recruited to receive oral AHCC as a postoperative adjunctive therapy in conjunction with standard chemotherapy. Patients diagnosed with Stage I, II or III gastric or colon cancer received 3.0g/day oral AHCC in divided doses (1g AHCC three times per day). Patients diagnosed with Stage IV gastric or colon cancer received 6.0 g/day oral AHCC in divided doses (2g AHCC three times per day). The cumulative survival rates for gastric and colon cancer patients were analyzed by Kaplan-Meier method.

Results: AHCC as a functional food improved the cumulative five-year survival rates of Stage IA to Stage IIIA gastric cancer (n = 83) and Stage II to Stage III colon cancer (n = 52) patients compared to other institutions.

Conclusion: AHCC may improve survival in patients with early stage gastric cancer or colon cancer.

Key Words: Active hexose correlated compound; AHCC; Biological response modifier; Functional food; Colon cancer; Gastric cancer.

Introduction

Gastric cancer is the second most common cause of cancer death worldwide (700,000 deaths in 2002) and colorectal cancer is the third most commonly diagnosed cancer worldwide (1 million diagnosed in 2002).[1] Decreasing incidence and mortality for both gastric cancer and colon cancer have been achieved with earlier detection of disease, improved surgical techniques and advances in novel chemotherapeutics.[2,3,4,5,6] However, gastric cancer and colon cancer continue to incur significant morbidity and mortality in patients despite these advances. Current treatment options for colon cancer and gastric cancer include surgical resection and/or fluoropyrimidine based chemotherapy regimes.[7,8] Curative surgical resection is the definitive treatment for both cancers in early stage disease. An estimated 50% of patients with gastric cancer are diagnosed beyond early stage disease and require postoperative adjuvant therapy with only modest improvements in progression free survival and overall survival.[9] According to the 2002 Global Cancer Statistics, gastric cancer has an estimated age-adjusted survival rate of 33-44% in the United States and 51 - 54% in Japan.[1] In the case of colon cancer, early detection has significantly improved with screening, yet an estimated 30-55% of patients diagnosed with colon cancer either present with or will develop liver metastasis.[10,11] Liver metastasis is considered the major cause of colon cancer mortality.[12] Advances in hepatic resection of metastatic lesions have led to significant improvement in survival for the estimated 10 – 25% of patients who are eligible for such procedure.[13,14,15] The five-year survival for patients with unresectable metastatic colon cancer is less than 10%.[12]

Tumor immunotherapy may provide another therapeutic option in an integrated approach to gastric cancer and colon cancer treatment. The use of biological response modifiers (BRMs) to elicit anti-tumor immune responses in the host is an expanding sector of integrative oncology research. BRMs have been shown to elicit immunologic response to tumor cells through both tumor antigen specific and nonspecific host immune stimulation.[16] Mushroom polysaccharides have long been known to modulate immune function and inhibit tumor growth *in vitro* and *in vivo*.[17] Polysaccharides isolated from mushrooms such as lentinan from *Lentinus edodes* (Shiitake) and protein-bound polysaccharide K (PSK) from *Coriolus versicolor* have been investigated for their anti-tumor effects in vitro.[17,18] Studies in which lentinan or PSK was administered orally to patients with gastric cancer or colon cancer in conjunction with chemotherapy have resulted in prognostic

improvements.[19,20,21,22] We investigated a unique mushroom polysaccharide, active hexose correlated compound (AHCC), for its potential immunotherapeutic role in gastric cancer and colon cancer.

Active hexose correlated compound (AHCC; Amino Up Chemical Co, Ltd., Sapporo, Japan) is a functional food that is prepared as an enzyme-fermented extract of Basidiomycete mushrooms.[43] AHCC is a potent biological response modifier capable of increasing innate and adaptive immune activity *in vivo*[23,24] and in humans.[25] Studies show that AHCC may stimulate an anti-tumor immune response in humans that could improve cancer treatment outcomes. In patients with hepatocellular carcinoma, oral administration of AHCC resulted in improved prognosis, quality of life and significant increase in overall survival.[26,27] When added to chemotherapeutic regimens in vivo, AHCC also demonstrated enhanced treatment efficacy.[28,29] No studies have yet reported the effect of AHCC on gastric cancer or colon cancer. AHCC is well tolerated with minimal adverse effects noted by healthy volunteers.[30] A study evaluating the hepatic metabolism of AHCC found that AHCC induced CYP2D6 at a rate similar to that of rifampicin.[31] Patients receiving AHCC concurrently with other medications should be monitored closely for possible drug interactions with substrates of the CYP2D6 pathway.

