Efficacy of Cereal-based Oral Nutrition Supplement on Nutritional Status, Inflammatory Cytokine Secretion and Quality of Life in Cancer Patients Under Cancer Therapy

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A rapid increase in cancer incidence accompanied by aging population requires evidence-based supportive cancer care practices. Cancer therapies often accompany adverse events which induce malnutrition and declined quality of life. We conducted an 8-week non-randomized clinical trial to evaluate efficacy of cereal-based oral nutritional supplement (ONS) intervention on nutritional status, quality of life and inflammatory responses in cancer patients undergoing cancer therapy with 5% < weight loss. The study included 34 patients (24 in control group, 10 in intervention group) with 15 drop-outs. ONS used in this intervention contained 0.5% arabinoxylan-rich fermented rice bran powder and 5.5% black rice powder as active ingredients in a regular cereal-based formula. Results showed that ONS intervention for 8 weeks did not show significant improvement in blood biomarkers of nutritional status or patient-generated subjective global assessment scores. However, 8-week of intervention showed reduced interleukin (IL)-6 and IL-1β secretion in lipopolysaccharide-stimulated peripheral blood mononuclear cells while IL-12p70 level was increased. For health-related quality of life (HRQoL) indices, emotional functioning and fatigue symptoms were improved after 4 weeks only in the intervention group although no difference was found at week 8. These results suggest that ONS intervention may improve chronic inflammatory status and HRQoL indices (at week 4) in cancer patients receiving treatments.

Key Words Food assistance, Nutritional support, Cancer, Quality of life, Malnutrition

INTRODUCTION

Cancer is a leading cause of deaths in different countries around the world, and the estimated new cancer cases in 2018 were 18.1 million [1]. Although advances in cancer treatments have increased the cancer survival rate, the majority of patients suffer from adverse events originated from cancer chemotherapy, radiotherapy and surgery. Malnutrition in cancer patients increases the risk of cancer deaths [2]. Cancer malnutrition is associated with cancer cachexia as well as cancer therapy-induced decreases in food intake. It has been noted that cancer cachexia occurs in 80% of patients [3]. The diagnosis of cancer cachexia requires one of following criteria; 1) weight loss greater than 5%, 2) weight loss greater than 2% in patients already exhibiting body mass index (BMI) < 20 kg/m^2, and 3) sarcopenia [4]. It

has been reported that cancer cachexia induces substantial metabolic alterations with respect to carbohydrate, fat and protein, which differ greatly from those seen in starvation [5]. Also, surgical procedures especially in patients with gastrointestinal tract cancers significantly affect food intake and bioavailability. Anti-cancer drugs often cause dysphagia, vomiting, and diarrhea. Radiotherapy and chemotherapy are known to induce mucositis leading to decreased food intake and malnutrition [6].

Therefore, nutritional intervention has been suggested as a critical supportive care to accomplish successful cancer treatment. In a recent systemic analysis based on 28 nutrition formula intervention studies, 65% of the studies suggests one or more of nutritional indices are improved by the intervention, and either immune function or inflammatory response was improved, implying that nutritional supplements may be an

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effective option to improve nutritional status [7].

Despite the importance of nutritional support for a successful cancer treatment, emphasis on research and development in nutritional supplement formula has been rather insufficient. Cancer patients often experience taste and smell changes, which possibly affect the palatability influencing nutritional intake. Previous studies have reported that cancer patients experience altered threshold for tastes [8-10]. Most common post-chemotherapy and post-radiotherapy taste alterations include bitter, metallic, chemical and nauseating tastes [11,12]. Therefore, palatability of oral nutritional supplements (ONS) needs to be one of the most important considerations in product development to support cancer management.

ONS used in this study included fermented rice bran and black rice. Active components in fermented rice bran and black rice are arabinoxylan and anthocyanins, respectively, which have been shown to possess immune-modulatory and anti-inflammatory activities [13-15]. Recently, ONS enriched with several active ingredients to improve immunological homeostasis have been introduced [5,16] Long-chain omega-3 fatty acids, eicosapentanoic acid and decosahexanoic acid are used as functional ingredients to reduce elevated proinflammatory cytokines in cancer patients under cancer therapy. Arginine was shown to prolong survival through enhancing immune responses [17]. Branched chain amino acids including leucine are suggested to suppress muscle loss in anorexic cancer patients improving quality of life (QoL) and survival rate [5].

In this study, we evaluated the intervention efficacy of cereal-based ONS containing fermented rice bran powder and super black rice powder in cancer patients undergoing cancer therapy with body weight loss more than 5% since diagnosis.

MATERIALS AND METHODS

Study participants
Patients were recruited from the Departments of Hemato-Oncology and Clinical Nutrition Medicine in Bundang Jesaeng Hospital between November 2014 and October 2015. Adult patients newly diagnosed as having malignant tumor(s) were screened for eligibility and 49 patients were enrolled. Inclusion criteria were as follows: currently receiving one or more cancer therapies, more than 5% of weight loss since the diagnosis, not taking any nutritional supplements. Patients who had acute infectious diseases, cardiac insufficiency, hepatic insufficiency or patients receiving hemodialysis were excluded. The study was approved by the Bundang Jesaeng Hospital ethics review board (IMG14-01). During the course of the study, 15 patients dropped out of the study and final analysis was performed in 24 patients in control group and 10 patients in the intervention group.

