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Alleviating effect of active hexose correlated compound (AHCC) on chemotherapy-related adverse events in patients with unresectable pancreatic ductal adenocarcinoma

Hiroaki Yanagimoto[a], Sohei Satoi[a], Tomohisa Yamamoto[a], Satoshi Hirooka[a], So Yamaki[a], Masaya Kotsuka[a], Hironori Ryota[a], Taku Michiura[a], Kentaro Inoue[a], Yoichi Matsui[a], Koji Tsuta[b], and Masanori Kon[a]

[a]Department of Surgery, Kansai Medical University, Hirakata, Japan; [b]Department of Pathology and Laboratory Medicine, Kansai Medical University, Hirakata, Japan

ABSTRACT

The present study was conducted to determine whether active hexose correlated compound (AHCC), a functional food extracted from cultured basidiomycetes, possesses the potential to attenuate adverse events in unresectable pancreas ductal adenocarcinoma (PDAC) patients receiving chemotherapy. Unresectable PDAC patients receiving gemcitabine treatment (GEM) as the first-line chemotherapy were prospectively divided into 2 groups according to AHCC intake (AHCC group, $n = 35$) or not (control group, $n = 40$). The patients in the AHCC group ingested 6.0 g of AHCC for 2 mo. Hematological and nonhematological toxicity was compared between the AHCC and control groups. The C-reactive protein (CRP) elevation and albumin decline of the AHCC group were significantly suppressed as compared to the control group during the GEM administration ($P = 0.0012$, $P = 0.0007$). Patients in the AHCC group had less frequency of taste disorder caused by GEM (17% vs. 56%, $P = 0.0007$). Frequency of grade 3 in the modified Glasgow Prognostic Score (mGPS) during chemotherapy was found significantly less in the AHCC group (14%) than the control group (53%, $P = 0.0005$). AHCC intake can be effective in reducing the adverse events associated with chemotherapy and may contribute to maintaining the QOL of patients with PDAC during GEM administration.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fifth most common cancer worldwide, and the prognosis of patients with the cancer is dismal. For patients with unresectable (UR) PDAC, the treatment options of chemotherapy (CT) are limited. Gemcitabine (GEM) was the current standard therapy until the FOLFIRINOX and the combination therapy of GEM and nanoparticle albumin-bound paclitaxel (GEM + nab TPX) came out (1–4). Although recent CT has made great advances and has exhibited prominent efficacy, concerns are raised for the impairment of the cancer patients' quality of life (QOL) owing to adverse events.

AHCC, which stands for active hexose correlated compound, is an extract from mycelia of Lentinula edodes. This is a mushroom of the basidiomycete family that is cultured in liquid medium in a large tank. AHCC is one of the functional foods used most frequently in cancer patients in clinical practices (5). In addition, AHCC is certified under the "Healthy Do" system (Hokkaido Food Functionality Labelling system) in which the Hokkaido Government recognizes the conduct of scientific research on the health effects of product components. Ito et al. revealed that cancer patients who had 3 g/day of AHCC intake during CT showed improvements in their adverse effects and QOL (6). In addition, Hangai et al. reported that AHCC intake (1 g of after each meal, total 3 g/day during CT) significantly suppressed neutrophil-related adverse events and the frequency of use of granulocyte colony-stimulating factor during the administration of anthracyclines and taxanes in 41 breast cancer patients (7). Regarding the study about the improvement of cancer prognosis, Matsui et al. elucidated the prognosis of hepatocellular carcinoma patients were improved by treatment with 3 g/day of AHCC (8) and Cowawintaweewat et al. also showed that 6 g/day of AHCC was effective to prolong the survival of advanced liver cancer patients (9). Furthermore, the combination use of 3–6 g of AHCC and 1.0–1.3 g of genistein concentrated polysaccharide also ameliorated the QOL of Stave IV nonsmall cell lung cancer patient receiving CT (10). These results indicate that 3–6 g of

CONTACT Sohei Satoi satoi@hirakata.kmu.ac.jp Department of Surgery, Kansai Medical University, 2-5-1, Shin-machi, Hirakata 573-1010, Japan.

AHCC administration have beneficial effects on cancer treatments.

On the other hand, there have been no clinical trials to determine whether AHCC reduces adverse events in pancreatic cancer patients undergoing CT. Therefore, the aim of this study is to evaluate the clinical effects of AHCC intake in reducing the adverse events caused by GEM among patients of UR-PDAC.