The purpose of this study was to evaluate the potential for AHCC to improve overall survival in postoperative gastric and colon carcinoma patients receiving standard chemotherapy. The primary endpoint of this study was cumulative five-year survival.

Patients and Methods

From April 1995 to April 2002, surgical patients who received a histopathological diagnosis of primary gastric or colon cancer at our hospital were recruited to receive AHCC as a postoperative adjunctive therapy in conjunction with standardized chemotherapy. Patients were recruited at our hospital by physician recommendation. The aim of this study was explained to all patients in advance and informed consent was obtained.

In all patients with primary gastric or colon cancer, stage of cancer, progression, invasion, metastasis to lymph nodes, and remission were diagnosed according to the *Guidelines for Gastric Cancer* (13th edition)[32] or the *Guidelines for Colon Cancer* (6th edition).[33] The study protocol conformed to the ethical guidance of our institute and was approved by the institutional review committee.

1. Gastric cancer

132 patients diagnosed with gastric cancer were recruited to receive AHCC as a postoperative adjunctive therapy. The male:female ratio of patients was 2 to 1 and the average age was 62.5 years old (28 - 82 years old). Clinical staging of patients included 32 with Stage IA, 27 with Stage IB, 13 with Stage II, 11 with Stage IIIA, 14 with Stage IIIB and 35 with Stage IV gastric cancer. (Table 1) Patients Stage IA to Stage IIIB received 3.0 g/day of AHCC orally in divided doses, self-administered as 1g of powdered AHCC three times per day. Patients with Stage IV disease received 6.0g/day of AHCC orally in divided doses, self-administered as 2g of powdered AHCC three times per day. (Table 2) Patients with Stage I gastric cancer received no chemotherapy as per current treatment guidelines. Patients with Stage II to Stage IV disease were treated with a combination low-dose FP therapy of 250 mg/day of 5-fluorouracil (5-FU) and 5 mg/day of cis-diamminedichloroplatinum(II)a (CDDP) 5 times per week for 4 weeks. Low dose FP therapy was initiated 3 weeks postoperatively and was followed by oral administration of the fluoropyrimidine UFT (tegafur and uracil).

2. Colon Cancer

113 patients diagnosed with colon cancer were recruited to receive AHCC as a postoperative adjunctive therapy. The ratio of male to female was one to one and the average age was 58.3 years old (26 - 85 years old). Clinical staging of patients revealed 5 with Stage 0, 28 with Stage I, 16 with Stage II, 21 with Stage IIIA, 15 with Stage IIIB and 28 with Stage IV disease. (Table 3) Patients Stage 0 to Stage IIIB received 3.0 g/day of AHCC orally in divided doses, self-administered as 1g of powdered AHCC three times per day. Patients with Stage IV disease received 6.0 g/day of AHCC orally in divided doses, self-administered as 2g of powdered AHCC three times per day. (Table 4) Patients with Stage I disease received no chemotherapy as per current treatment guidelines. Patients with Stage II to IV disease were treated with a low -dose irinotecan (CPT-11) therapy of 8 mg/day for 4weeks (5 times a week). CPT-11 therapy was initiated 3 weeks postoperatively and was followed by oral administration of the fluoropyrimidine UFT.

The cumulative survival rates of gastric and colon cancer patients were analyzed by the Kaplan-Meier method.

Results

Gastric Cancer

The cumulative survival rates for patients in this study with gastric cancer are represented in Table 5. Five-year survival rate was 100% for Stage IA and Stage IB gastric cancer patients. Although both two-year survival rates for Stage II and Stage IIIA gastric cancer were 100%, five-year survival rates were 92.3% and 82.8%, respectively. In Stage IIIB patients, one-year survival rate was 100% and five-year survival rate was 35.7%. One-year and five-year survival rates for Stage IV gastric cancer patients were 28.6% and 14.3% respectively. The median cumulative survival rate for gastric cancer patients in this study was 3.2 years.