Study design and ONS preparation
This study is a non-randomized intervention trial and cancer patients eligible for the study were allocated to the experimental group and then the control group. The intervention period was 8 weeks and patients visited study center three times (week 0, 4 and 8) to have clinical and biochemical measurements taken (Fig. 1). Three-day dietary records were collected at each visit during the intervention. Both control and experimental groups received regular nutrition counseling and education, while only experimental group was asked to take ONS twice a day. To determine the compliance, patients in experimental group were asked to record the amount of ONS consumed. ONS was supplied by Erom Co. (Chuncheon, Korea) in a powder form, and the experimental group consumed two packages (pkg) of ONS (40 g/pkg, 150 kcal/pkg)/d dissolved in 200 mL (per pkg) of water or milk. The composition of the ONS is provided in Table S1.

Anthropometric and clinical measurements
Anthropometric measurements were taken at each visit. Patient-Generated Subjective Global Assessment (PG-SGA) was used to evaluate improvements in nutritional status of the study participants. A trained dietitian filled out
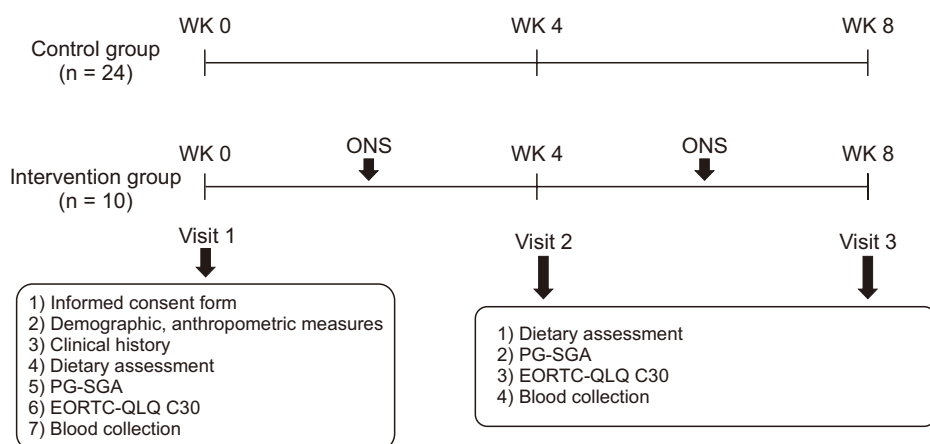

Figure 1. Study design. ONS, oral nutritional supplement; PG-SGA, patient-generated subjective global assessment; EORTC-QLQ C30, European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire - Core Questionnaire.

questionnaires in A section of the PG-SGA by face-to-face interview (weight changes, food intake, clinical symptoms associated with eating behavior, and activities and functions). Body temperature, triceps skinfold thickness, mid-arm muscle circumference were also used to determine PG-SGA score. Dietary intake was assessed by using a 3-day 24-hour recall and concurrent dietary records at each visit. A dietitian interviewed patients for their 3-day recall and patients were asked to record their dietary intake by using food model and food weight table. Nutrient intake was analyzed by Can-pro 4.0 (Korean Nutrition Society, Seoul, Korea). Patients were also telephone-interviewed by a dietitian for their ONS intake. QoL was determined by using European Organization for Research and Treatment of Cancer (EORTC)-Quality of Life Questionnaire - Core Questionnaire developed by EORTC. The questionnaire is composed of 30 questions including global health status, functional scales and symptom scales.

Biochemical measurements

Venous blood samples were collected at each visit and

nutritional biomarkers were analyzed at the central laboratory of Bundang Jesaeng Hospital. Peripheral blood mononuclear cells (PBMCs) were prepared from venous blood collected in heparin tube using Axis Shield Poc As™ LymphoPrep™ (Thermo Fisher Scientific, Oslo, Norway). PBMCs were incubated in RPMI1640 media containing glutamine, penicillin-streptomycin and 10% fetal bovine serum for 6 hours followed by *Escherichia coli* lipopolysaccharide treatment for 24 hours. Concentrations of interleukin (IL)-12p70, TNF-α, IL-10, IL-6, IL-1β, and IL-8 were measured in the media using Human Cytokine Beads array (BD Biosciences, Franklin, NJ, USA).

Statistical analyses

Per protocol analyses were applied. All measurements were expressed as mean ± SD. Anthropometric measures were compared by Student t-test where it is applicable. Differences (differences between control group and experimental group for changes in each measures; week 0 vs. week 4, week 4 vs. week 8, week 0 vs. week 8) in nutrient intake, biochemical