Patients and methods

Patient eligibility

This study was an open-label, nonrandomized prospective cohort study. The following inclusion criteria were mandatory to the study: 1) UR patients with histologically or cytologically proven adenocarcinoma of the pancreas; 2) Eastern Cooperative Oncology Group performance status of 0–1; 3) age between 18 and 75 years; 4) no central nervous system metastases; 5) life expectancy of at least 3 mo; and 6) adequate hematological (neutrophil count 1500/L; platelet count 100,000/mL), renal (serum creatinine $<1.5 \times$ the upper limit of normal (ULN) value), and hepatic (alkaline phosphatase $<3 \times$ ULN value and bilirubin $<1.5 \times$ ULN value) functions. The exclusion criteria were the following: 1) pregnancy, autoimmune disease and active infections and 2) positive hepatitis B and C antigens. The study protocol was approved by the Institutional Review Board at Kansai Medical University, Osaka, Japan. A complete written informed consent was obtained from all patients at the time of enrollment in accordance with the provisions of the Declaration of Helsinki.

Patients were prospectively divided into an AHCC treatment group (AHCC group) and a nontreatment group (control group) according to the patients' wishes. GEM was given intravenously at a dose of 1000 mg/m^2 over 30 min once a week for 3 wk, followed by a week of rest. The AHCC group received AHCC at 6.0 g/day based on the previous studies (9,10). The administration period was determined to be 8 wk along with the 2 cycles of GEM treatment since Ito and Hangai adjusted the administration length to the CT period (6,7) and the enhancements of dendritic cell and NK cell expressions were observed after over 4-wk AHCC administration (11,12). Patients in both groups did not take any other functional foods, including vitamin tablets, during the study.

Dose reduction of GEM

When grade 3–4 neutropenia or grade 2–3 thrombocytopenia was observed, the dose of GEM was reduced by 20%. The patients discontinued from therapy when the treatment was associated with 1) grade 3–4 neutropenia complicated by fever; 2) grade 4 neutropenia lasting longer than 4 days; 3) grade 4 thrombocytopenia; 4) any other grade 3–4 nonhematologic toxicity except anorexia, nausea, and vomiting in the absence of appropriate antiemetics; or 5) delay of recovery from treatment-related toxicity for more than 2 wk.

Manufacturing process of AHCC

In general, basidiomycetes forms the sexual organ, called the *carpophore* (fruit body), to produce basidiospores under certain conditions (light, temperature, humidity, change of nutritional status etc.) to accomplish sufficient growth of the mycelia. However, when the basidiomycetes are cultured in a liquid medium, they proliferate and form globular fungal bodies rather than carpophores (13). It is thought that AHCC is produced using these bodies of mycelia of basidiomycetes and contains medium components modified by the mycelia-produced diverse enzymes.

In terms of the actual AHCC manufacturing procedure, the mycelia of the edible shiitake are subjected to a liquid culture whose quantity is enlarged in 15,000-L tanks. After fermentation, AHCC is produced through manufacturing processes which include separation, concentration, sterilization and freeze drying (14).

Ingredient composition and structure

AHCC is abundant in carbohydrates as compared to agaricus (*Agaricus blazei Murill*) and dry shiitake (*Lentinus edodes*). It is thought that these carbohydrate elements are mainly polysaccharides. In the basidiomycete (mushroom)-derived substances, β-glucan is known as a physiologically active ingredient (14). However, AHCC substantially differs from other mushrooms and from mushroom-derived food products in that it contains only 2% of β-glucan while the α-glucan is in abundance. The presence of α-1,4-glucan, in which the hydroxyl groups of C-2 and/or C-3 positions are partially acylated, is particularly reported and is considered to be one of the active ingredients. It is deduced that this partially acylated α-glucan is not obtained by a simple extraction from a basiodiomycete culture broth but generated by an enzymatic modification of the normal α-glucan in the unique patented manufacturing process of AHCC (14).

Clinical outcomes

The evaluation of the adverse events and clinical responses was carried out using the data until disease progression. The primary endpoint was to estimate the

alleviating effect of AHCC for the adverse events caused by GEM in patients with PDAC, while the secondary endpoint was to assess the clinical response rate and overall survival (OS).