Table 6 compares the cumulative five-year survival rates for gastric cancer patients in our study with the survival rates at other Japanese institutions. The Japanese Gastric Cancer Association (JGCA) has reported five-year survival rates for gastric cancer as follows: Stage IA 93.4%, Stage IB 87.0%, Stage II 68.3%, Stage IIIA 50.1%, Stage IIIB 30.8%, and Stage IV 16.6%.[34] The Guidelines for Gastric Cancer (12th edition) stated that five-year cumulative survival rates at other institutions were as follows: Stage IA 91.5~93.4%, Stage IB 85.5~88.7%, Stage II 74.9~75.9%, Stage IIIA 53.6~61.7%, Stage IIIB 40.4~42.4%, Stage IVA 14.3~19.7%, and Stage IVB 4% .[35,36,37] Patients with gastric cancer who received postoperative adjunctive chemotherapy (Stage II – IV only) and AHCC at our institution incurred cumulative five-year survival rates of Stage IA 100%, Stage IB 100%, Stage II 92.3%, Stage IIIA 82.8%, Stage IIIB 35.7%, and Stage IV 14.3%. Higher cumulative five-year survival rates were achieved in our study compared to other institutions for Stage IA to Stage IIIA gastric cancer patients. Patients with stage IIIB – IV gastric cancer who participated in our study experienced similar five-year survival rates as those reported by the JGCA and other institutions.

Colon Cancer

The cumulative five-year survival rate for patients in this study with colon cancer is represented in Table 7. Five-year survival rates for Stage 0, Stage I and Stage II colon cancer were 100%. In Stage IIIA colon cancer patients, three-year and five-year survival rates were 100% and 95.2%, respectively. One-year survival rate for Stage IIIB colon cancer was 86.7%, and five-year survival rate was 73.3%. In Stage IV colon cancer patients one –year survival rate was 46.4% and five-year survival rate was 7.1%. The median cumulative survival rate for colon cancer patients in this study was 3.6 years.

Table 8 represents the cumulative five-year survival rates for colon cancer patients in our study compared to the survival rates at other Japanese institutions. The five-year cumulative survival rates for colon cancer patients reported by other Japanese institutions are as follows: Stage 0 100%, Stage I 93 - 100%, Stage II 81 - 88%, Stage IIIA 73 - 76%, Stage IIIB 63-78%, and Stage IV 0 - 17%. [38,39,40] Patients with colon cancer who received postoperative adjunctive chemotherapy (Stage II – IV only) and AHCC at our institution incurred cumulative five-year survival rates of Stage 0 100%, Stage I 100%, Stage II 100%, Stage IIIA

95.2%, Stage IIIB 73.3%, and Stage IV 7.1%. Patients with Stage II and Stage IIIA colon cancer who received oral AHCC with adjunctive chemotherapy at our institution showed improved cumulative survival rates compared to other institutions, but there was no improvement in survival for patients with Stage 0 – I nor Stage IIIB – IV disease.

Discussion

In postoperative gastric cancer and colon cancer therapy, a combination of AHCC as a functional food improved the cumulative survival rates of Stage IA to Stage IIIA gastric cancer patients and Stage II to Stage III colon cancer patients. No improvement in cumulative survival was noted for patients with late stage gastric cancer or colon cancer, nor for very early stage colon cancer.

Investigation into the clinical efficacy of AHCC as an adjunctive anti-tumor agent has previously been limited to hepatocellular carcinoma.26,27 In a small, randomized, placebo controlled study, administration of oral AHCC for 3 months to patients with advanced hepatocellular carcinoma resulted in significant improvement in prognosis and quality of life. 27 Another small, non-randomized, non-placebo controlled study showed significant increase in overall survival rate and reduced recurrence in postoperative hepatocellular carcinoma patients receiving oral AHCC compared to controls. 26 AHCC also appears to enhance the efficacy of certain chemotherapeutics while reducing toxicity in vivo. AHCC co-administered with cisplatin (cis-diamine-dichloroplatinum (II) or CDDP) to tumor-bearing mice resulted in significantly reduced tumor size and weight as well as decreased cisplatin-induced body weight loss, anorexia, nephrotoxicity and hematopoietic toxicity compared to control mice receiving cisplatin alone.28 In another study, ACHH administered in conjunction with UFT (tegafur and uracil) to rats with transplanted mammary adenocarcinoma resulted in a significant decrease in tumor size and weight and decreased metastasis to lymph nodes compared to control rats receiving UFT alone. 29 No studies have previously examined the efficacy of administering AHCC in conjunction with standard chemotherapy for patients with gastric or colon cancer.