Table 1. Baseline characteristics of study patients

	Control group (n = 24)	Intervention group (n = 10)	P-value[a]
Age (yr)	6.54 ± 10.46	63.7 0 ± 11.25	0.9850
Height (cm)	161.39 ± 10.05	160.06 ± 10.21	0.8659
Body mass index (kg/m^2)	22.85 ± 3.16	23.92 ± 4.16	0.2892
Current body weight (kg)	59.60 ± 10.06	60.54 ± 7.13	0.7079
Past body weight (kg)	66.45 ± 12.60	65.84 ± 8.90	0.9401
Body weight change (%)	9.92 ± 5.06	7.82 ± 4.54	0.2572
Sex			
Male	16 (66.67)	7 (70.00)	
Female	8 (33.33)	3 (30.00)	
Primary diagnosis			
Anal	1 (4.17)	0 (0.00)	
Colon	9 (37.50)	5 (50.00)	
Esophageal	2 (8.33)	0 (0.00)	
Gallbladder	1 (4.17)	1 (10.00)	
Lung	2 (8.33)	2 (20.00)	
Lymphoma	1 (4.17)	0 (0.00)	
Rectal	3 (12.50)	2 (20.00)	
Stomach	5 (20.83)	0 (0.00)	
Complication			
Diabetes	6 (25.00)	3 (30.00)	
Hypertension	2 (8.33)	2 (20.00)	
Hyperlipidemia	0 (0.00)	1 (10.00)	
Others	4 (16.67)	1 (10.00)	
Smoking status			
Never	14 (58.33)	3 (30.00)	
Former	8 (33.33)	7 (70.00)	
Current	2 (8.33)	0 (0.00)	
Drinking			
Never	10 (41.67)	4 (40.00)	
Former	11 (45.83)	6 (60.00)	
Current	3 (12.50)	0 (0.00)	

Values are presented as mean ± SD or number (%). [a]Differences between control group and intervention group were compared by using Student's t-test.

nutritional indices, PG-SGA score and cytokine secretion in lipopolysaccharides (LPS)-stimulated PBMC was compared by Wilcoxon signed rank test and Mann–Whitney test. In measures which did not show statistical differences, further comparisons were performed for differences between control group and experimental group at each week, and differences between each week within the group by using Student t-test.

RESULTS

This study included 24 control participants and 10 ONS intervention participants. Anthropometric measures did not differ significantly between two groups (Table 1). Primary diagnosis in the control group were 9 colon, 5 stomach, 3 rectum, 2 esophageal, 2 lung, 1 anal, 1 gallbladder, 1 lymphoma and that of the ONS intervention group were 5 colon, 2 rectum, 2 lung, 1 gallbladder. Percentage of patients in cancer stage were 17.9% (stage II), 32.1% (stage III), 50% (stage IV) in the control group and 30% (stage I), 40% (stage II), 30% (stage III) in the intervention group. Percentages of the patients who received surgery, chemotherapy and

radiotherapy were 46.4%, 94.4%, 14.3% in the control group and 60%, 90%, 30% in the intervention group. Among 49 patients enrolled, 15 patients dropped out of the study. Reasons for drop-outs during the protocol were the transfer to another hospital (n = 1), symptom of diarrhea (n = 3), refusal to continue (n = 2), cancer therapy-associated adverse events (n = 5). Four of the patients died during the course of the study.

We have also analyzed basal dietary intake based on 3-day 24-hour recall and dietary intake record data (data not shown). Basal dietary intake did not include nutrient intake supplied by ONS intervention. Results showed no difference within and between groups except vitamin B1 and copper which were consumed in higher amounts in the intervention group at week 8 compared to those in the control group.

Biomarkers of nutritional status including albumin, prealbumin, cholesterol, and blood cell counts and sizes were determined (Table 2). Albumin and prealbumin concentrations were 3.76 g/dL (control) and 4.25 g/dL (intervention) which lies at lower end of normal range. Blood cholesterol concentrations were 162.79 mg/dL (control) and 161.70 mg/

Table 2. Changes in blood nutritional biomarkers

	Control group (n = 24)			Intervention group (n = 10)		
	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks
Albumin (g/dL)[NS]	3.76 ± 0.39	3.91 ± 0.82	3.72 ± 0.44	4.25 ± 1.15	4.01 ± 0.30	3.96 ± 0.36
Prealbumin (mg/dL)[NS]	17.15 ± 5.86	21.15 ± 8.15	19.46 ± 7.35	22.89 ± 8.40	25.92 ± 8.40	23.84 ± 9.67
Cholesterol (mg/dL)[NS]	162.79 ± 41.12	154.14 ± 37.35	155.64 ± 44.12	161.70 ± 17.70	159.10 ± 38.79	163.89 ± 50.94
WBC ($10^3/\mu$L)[NS]	6.81 ± 2.46	6.02 ± 3.78	6.73 ± 3.51	9.81 ± 6.54	6.67 ± 4.28	6.84 ± 3.30
RBC ($100^3/\mu$L)[NS]	3.99 ± 0.60	3.86 ± 0.68	3.79 ± 0.68	4.03 ± 0.35	3.99 ± 0.69	4.87 ± 3.02
Hb (g/dL)[NS]	11.49 ± 1.98	11.18 ± 1.68	11.17 ± 1.74	12.02 ± 1.24	11.91 ± 1.95	14.91 ± 9.55
Hct (%)[NS]	34.97 ± 5.00	34.23 ± 5.25	34.26 ± 5.03	35.70 ± 3.15	35.56 ± 5.12	40.64 ± 16.28
MCV (fL)[NS]	88.15 ± 7.17	89.20 ± 6.29	91.12 ± 6.34	88.58 ± 4.26	89.71 ± 4.48	84.20 ± 22.01
MCHC (g/dL)[NS]	32.78 ± 1.62	32.72 ± 1.32	32.59 ± 1.10	33.63 ± 1.12	33.43 ± 1.38	50.97 ± 53.27
MPV (fL)[NS]	9.60 ± 0.70	9.28 ± 0.75	9.28 ± 0.90	9.56 ± 1.10	9.27 ± 1.11	8.34 ± 3.19
Lymphocyte (%)[NS]	26.69 ± 9.23	32.36 ± 14.59	30.77 ± 16.64	25.48 ± 15.27	32.72 ± 15.43	25.80 ± 18.52
Eosinophil (%)[NS]	2.57 ± 1.80	1.90 ± 3.06	2.14 ± 2.99	4.05 ± 5.01	2.51 ± 3.40	1.60 ± 1.63
Basophil (%)[NS]	0.44 ± 0.33	0.52 ± 0.36	0.39 ± 0.31	0.53 ± 0.60	0.43 ± 0.21	0.36 ± 0.37