Blood samples were collected every week for 8 wk. The assessment of hematological and nonhematological toxicity was performed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE Ver 3.0) grading (15) every week during the CT. To evaluate the taste disorder (TD) subjectively, the patients were requested to complete a questionnaire of symptoms related to TD defined in CTCAE 3.0. The modified Glasgow Prognostic Score (mGPS) is a score system based on both C-reactive protein (CRP) and albumin. Accordingly, patients who had both elevated CRP (>0.5 mg/dl) and hypoalbuminemia (<3.5 g/dl) were assigned a score of 3. Although patients with either elevated CRP (>0.5 mg/dl) or hypoalbuminurea (<3.5 g/dl) were assigned scores of 2 and 1, respectively. Finally, patients with neither of these abnormalities were assigned a score of 0 (16). A contrast-enhanced CT scan was done for evaluating the clinical response rate using Response Evaluation Criteria in Solid Tumor (RECIST) every 2 mo until disease progression (17).

Statistical analysis

The statistical analyses were performed using the JMP statistical program version 5.1 (SAS Institute Inc., Cary, NC). The numerical values were given as the median (range) and compared between the AHCC and control groups. The countable data was compared using the Mann-Whitney U test, and the category data was compared using Fisher's exact test or the chi-square test. *OS* was defined as the time from the initiation date of CT to death because all patients had the event of death. The Kaplan-Meier curve in each group was plotted, and the difference in OS was compared using a log-rank test between both groups. A 2-tailed *P*-value of <0.05 was considered to be statistically significant.

Results

Clinical backgrounds

The subject characteristics are shown in Table 1. From December 2007 to July 2009, 75 patients were prospectively enrolled in this study and classified as an AHCC group ($n = 35$) and a control group ($n = 40$). There were no significant differences in most parameters except the platelet counts at the baseline level between the groups. No differences were found in the albumin level, CRP level, mGPS score, or frequency of TD between the groups.

Toxicity

Significant toxicities defined as grade 3–4 by the CTCAE version 3.0 (13) were predominantly hematologic in nature, with the most common, neutropenia (Table 2), considered to be caused by GEM itself. No occurrences of febrile neutropenia were recorded during the course of the current study. Grade 3–4 anemia and thrombocytopenia occurred infrequently. No significant difference was found between the groups in neutropenia, thrombocytopenia, and hepatic dysfunction in grade 3–4. Most of these hematologic toxicities were transient and reversible. Grade 3–4 nonhematologic toxicities were not observed. The lowest hemoglobin (Hb) level during CT in the AHCC group was significantly higher than the

Table 1. Characteristics of study subjects (pretreatment).

	AHCC group ($n = 35$)	Control group ($n = 40$)	*p*
Age (y)	65 (42–80)	65 (41–80)	0.8693
M:F	17:18	23:17	0.646
WBC ($\times 10^2/\mu$l)	6200 (3912–11300)	6100 (3814–21300)	0.6611
Hb (g/dl)	12.0 (8.0–14.2)	11.9 (7.6–14.1)	0.4034
PLT ($\times 10^4/\mu$l)	27.0 (13.5–62.4)	22.9 (13.3–41.6)	0.0107
T Bil (mg/dl)	0.6 (0.3–5.7)	0.6 (0.3–2.3)	0.3427
AST (U/l)	23 (13–134)	22 (12–124)	0.8002
ALT (U/l)	22 (6–116)	21 (9–106)	0.9661
Albumin (g/dl)	3.9 (1.9–4.4)	3.8 (2.1–4.7)	0.5630
CRP (mg/dl)	0.24 (0.01–4.38)	0.21 (0.02–5.24)	0.7005
Metastasis liver/Perit/LN/none	20 / 11 / 2 / 2	18 / 15 / 1 / 6	0.9421
Tumor size (mm)	40 (17–70)	41 (13–80)	0.6574
CA19-9 (U/ml)	695.0 (4.8–35305.0)	495.9 (1.4–118400.0)	0.6203
Taste disorder (%)	4(11)	4(10)	0.8415
mGPS(0/1/2/3)	18/8/5/4	24/6/7/3	0.7990

AHCC = active hexose correlated compound; WBC = white blood counts; Hb = hemoglobin; PLT = platelets; T Bil = total bilirubin; AST = aspartate aminotransferase; ALT = alanine aminotransferase; CRP = C-reactive protein; Perit = peritoneal; LN = lymph node; CA19-9 = carbohydrate antigen 19–9; mGPS = modified Glasgow Prognostic Score.

