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Effects of Eight-Week Whey Protein Supplementation in Palliative Care Patients with Advanced Cancer: A Double-Blind Randomized Controlled Pilot Trial

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- Cancer
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Abstract

Background: Evidence of the effect of whey protein (WP) supplementation in palliative cancer patients is limited. This study evaluated the effectiveness of an 8-week WP supplementation on quality of life (QOL) and predefined outcomes in Hong Kong Chinese palliative care patients with advanced cancer.

Methods: This was a randomized, double-blind placebo-controlled clinical trial. Palliative care patients with advanced cancer were randomized to receive one sachet of WP supplement at 36 g daily (intervention), or casein at 36 g daily (placebo) for 8 weeks. Outcome measures, including QOL, weight, body fat %, lean body mass, biceps and triceps circumferences, waist circumference, handgrip strength, 6-minute walking test, up & go test, Barthel Index, Karnofsky Performance Scale Index, London Handicap Scale, Elderly Mobility Scale and glutathione (GSH) level, were assessed at week 0, 4 and 8. The intention-to-treat or per-protocol principle was applied to examine the effects of the intervention on each outcome, with the use of linear mixed-effects model analysis.

Results: A total of 92 patients (mean age 60.9±13.7, male 54.3%) were randomized and completed the baseline assessment. There was no significant group difference in the changes of QOL, anthropometry, physical function or intracellular GSH level over time (all p for interaction >0.05), either by intention-to-treat or per-protocol analysis.

Conclusion: In Chinese palliative care patients with advanced cancer, there were no significant differences in the changes of QOL, anthropometry, physical function and intracellular GSH level over time between the group receiving an 8-week WP supplementation daily and casein supplementation daily.

ABBREVIATIONS

BIA: bioelectrical impedance analyzer, **BMI:** body mass index, **CT:** chemotherapy, **EMS:** Elderly Mobility Scale, **GSH:** glutathione, **ITT:** intention-to-treat, **MQOL-HK:** McGill Quality of Life Questionnaire for Hong Kong Chinese, **PP:** per protocol, **TUG:** Timed up & go, **WP:** whey protein, **QOL:** quality of life

INTRODUCTION

Cancer is a leading cause of death worldwide [1]. It is estimated that the deaths of 10-20% of cancer patients occur as a result of malnutrition rather than the malignancy of the disease itself [2]. Cancer patients are at high risk of malnutrition because of the disease and its treatment. Systemic inflammation is frequently activated in cancer patients [3]. This can vary in degree but is associated with poor performance status, weight loss, fat and muscle mass loss, development of fatigue and anorexia [4]. These adverse effects may result in an unfavorable prognosis, increased toxicity of anticancer treatments and ultimately reductions or interruptions of scheduled treatment and reduced quality of life [3, 5-7]. Given the potential nutritional deficits and metabolic derangements, it is essential to initiate nutritional care among cancer patients.

Whey protein (WP) supplementation has a great potential to support cancer patients by stimulating muscle protein synthesis and providing substrates for the synthesis of the antioxidant glutathione (GSH) [8]. GSH could protect cells against free radicals,

ionize radiation, reactive oxygen species and carcinogens [9, 10]. WP supplementation has been shown to improve lean mass in colorectal cancer patients undergoing chemotherapy (CT) [11], and increase the GSH level in cancer patients undergoing CT [12]. In contrast, no significant effect of WP supplementation on body weight, body composition, handgrip strength and walking distance was observed in non-small-cell lung cancer patients undergoing CT [13]. To the best of our knowledge, no trials examining the effect of WP supplementation in cancer patients receiving palliative care are available.

Since the goal of palliative care is to improve the quality of life (QOL) of patients and their families [14], this study aimed to evaluate the effectiveness of an 8-week WP supplementation on QOL (primary outcome) and other predefined outcomes (anthropometry, physical function and GSH level) in Hong Kong Chinese palliative care patients with advanced cancer.