Values are presented as mean ± SD. NS indicates no significance in statistical analyses (Wilcoxon signed rank test, Mann–Whitney test, and Student's t-test at $P < 0.05$) was found. WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; MPV, mean platelet volume.

Table 3. Changes in PG-SGA

	Control group (n = 24)			Intervention group (n = 10)		
	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks
Total PG-SGA[NS]	11.88 ± 3.43	8.33 ± 3.07	9.13 ± 4.05	10.60 ± 3.75	9.70 ± 3.80	9.38 ± 4.07
SGA A[NS]	5.67 ± 3.06	2.67 ± 2.99	3.46 ± 3.66	5.10 ± 3.21	4.10 ± 3.03	3.63 ± 3.38
SGA B[NS]	1.54 ± 0.51	1.50 ± 0.59	1.54 ± 0.51	1.60 ± 0.52	1.60 ± 0.52	1.50 ± 0.53
SGA C[NS]	0.00 ± 0.00	0.13 ± 0.34	0.17 ± 0.38	0.20 ± 0.42	0.20 ± 0.42	0.13 ± 0.35
SGA D[NS]	4.67 ± 1.05	4.04 ± 1.52	3.96 ± 1.12	3.70 ± 1.06[a]	3.80 ± 1.03	3.50 ± 1.07

Value are presented as mean ± SD. NS indicates no significance in statistical analyses (Wilcoxon Signed Rank test, Mann–Whitney test and Student's t-test at $P < 0.05$) was found. PG-SGA, patient-generated subjective global assessment; SGA A, score from worksheet 1; SGA B, score from worksheet 2; SGA C, score from worksheet 3; SGA D, score from worksheet 4. [a]Significantly different between control and experimental group at baseline ($P < 0.05$, Student t-test).

dL (intervention) at baseline, which is relatively low compared to their healthy counterparts. Hemoglobin concentrations in both control and intervention groups were slightly below the normal range, and the concentration was slightly increased only in the ONS intervention group. Red blood cell counts were also below the normal value range both in control and intervention group, while white blood cell counts were within the normal range. In all biomarkers, however no difference was observed between and within groups during the 8 week intervention period.

PG-SGA scores at baseline were 11.88 and 10.60 in control and intervention group, respectively (Table 3). No significant difference within and between groups was observed. Scores from total and A, B, C sections (A: self-recorded information on weight, food intake, symptoms, activities and functions, B:

nutrient requirement due to specific diseases; C: metabolic demands, D: physical examinations) were not different, while SGA D score of intervention group was significantly higher at baseline compared to that of the control group.

Inflammatory status of the patients were indirectly measured by using cytokine secretion in LPS-treated PBMC (Table 4). At week 8, decreases in concentrations of IL-6 and IL-8 were significant only the intervention group. However, the concentration of IL-12p70 was increased at week 8 in the intervention group.

Results from QoL measures indicated the emotional functioning score was significantly improved at week 4 compared to those at baseline only in the intervention group (Table 5). Also, fatigue symptom was improved at week 4 compared to that of week 1 in the intervention group and the

Table 4. Changes in inflammatory cytokines in LPS-stimulated PBMC

	Control group (n = 24)			Intervention group (n = 10)		
	Baseline	8 weeks	△8 weeks-baseline	Baseline	8 weeks	△8 weeks-baseline
IL-12p70 (pg/mL)	0.36 ± 0.82	0.02 ± 0.06	−0.45 ± 0.93	0.85 ± 1.07	7.85 ± 9.62[a]	7.17 ± 8.98[a]
TNF-α (ng/mL)	1.51 ± 1.56	2.89 ± 2.66	1.77 ± 2.28	0.94 ± 0.69	3.55 ± 4.23	2.86 ± 4.35
IL-10 (pg/mL)	467.74 ± 560.80	743.99 ± 648.30	292.32 ± 829.48	261.04 ± 391.34	472.39 ± 337.01	219.33 ± 393.06[c]
IL-6 (ng/mL)	19.33 ± 18.30	84.70 ± 48.71	77.10 ± 39.18	29.08 ± 34.30	30.18 ± 38.48[a]	15.96 ± 42.33[b]
IL-1β (ng/mL)	2.13 ± 1.69	6.82 ± 6.09	6.13 ± 5.81	2.09 ± 1.83	2.36 ± 2.85[a]	0.74 ± 3.17[b]
IL-8 (ng/mL)	26.12 ± 9.88	46.44 ± 8.77	21.31 ± 11.52	29.45 ± 12.83	32.34 ± 17.98[a]	7.81 ± 17.57

Value are presented as mean ± SD. LPS, lipopolysaccharides; PBMC, peripheral blood mononuclear cell; IL, interleukin. [a]Significantly different between control and experimental group at week 8 ($P < 0.05$, Student's t-test). [b]Significantly different within treatment change-from-baseline ($P < 0.05$, Wilcoxon signed rank test). [c]Significantly different between treatment change-from baseline ($P = 0.056$, Mann–Whitney test).