Table 2. Hematological and nonhematological toxicity.

	AHCC group ($n = 35$)		Control group ($n = 40$)	
	Grade 1–4 (%)	Grade 3–4 (%)	Grade 1–4 (%)	Grade 3–4 (%)
Hematological toxicity				
Leukocytes	30 (86)	2 (6)	33 (83)	4 (10)
Neutrophils	30 (86)	16 (48)	35 (88)	16 (40)
Hemoglobin	33 (94)	2 (6)	37 (93)	4 (10)
Platelets	28 (80)	0 (0)	31 (78)	4 (10)
Nonhematological				
Alanine aminotransferase	7 (20)	0 (0)	9 (23)	0 (0)
Creatinine	5 (14)	0 (0)	7 (18)	0 (0)
Nausea	10 (29)	0 (0)	16 (40)	0 (0)
Vomiting	7 (20)	0 (0)	11 (28)	0 (0)
Anorexia	12 (34)	0 (0)	18 (45)	0 (0)
Fatigue	9 (26)	0 (0)	11 (28)	0 (0)
Fever	9 (26)	0 (0)	11 (28)	0 (0)
Rash	14 (40)	0 (0)	16 (40)	0 (0)

AHCC = active hexose correlated compound.

control group [10.6 g/dL (7.3–12.6) vs. 10.3 g/dL (6.7–12.6), $P = 0.0360$, Table 3]. In addition, the highest CRP level during CT in the AHCC group was significantly lower than the control group [0.48 mg/dL (0.02–17.53) vs. 1.92 mg/dL (0.05–20.20), $P < 0.0001$]. The lowest serum albumin level during CT in the AHCC group was significantly higher than the control group [3.8g/dL (2.6–4.4) vs. 3.4g/dL (1.9–4.7), $P = 0.0074$]. As shown in Fig. 1, the pre–post ratio of albumin in the AHCC group was significantly higher than the control group ($P = 0.0007$). The pre–post ratio of CRP in the AHCC group was significantly lower than in control group ($p = 0.0012$). There were 4 patients in each group who had TD at the baseline level. The occurrence of TD during CT in the AHCC group was significantly lower than the control group [n = 6/35 (17%) vs. n = 22/40 (55%), $P = 0.0007$]. The mGPS score (0/1/2/3) during CT in the AHCC group was significantly better than the control group (0/1/2/3: 15/4/11/5 vs. 3/1/15/21, $P = 0.0002$). Significantly lower frequency of grade 3 in mGPS was found in the AHCC group (5/35) relative to the control group (21/40, $P = 0.0005$).

Response rate and overall survival between two groups

The response rate according to RECIST 1.0 was 17% in the AHCC group compared with 12% in the control group ($P = 0.571$). The disease control rate in the AHCC group was significantly higher than the control group (74% vs. 50%, $P = 0.003$).

The median survival time was 9.0 m (95% confidence interval: 7.4–14.0 mo) in the AHCC group and 6.7 months (95% confidence interval: 4.6–9.3 mo) in the control group ($P = 0.081$, Fig. 2). The higher tendency for overall survival was observed in the AHCC group relative to the control group.

Discussion

In a survey carried out by the Ministry of Health, Labor and Welfare research group in Japan, AHCC has been enumerated as the second most used health food next to agaricus, which is a fungus, among cancer patients in Japan (5). Recent experimental studies of AHCC have

Table 3. Comparison of toxicity (pre- vs posttreatment) in active hexose correlated compound (AHCC) and control groups.

	AHCC group ($n = 35$)			Control group ($n = 40$)		
	Pretreatment	Posttreatment	*P*	Pretreatment	Posttreatment	*P*
WBC ($\times 10^2/\mu$l)	6200 (3912–11300)	2600 (1500–5300)	<0.0001	6100 (3814–21300)	2800 (1700–17100)	<0.0001
Hb (g/dl)	12.0 (8.0–14.2)	10.6 (7.3–12.6)	<0.0001	11.9 (7.6–14.1)	10.3 (6.7–12.6)	<0.0001
PLT ($\times 10^4/\mu$l)	27.0 (13.5–62.4)	11.0 (6.2–34.7)	<0.0001	22.9 (13.3–41.6)	10.9 (3.6–31.1)	<0.0001
Albumin (g/dl)	3.9 (1.9–4.4)	3.8 (2.6–4.4)	0.7093	3.8 (2.1–4.7)	3.4 (1.9–4.7)	<0.0001
CRP (mg/dl)	0.24 (0.01–4.38)	0.48 (0.02–17.53)	0.1721	0.21 (0.02–5.24)	1.92 (0.05–20.20)	0.0002
Taste disorder (%)	4(11)	6 (17)	0.7113	4(10)	22 (56)	<0.0001
mGPS (0/1/2/3)	18/8/5/4	15/4/11/5	0.2382	24/6/7/3	3/1/15/21	<0.0001