Mushrooms have been used by traditional healers to prevent and treat disease for thousands of years.19 Research over the past 50 years has revealed the ability of mushrooms to inhibit tumor growth and modulate immune function in vitro and in vivo.17 The immune stimulating and anti-tumor activity of mushrooms is attributed to β-glucans found in the polysaccharide fraction.[41] β-glucans have been shown to stimulate the activity and proliferation of a multitude of immune cells that span both the innate and adaptive immune response, including monocytes, macrophages, natural killer (NK) cells, neutrophils, dendritic cells and cytotoxic T cells.[42] Another bioactive constituent found in AHCC, α-1,4-glucan polysaccharide, is attributed to the immune stimulating activity of AHCC.[43] Clinical studies in Japan have shown improved outcomes in gastric and colorectal cancer with administration of mushroom polysaccharides such as such as lentinan from Lentinus edodes (Shiitake) and protein-bound polysaccharide K (PSK) from Coriolus versicolor.[44,45,46,47] In our investigation, AHCC as a functional food improved the cumulative survival rates of postoperative gastric cancer and colon cancer patients.

AHCC is believed to mediate its effects on the host through both the innate and adaptive immune responses in vivo23 and in humans.30,48 In one study, mice fed AHCC followed by inoculation with either melanoma or lymphoma cells resulted in activation and proliferation of innate immune natural killer (NK) cells and gamma delta T cells.23 This study also reported delayed tumor development, reduced tumor size and stimulation of tumor antigen specific T lymphocytes in mice administered AHCC compared to controls. AHCC appears to also stimulate an immune response in humans. A group of healthy volunteers who ingested 3.0 g/day AHCC showed a significant increase in dendritic cell proliferation and activity.30 In another study, two weeks of 3.0 g/day oral ingestion of AHCC by eleven patients with different types of advanced cancer resulted in a 2.5 fold increase of NK cell activity above baseline in nine of the eleven patients.[48] NK cells and dendritic cells are believed to be integral to both non-specific (innate) and tumor antigen specific (adaptive) immune activation against tumor cells.[49,50,51] Further research is needed to better understand the molecular mechanisms of immune modulation by AHCC and to explore the potential use of AHCC in the treatment of cancer.

The results of this study are limited by small size and lack of randomization to treatment group and control group. Cumulative survival rates were only comparable to survival rates published by other Japanese institutions. The Japanese Gastric Cancer Association published the first version of the gastric cancer treatment guidelines in March, 2001.34 This clinical trial mostly corresponded to the guidelines, but this assessment was retrospective. In particular, extensive debulking surgery has been standard treatment in Stage IV gastric cancer patients since 1995. Stage IV Colon cancer patients as well as gastric cancer patients in this study received extensive debulking surgery when appropriate. Prior to this study there have been no clinical trials performed to assess the adjunctive therapeutic efficacy of AHCC in gastric and colon cancer.

Conclusion

For seven years, from April 1995 to April 2002, AHCC was combined as a postoperative adjunctive therapy, and the results were obtained as follows:

1. In gastric cancer patients from Stage IA to Stage IIIA, five-year cumulative survival rates for patients were superior to that of other Japanese institutions. No survival benefit was noted in patients Stage IIIB to Stage IV gastric cancer.

2. In colon cancer patients from Stage II to Stage IIIA, five-year cumulative survival rates were superior to that of other Japanese institutions. No survival benefit was noted in patients Stage 0 - I or Stage IIIB – IV colon cancer.

In the search for more effective ways to treat cancer, tumor immunotherapy is a promising frontier for integrative cancer therapeutics. AHCC is a potent biological response modifier that warrants further investigation as an adjunctive immunotherapeutic in gastric and colon cancer treatment.

Medical Editor's Note: Some aspects of the above study preclude a definitive conclusion that AHCC intervention will increase survival of patients with early stage gastric or colon cancers. While the study indicates a trend toward increased survival in comparison to historical controls, statistical significance is not assigned to these trends thereby making it impossible to make a definitive conclusion that AHCC prolonged survival.

Conflict of Interest Disclosure: The author does not have any conflicts of interests associated with this study.

Tables and References to follow:

Table 1 Gastric cancer stage at diagnosis for patients treated with AHCC.