Table 5. Changes in QoL score

	Control group (n = 24)			Intervention group (n = 10)		
	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks
Global health status/QoL	56.60 ± 22.79	54.17 ± 28.97	54.86 ± 30.39	59.17 ± 21.32	63.33 ± 30.48	62.04 ± 22.09
Functional scales						
Physical functioning	55.56 ± 27.64	61.67 ± 24.18	60.83 ± 29.83	64.67 ± 31.43	76.00 ± 23.35	71.85 ± 21.29
Role functioning	70.83 ± 28.34	68.06 ± 31.44	57.64 ± 40.82	75.00 ± 31.67	68.33 ± 38.85	66.67 ± 44.10
Emotional functioning	73.61 ± 23.40	73.61 ± 31.34	76.39 ± 25.97	61.67 ± 33.15	90.83 ± 9.98[a,d]	80.56 ± 23.20[b]
Cognitive functioning	72.92 ± 29.82	70.83 ± 32.32	71.53 ± 32.03	81.67 ± 32.82	86.67 ± 25.82	81.48 ± 21.15
Social functioning	68.75 ± 31.97	72.22 ± 28.94	65.28 ± 36.09	75.00 ± 22.57	81.67 ± 22.84	79.63 ± 18.22
Symptom scales						
Fatigue	51.39 ± 25.76	52.78 ± 30.60	50.93 ± 28.92	43.33 ± 27.44	31.11 ± 25.01[d]	29.63 ± 22.91[c]
Nausea and vomiting	20.14 ± 30.68	20.83 ± 30.40	15.28 ± 28.20	13.33 ± 18.92	16.67 ± 33.33	11.11 ± 22.05
Pain	41.67 ± 35.78	36.81 ± 35.77	29.17 ± 30.40	25.00 ± 35.36	20.00 ± 24.60	25.00 ± 38.83
Dyspnea	34.72 ± 30.26	29.17 ± 33.06	22.22 ± 32.10	26.67 ± 40.98	33.33 ± 41.57	20.83 ± 35.36
Insomnia	45.83 ± 44.84	37.50 ± 47.46	36.11 ± 46.02	26.67 ± 43.89	33.33 ± 41.57	20.83 ± 30.54
Appetite loss	44.44 ± 45.75	26.39 ± 36.75	36.11 ± 42.75	23.33 ± 38.65	30.00 ± 42.89	29.17 ± 37.53
Constipation	22.22 ± 27.22	22.22 ± 32.10	19.44 ± 30.95	13.33 ± 32.20	13.33 ± 32.20	16.67 ± 35.63
Diarrhea	25.00 ± 40.82	20.83 ± 32.32	25.00 ± 37.11	23.33 ± 41.72	26.67 ± 40.98	33.33 ± 47.14
Financial difficulties	29.17 ± 34.49	26.39 ± 31.05	34.72 ± 36.09	26.67 ± 26.29	23.33 ± 31.62	41.67 ± 29.55

Value are presented as mean ± SD. QoL, quality of life. [a]Significantly different between treatment change-from-baseline ($P < 0.05$, Mann–Whitney test). [b]Significantly different between treatment change-from-baseline ($P < 0.05$, Mann–Whitney test). [c]Significantly different between control and experimental group at week 8 ($P < 0.05$, Student's t-test). [d]Significantly different within treatment change-from-baseline ($P < 0.05$, Wilcoxon signed rank test).

difference between baseline and week 8 was significantly larger only in the intervention group.

DISCUSSION

In this study, we examined the efficacy of cereal-based ONS intervention to improve nutritional status and QoL scores in cancer patients.

Most of cancer patients receiving cancer treatment experience appetite loss and taste aversion. However, little consideration has been made to develop patient-oriented ONS products. In our previous study, the palatability test for different cereal-based ONS trial products in cancer patients and their age- and sex-matched control subjects were performed [18]. We found that cancer patients were more sensitive to taste, viscosity and flavor of the products compared to the control group. The patient group gave higher evaluation scores to products possessing familiar sensory characteristics. These results suggest that ONS product development targeting cancer patients should consider treatment- and tumor-associated changes in appetite. Based on these results, we used cereal-based ONS product that scored highest preference.