WBC = white blood counts; Hb = hemoglobin; PLT = platelets; T Bil = total bilirubin; AST = aspartate aminotransferase; ALT = alanine aminotransferase; CRP = C-reactive protein; mGPS = modified Glasgow Prognostic Score.

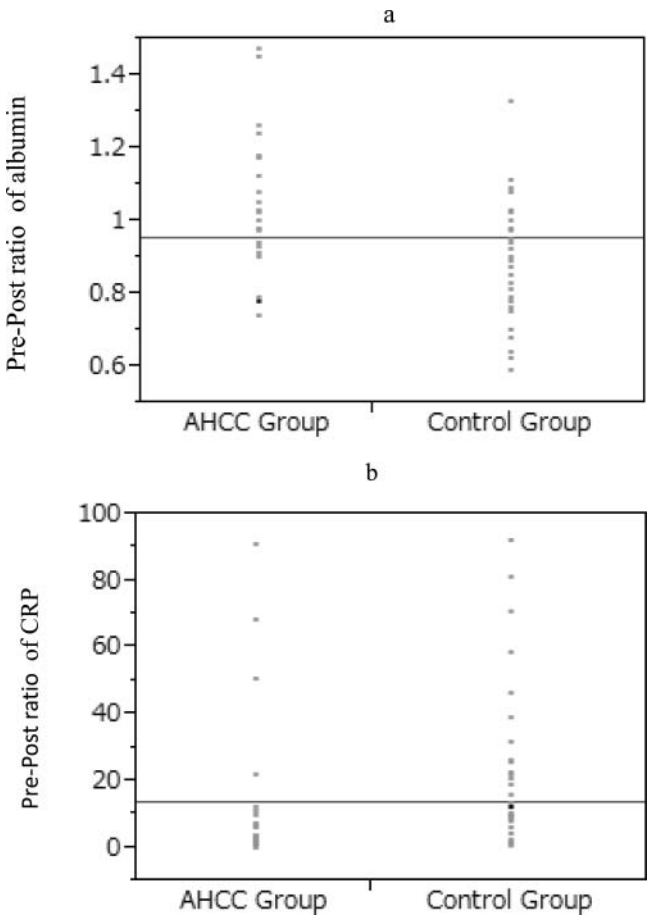
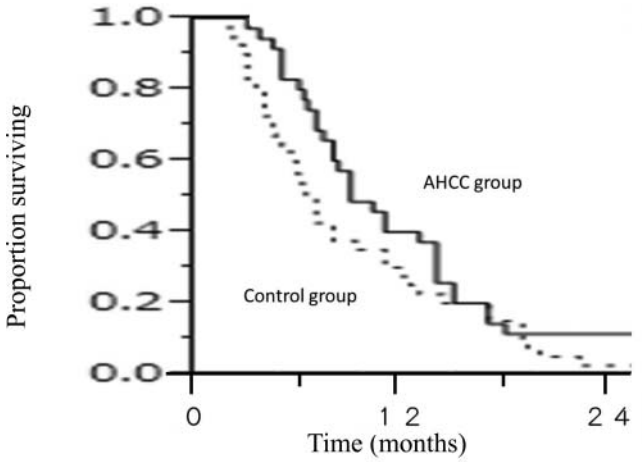


Figure. 1. A: The pre–post ratio of albumin in the active hexose correlated compound (AHCC) group was significantly higher than in the control group ($P = 0.0007$). B: The pre–post ratio ratio of CRP in the AHCC group was significantly lower than in the control group ($P = 0.0012$).