Stage	Number of Patients
Stage ⅠA	32
Stage ⅠB	27
Stage Ⅱ	13
Stage ⅢA	11
Stage ⅢB	14
Stage Ⅳ	35
Total Patients	132

Table 2 Treatment strategy for gastric cancer

1. Surgery	
Stage ⅠA, ⅠB	Limited operation
Stage Ⅱ, ⅢA, ⅢB	Standard operation
StageⅣ	Extended operation and debulking operation
2. Chemotherapy	
Stage IA, IB	Limited operation
Stage Ⅱ～Ⅳ	Low-dose FP treatment:
	5-FU[1] : 250 mg/day×4weeks
	CDDP[2] : 5mg/day×5days×4weeks
	Oral Fluoropyrimidine:
	UFT[3] : 300 mg/day
3. AHCC[4] therapy	
Stage ⅠA～ⅢB	:AHCC 3.0 g/day
StageⅣ	:AHCC 6.0 g/day

[1] 5-FU = 5-fluorouracil
[2] CDDP = cis-diamminedichloroplatinum(II)a or cisplatin
[3] UFT = Tegafur and Uracil
[4] AHCC = active hexose correlated compound

Table 3 Colon Cancer Stage at Diagnosis

Stage	Number of Patients
Stage0	5
Stage Ⅰ	28
Stage Ⅱ	16
Stage Ⅲa	21
Stage Ⅲb	15
Stage Ⅳ	28
Total Patients	113

Table 4 Treatment strategy for colon cancer

1. Surgery	
Stage0, Ⅰ	Limited operation
Stage Ⅱ, ⅢA, ⅢB	Standard operation
StageⅣ	Extended operation and debulking operation
2. Chemotherapy	
Stage0, Ⅰ	none
Stage Ⅱ～Ⅳ	Low dose Irinotecan (CPT-11) treatment:
	(CPT-11:8mg/day×5days×4weeks)
	Oral fluoropyrimidine:
	UFT[5]: 300 mg/day
3. AHCC[6] therapy	
Stage0～Ⅲb	:AHCC 3.0 g/day
Stage Ⅳ	:AHCC 6.0 g/day

[5] UFT = Tegafur and Uracil
[6] AHCC = amino hexose correlated compound

Table 5 Cumulative survival rate by clinical stage of gastric cancer.

	1Year survival %	2Year survival %	3Year survival %	4Year survival %	5Year survival %
Stage IA	100	100	100	100	100
Stage IB	100	100	100	100	100
Stage II	100	100	92.3	92.3	92.3
Stage IIIA	100	100	91.9	82.8	82.8
Stage IIIB	100	57.1	42.9	35.7	35.7
Stage IV	28.6	22.9	14.3	14.3	14.3

Table 6 Cumulative 5 Year Survival Rate for Gastric Cancer by Institution

	5 Year Survival % AHCC Study	5 Year Survival % Japanese Gastric Cancer Association [33]	5 Year Survival % Other Japanese Institutions [34,35,36]
Stage IA	100%	93.4%	91.5 - 93.4%
Stage IB	100%	87.0%	85.5 – 88.7%
Stage II	92.3%	68.3%	74.9 - 75.9%
Stage IIIA	82.8%	50.1%	53.6 - 61.7%
Stage IIIB	35.7%	30.8%	40.4 - 42.4%
Stage IV	14.3%	16.6%	Stage IVA: 14.3 - 19.7% Stage IVB: 4%

Table 7 Cumulative survival rate by clinical stage of colon cancer.

	1 Year survival %	2 Year survival %	3 Year survival %	4 Year survival %	5 Year survival %
StageO	100	100	100	100	100
Stage Ⅰ	100	100	100	100	100
Stage Ⅱ	100	100	100	100	100
Stage ⅢA	100	100	100	95.2	95.2
Stage ⅢB	86.7	86.7	86.7	73.3	73.3
Stage Ⅳ	46.4	28.6	10.7	10.7	7.1

Table 8 Cumulative 5 Year Survival Rates for Colon Cancer by Institution

	5 Year Survival % AHCC Study	5 Year Survival % Other Japanese Institutions[37, 38, 39]
Stage 0	100%	100%
Stage I	100%	93 - 100%
Stage II	100%	81 - 88%
Stage IIIA	95.2%	73 - 76%
Stage IIIB	73.3%	63 - 78%
Stage IV	7.1%	0 - 17%

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