Despite malnutrition frequently occurs in cancer patients, nutritional status determinations in cancer patients have not been treated differently from those for other disease-oriented or age-related malnourished individuals. PG-SGA is the most widely accepted nutrition screening tools for assessing nutritional status of cancer patients [19]. However, subjective measurements in these tools may cause variations in different clinical settings and few validation studies has been performed [20]. Although discrepancies between PG-SGA scores and other nutritional assessment tools in the evaluation of nutritional status were reported [21], PG-SGA has been suggested as a tool reflecting dynamic nutritional status of the patient [22]. We found no significant improvement in PG-SGA scores between two groups possibly due to the small sample size and wide variability in weight loss stages of study subjects. It has been clearly indicated that there is significant association between PG-SGA numerical scores (or categories) and disease status. However, only a handful of research results have been reported for the efficacy of nutrition intervention on PG-SGA scores. A recent ONS intervention trial in pancreatic and bile duct cancer patients indicated 8 weeks of nutrition intervention significantly increased the PG-SGA [23]. Although the authors did not mention % of weight loss at the initiation of intervention, the majority of study subjects were in stage IV implying possibility of severe weight loss. In our study, we included subjects whose weight loss was between 5% to 10% due to applicability of ONS products which may explain no appreciable improvement in ONS group. We have observed PG-SGA and nutrition risk index scores were not associated with treatment-induced adverse events in malnourished stomach cancer patients in our previous study [24] possibly due to the nature of study subjects whose nutritional status was rather stable with a mean PG-SGA score of 7.42. Although PG-SGA scores were 11.88 in the control group and 10.60 in the intervention group at baseline, scores were improved and stabilized in both groups during the intervention possibly due to nutrition counselling and education.

We used a wide range of nutritional status indices other than the PG-SGA score in this study. Previously, the efficacy of ONS in malnourished cancer patients were systematically reviewed [7]. Among qualified 28 intervention studies performed between 2001 and 2015, 20 studies used biochemical measures mostly albumin, prealbumin and transferrin to evaluate the efficacy. Also, 18 studies measured markers of immune responses and inflammatory status. Our study results showed ONS intervention did not improve circulating concentrations of nutritional status biomarkers although hemoglobin concentration was slightly increased only in the intervention group. A recent study showed that nasopharyngeal cancer patients receiving chemoradiotherapy had higher white blood cell counts when the patients were treated with home enteral nutrition [25]. The hemoglobin concentration was negatively associated with PG-SGA score in colorectal cancer patients [26] and nutrition intervention improved the compliance rate of chemotherapy and nutritional status measured by blood concentrations of hemoglobin and albumin [27]. Improved postoperative hemoglobin and albumin status was also observed in primary lung cancer patients receiving ONS [28], and a higher PG-SGA score was suggested to increase the risk of anemia [29]. In cutaneous melanoma patients, female patients with lymph node involvement and metastatic disease were more likely to have a lower hemoglobin concentration [30], and hemoglobin has been suggested as a prognostic marker in head and neck squamous cell carcinoma patients [31]. Although albumin is the most widely used blood biomarker to determine the nutritional status in malnourished population, only 11% of the 28 ONS intervention studies showed significant improvements in cancer patients [7], and results from our study also showed no significant difference in a serum albumin concentration between ONS intervention group and control group.

Cereal-based ONS products used in this study contain fermented rice bran. Studies have suggested that fermentation of rice bran produces arabinoxylan, a functional polysaccharide possessing immune stimulatory activities [32]. A recent report has suggested that arabinoxylan rice bran can be used to alleviate radiation-induced suppressions in complete blood counts [33]. We have also shown that 2.5% to 5% dietary supplementation of wheat bran arabinoxylan significantly suppresses the intestinal mucosa mRNA expression of proinflammatory cytokines as well as the number of apoptotic cells in BALB/c mice treated

with 5-fluorouracil, a widely used anti-cancer drug causing mucositis [16]. Although no significant difference was found in body weight, a 5-fluorouracil-induced decrease in thymus weight was significantly recovered in animals fed diet supplemented with arabinoxylan. In this study, we observed significant decreases in IL-6 and IL-1β production in LPS-stimulated PBMC isolated from study subjects and these results are in agreement with results of our preclinical study [16]. Apart from fermented rice bran, other major functional ingredients in ONS product used in this study include black rice powder (5% w/w) and chiaseed powder (5% w/w), which are high in anthocyanin and omega-3 fatty acids, respectively. These compounds are well known to possess anti-inflammatory activities which presumably contributed to the suppressed production of pro-inflammatory cytokines. Since chemotherapy or radiotherapy induced inflammatory responses in tissue epithelium especially in digestive tract contribute to mucositis resulting in decreased food intake, ONS products containing anti-inflammatory functional components may not only increase the nutrient intake but also decrease therapy-induced epithelial inflammation.

Health-related quality of life (HRQoL) is one of the most important supportive care issue in cancer patients. A systematic review and meta-analysis to examine the efficacy of ONS intervention in malnourished cancer patients indicated that ONS intervention exerted significant improvements only in some aspects of HRQoL such as emotional functioning, dyspnea, loss of appetite and global QoL, but no significant difference was found in body weight or mortality [34]. We observed emotional functioning and fatigue symptoms were improved after 4 weeks of intervention although no difference was found at week 8. A recent study with bile duct/pancreatic patients also showed ONS intervention for 8 weeks improved fatigue in the symptomatic scale category [23]. Cancer-related fatigue (CRF) is defined as an unusual, persistent, and subjective sense of tiredness that is not proportional to recent activity and interferes with usual functioning [35]. Earlier systematic analyses have indicated that exercise is an effective mean to improve CRF while evidences for nutritional supplements is not established [36]. A most recent meta-analysis including 15 intervention studies demonstrated nutrition therapy did not show definite effects on CRF and QoL in cancer patients [37]. Among these intervention trials, however, plant-based anti-inflammatory diets suggested possible benefits on CRF [38,39]. We also found that ONS intervention alleviated symptoms of nausea and vomiting. Chemotherapy often induces nausea and vomiting which adversely affect food intake and QoL. Chemotherapeutic agents are known to trigger the secretion of neurotransmitters such as serotonin and substance P mitigating vagal signaling [40]. Currently a limited number of studies have investigated the efficacy of nutrition intervention for cancer treatment associated nausea and vomiting nutrition intervention in palliative cancer patients improved