Patient at risk	6m	12m	18m	24m	30m
Control group	21	12	7	2	0
(n=40)	53%	28	18	5	0
AHCC group	28	13	3	2	1
(n=35)	80%	37	8.5	5.7	2.8

Figure. 2. The overall survival in the active hexose correlated compound (AHCC group; $n = 35$, solid line) and the control group ($n = 40$, broken line). Overall survival in the AHCC group had a higher tendency relative to the control group ($P = 0.081$).

shown useful results in the treatment of various diseases including cancer and hepatitis as a complementary and alternative medicine in substantial medical institutions (18). Other studies have demonstrated that AHCC was effective in the treatment of infectious and inflammatory diseases as well as cancer (19–21). AHCC has been proved to be a safe food by various preclinical safety assessments. This has been supported by basic studies conducted on its interaction with drugs (22–24). Besides, the results of a randomized control trial on healthy volunteers strongly support the safety of AHCC as a supplement in clinical practice (11). In the article, Terakawa et al. also mentioned that AHCC intake was associated with an overall increase in dendritic cell (DC) counts and enhancement of DC1 functions related to specific immunity events in healthy volunteers. Moreover, it is clinically shown that AHCC intake results in improved liver function, preventing the recurrence of hepatocellular carcinoma after liver resection, and prolonging survival rates among postoperative patients suffering from hepatocellular carcinoma (8).

Likewise, some studies on animals have reported that AHCC intake is associated with reduction of adverse events during CT (25–27). Hirose et al. reported that AHCC could improve bone marrow repression caused by cisplatin with a significant difference in an animal model (27). Moreover, because the cell viability in the AHCC group was significantly much higher than the control group, they suggest that AHCC might recover immune depression induced by the tumor cells themselves as well as cisplatin. So far, there have been no clinical reports on the functional effect of AHCC on CT in PDAC patients. Generally, GEM frequently has adverse events with 72.7% in neutropenia, 63.6% in anemia, 54.5% in thrombocytopenia, 72.7% in anorexia, and 36.4% in general fatigue (28). In this study, approximately 90% of the recruited subjects were patients with hematologic adverse events and 40% in anorexia or general fatigue. Although there was no significant difference in the frequency of hematologic adverse events during GEM in this study, the hemoglobin level in the AHCC group was maintained relative to the control group. The frequency of taste disturbance during CT in the AHCC group was significantly lower than in the control group and the mGPS score was better. These findings indicate that AHCC intake can ameliorate the adverse events induced by GEM. Similarly, the disease control rate in the AHCC group was better, and the group showed a higher tendency of OS.

TD can be frequently observed in cancer patients undergoing CT. It is reported to be one of the most distressing side effects, along with fatigue, nausea, vomiting, and hair loss (29). Anorexia can be associated with the development of TD, because of the destruction of taste buds and their related nerves, as well as the suppression of saliva and zinc deficiency by CT. Because the patient would need higher energy compared to basal metabolism during CT, the low nutrient condition caused by TD leads to serious problems, hindering the treatment and recovery from adverse events. High prevalence of TD has been reported in the range of 46–77% (30). TD often starts with the beginning of CT (31) and persists from a few hours to weeks or even months (32). Despite its frequent occurrence, the literature on this issue is scarce. Causes for TD in CT patients in general are manifold and often remain undetermined. Some authors suggest that the tumor itself contributes to the manifestation of TD (33–35). Other factors known to influence taste sensation are poor oral hygiene, gastrointestinal reflux, infections, as well as some medications, especially antibiotics (36). In this study, there were no patients who showed obvious deficiency of vitamins or zinc and clinically oral candidasis. There is no appropriate treatment for developed TD, yet it is important to prevent TD development during CT. AHCC intake may prevent the development of TD, resulting in lower frequency of anemia and anorexia during CT. The AHCC group showed a higher mGPS score which is associated with a better survival rate among cancer patients (37,38). The mGPS score maintained during CT may be related to the higher DCR and OS in the AHCC group.

There were several limitations in this study. Firstly, AHCC intake was decided by the patient. Secondly, it was a nonrandomized study. Finally, this study consisted of a relatively small number of participants from a single institution. However, it is the first article to show a clinical effect of AHCC on adverse events in patients with UR-PDAC.

In conclusion, AHCC intake can be effective in reducing the adverse events associated with CT, and may contribute to maintaining the QOL of patients with PDAC during GEM administration. The results of this study warrant further investigation to be confirmed in a double-blind randomized Phase II trial.

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