patient-rated symptom of nausea and vomiting while there was difference in other measures [41]. Another intervention study using a home delivery meal service found significantly positive association between energy and protein intake and QoL indicating improved food intake [42]. Contrary to these findings, ONS intervention in patients with nasopharyngeal cancer during chemotherapy improved body weight, BMI and prealbumin, while no difference was observed for QoL [43]. Further nutrition interventions are needed to prove cause-effect relationship between nutrition intervention and chemo- or radio-therapy associated adverse events. In conclusion, our study results provided evidence that ONS with immune-modulatory functional components may reduce circulating concentrations of pro-inflammatory cytokines and improve some of QoL indices in a short-time period.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

SUPPLEMENTARY MATERIALS

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, et al. ESPEN expert group recommendations for action against

cancer-related malnutrition. Clin Nutr 2017;36:1187-96.

3. Fearon KC, Glass DJ, Guttridge DC. Cancer cachexia: mediators, signaling, and metabolic pathways. Cell Metab 2012;16:153-66.

4. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011;12:489-95.

5. Bozzetti F. Nutritional support of the oncology patient. Crit Rev Oncol Hematol 2013;87:172-200.

6. Bhosle J, Hall G. Principles of cancer treatment by chemotherapy. Surgery 2006;24:66-9.

7. Kim JM, Sung MK. The efficacy of oral nutritional intervention in malnourished cancer patients: a systemic review. Clin Nutr Res 2016;5:219-36.

8. Hutton JL, Baracos VE, Wismer WV. Chemosensory dysfunction is a primary factor in the evolution of declining nutritional status and quality of life in patients with advanced cancer. J Pain Symptom Manage 2007;33:156-65.

9. Steinbach S, Hummel T, Böhner C, Berktold S, Hundt W, Kriner M, et al. Qualitative and quantitative assessment of taste and smell changes in patients undergoing chemotherapy for breast cancer or gynecologic malignancies. J Clin Oncol 2009;27:1899-905.

10. Belqaid K, Tishelman C, McGreevy J, Månsson-Brahme E, Orrevall Y, Wismer W, et al. A longitudinal study of changing characteristics of self-reported taste and smell alterations in patients treated for lung cancer. Eur J Oncol Nurs 2016;21:232-41.

11. Epstein JB, Barasch A. Taste disorders in cancer patients: pathogenesis, and approach to assessment and management. Oral Oncol 2010;46:77-81.

12. McGreevy J, Orrevall Y, Belqaid K, Wismer W, Tishelman C, Bernhardson BM. Characteristics of taste and smell alterations reported by patients after starting treatment for lung cancer. Support Care Cancer 2014;22:2635-44.

13. Ooi SL, McMullen D, Golombick T, Nut D, Pak SC. Evidence-based review of BioBran/MGN-3 arabinoxylan compound as a complementary therapy for conventional cancer treatment. Integr Cancer Ther 2018;17:165-78.

14. Song M, Baik HW, Hong SG, Sung MK. Wheat bran arabinoxylan supplementation alleviates 5-fluorouracil induced mucositis and myelosuppression in BALB/c mice. J Funct Foods 21 2016;21:312-20.

15. Park MY, Kim JM, Kim JS, Choung MG, Sung MK. Chemopreventive action of anthocyanin-rich black soybean fraction in APC (Min/+) intestinal polyposis model. J Cancer Prev 2015;20:193-201.

16. Senkal M, Haaker R, Linseisen J, Wolfram G, Homann HH, Stehle P. Preoperative oral supplementation with long-chain Omega-3 fatty acids beneficially alters phospholipid fatty acid patterns in liver, gut mucosa, and tumor tissue. JPEN J Parenter Enteral Nutr 2005;29:236-40.

17. Stechmiller JK, Childress B, Porter T. Arginine immunonutrition in critically ill patients: a clinical dilemma. Am J Crit Care 2004;13:17-23.

18. Baik HW, Sung MK, Lee YS, Song MK, Bae YJ. The palatability of cereal based nutritional supplements in cancer patients. Clin Nutr Res 2014;3:48-55.

19. Mendes NP, Barros TA, Rosa COB, Franceschini SDCC. Nutritional screening tools used and validated for cancer patients: a systematic review. Nutr Cancer 2019;71:898-907.

20. Lee HO, Han SR, Choi SI, Lee JJ, Kim SH, Ahn HS, et al. Effects of intensive nutrition education on nutritional status and quality of life among postgastrectomy patients. Ann Surg Treat Res 2016;90:79-88.

21. Pinho J, Ottery FD, Pinto P, Santoalha I, Moreira D, Gondar C, et al. Agreement between Patient-Generated Subjective Global Assessment (PG-SGA) and Mini Nutritional Assessment (MNA) in long-stay nursing home residents. Clin Nutr 2016;35(Suppl 1):S108.

22. Jager-Wittenaar H, Ottery FD. Assessing nutritional status in cancer: role of the Patient-Generated Subjective Global Assessment. Curr Opin Clin Nutr Metab Care 2017;20:322-9.

23. Kim SH, Lee SM, Jeung HC, Lee IJ, Park JS, Song M, et al. The effect of nutrition intervention with oral nutritional supplements on pancreatic and bile duct cancer patients undergoing chemotherapy. Nutrients 2019;11:E1145.

24. Seo SH, Kim SE, Kang YK, Ryoo BY, Ryu MH, Jeong JH, et al. Association of nutritional status-related indices and chemotherapy-induced adverse events in gastric cancer patients. BMC Cancer 2016;16:900.

25. Li X, Zhou J, Chu C, You Q, Zhong R, Rao Z, et al. Home enteral nutrition may prevent myelosuppression of patients with nasopharyngeal carcinoma treated by concurrent chemoradiotherapy. Head Neck 2019;41:3525-34.

26. Sharour LA. Cancer-related fatigue, laboratory markers as indicators for nutritional status among patients with colorectal cancer [published online ahead of print October 1, 2019]. Nutr Cancer. doi: 10.1080/01635581.2019.1669674.

27. Xie FL, Wang YQ, Peng LF, Lin FY, He YL, Jiang ZQ. Beneficial effect of educational and nutritional intervention on the nutritional status and compliance of gastric cancer patients undergoing chemotherapy: a randomized trial. Nutr Cancer 2017;69:762-71.

28. Yang J, Zhang Q, Wang X. Role of nutritional support for postoperative recovery of respiratory function in patients with primary lung cancer. Oncol Lett 2018;16:5978-82.

29. Wu M, Lian XJ, Jia JM, Cao WT, Yan N, Xin YM, et al. The role of the Patient-Generated Subjective Global Assessment (PG-SGA) and biochemical markers in predicting anemia patients with cancer. Support Care Cancer 2019;27:1443-8.

30. Tas F, Erturk K. Anemia in cutaneous malignant melanoma: low blood hemoglobin level is associated with nodal involvement, metastatic disease, and worse survival. Nutr Cancer 2018;70:236-40.

31. Moon H, Roh JL, Lee SW, Kim SB, Choi SH, Nam SY, et al. Prognostic value of nutritional and hematologic markers in head and neck squamous cell carcinoma treated by chemoradiotherapy. Radiother Oncol 2016;118:330-4.

32. Cholujova D, Jakubikova J, Czako B, Martisova M, Hunakova L, Duraj J, et al. MGN-3 arabinoxylan rice bran modulates innate immunity in multiple myeloma patients. Cancer Immunol Immunother 2013;62:437-45.

33. Ghoneum M, Badr El-Din NK, Abdel Fattah SM, Tolentino L. Arabinoxylan rice bran (MGN-3/Biobran) provides protection against whole-body γ-irradiation in mice via restoration of hematopoietic tissues. J Radiat Res 2013;54:419-29.

34. Zhang F, Shen A, Jin Y, Qiang W. The management strategies of cancer-associated anorexia: a critical appraisal of systematic reviews. BMC Complement Altern Med 2018;18:236.

35. Berger AM, Mooney K, Alvarez-Perez A, Breitbart WS, Carpenter KM, Cella D, et al. Cancer-related fatigue, version 2.2015. J Natl Compr Canc Netw 2015;13:1012-39.

36. Mitchell SA, Beck SL, Hood LE, Moore K, Tanner ER. Putting evidence into practice: evidence-based interventions for fatigue during and following cancer and its treatment. Clin J Oncol Nurs 2007;11:99-113.

37. Baguley BJ, Skinner TL, Wright ORL. Nutrition therapy for the management of cancer-related fatigue and quality of life: a systematic review and meta-analysis. Br J Nutr 2019;122:527-41.

38. Paxton RJ, Garcia-Prieto C, Berglund M, Hernandez M, Hajek RA, Handy B, et al. A randomized parallel-group dietary study for stages II-IV ovarian cancer survivors. Gynecol Oncol 2012;124:410-6.

39. Zick SM, Colacino J, Cornellier M, Khabir T, Surnow K, Djuric Z. Fatigue reduction diet in breast cancer survivors: a pilot randomized clinical trial. Breast Cancer Res Treat 2017;161:299-310.

40. Adel N. Overview of chemotherapy-induced nausea and vomiting and evidence-based therapies. Am J Manag Care 2017;23(14 Suppl):S259-65.

41. Uster A, Ruehlin M, Mey S, Gisi D, Knols R, Imoberdorf R, et al. Effects of nutrition and physical exercise intervention in palliative cancer patients: a randomized controlled trial. Clin Nutr 2018;37:1202-9.

42. Leedo E, Gade J, Granov S, Mellemgaard A, Klausen TW, Rask K, et al. The effect of a home delivery meal service of energy- and protein-rich meals on quality of life in malnourished outpatients suffering from lung cancer: a randomized controlled trial. Nutr Cancer 2017;69:444-53.

43. Jiang W, Ding H, Li W, Ling Y, Hu C, Shen C. Benefits of oral nutritional supplements in patients with locally advanced nasopharyngeal cancer during concurrent chemoradiotherapy: an exploratory prospective randomized trial. Nutr Cancer 2018;70:1299-307.