MATERIALS AND METHODS

Patients selection

This pilot study was conducted between October 2002 to May 2004, with a temporary halt in recruiting cases during the severe acute respiratory syndrome (SARS) outbreak period in Hong Kong. Patients were recruited from the inpatient service of hospice and palliative care at the Shatin Hospital in Hong Kong. Inclusion criteria were i) aged ≥18 years old, ii) with advanced cancer receiving palliative care, and iii) not receiving any type of artificial nutrition (enteral or parenteral). Exclusion criteria were i) history of allergy to WP, ii) less than 8 weeks of expected life expectancy, and iii) cognitive impairment with Abbreviated Mental Test of <6 points [15].

Study design

This was a randomized, double-blind, placebo-controlled clinical trial. Randomization was done by blocks of 10. Sealed envelopes were prepared, with five labels of 'A' and five labels of 'B' in each envelope. After informed consent was given, patients were randomized into either placebo control or intervention groups. Patients drew a label out by himself or herself without looking into the envelope. The sachet labeled 'A' or 'B' was given to the patients accordingly. All the assessors (clinicians and laboratory technicians) and patients were blinded to whether the patient was in the placebo or intervention group. Assignment to the placebo or intervention group was disclosed only after the whole study was completed. Patients were assessed at weeks 0, 4 and 8 for outcome measurements.

Intervention and placebo group

Patients in the intervention group were given one sachet of ImuPower® per day (36 g whey protein daily) for 8 weeks. They were instructed to take the supplement with his/her usual drinks and with lukewarm water only. Patients in the placebo group were given one sachet of identical-looking packs of casein per day (36 g casein protein) for 8 weeks. They were given the same instruction on how to take the supplement and the same clinical management of his/her cancer as that of the intervention group.

Data collection

Demographic data including age, sex and type of cancer were collected at baseline. The primary outcome was QOL and secondary outcomes were anthropometry, physical function, and glutathione level.

Quality of life

The translated and modified version of the McGill Quality of Life Questionnaire for Hong Kong Chinese (MQOL-HK) was used to assess the quality of life (QOL) of patients with a life-threatening illness [16]. The MQOL-HK has been validated cross-culturally in Hong Kong and was shown to be acceptable, valid and reliable. Five essential domains were assessed: physical, psychological, existential well-being, support and sexuality. It contains 18 items and a single item rating the overall QOL. The response categories were based on a numerical scale from 0 to 10, with verbal anchors at the ends of the scale. For the final statistical analysis, all scores are transposed on a 0 to 10 scale, with 0 indicating the least and 10 the most desirable situation. The domain score was calculated as the mean of the individual item scores of that domain, whereas the total QOL score was calculated as the mean of all the domain scores.

Anthropometry

Body weight was measured using a standard weighing scale with patients wearing light clothing. Height was measured using a stadiometer or estimated from an arm-span. Body Mass Index (BMI) was calculated by body weight in kg divided by height in squared meter. Skinfold thickness of biceps and triceps were measured using a skinfold caliper to the nearest 0.1 cm. Waist circumference was measured to the nearest 0.1 cm using a measuring tape. Percent body fat and lean body mass (kg) were measured using a Bioelectrical Impedance Analyzer (BIA).

Physical function

The handgrip strength of each hand was measured using a handheld dynamometer. Submaximal level of functional capacity was assessed using the six minutes walking test. Patients were instructed to walk on a flat, hard surface in a period of six minutes at a speed suitable to their condition. They were allowed to stop or slow down if required and resume walking as soon as possible. The six minutes walking distance was calculated and expressed in meters. Timed up & go (TUG) test was used to assess patients' mobility [17]. Patients were timed while they rise from an armchair, walk at a comfortable and safe pace to a line on the floor three metres away, turn and walk back to the chair and sit down again. The time to complete the TUG test was recorded as seconds. Walking aid was allowed if needed for six minutes walking test and TUG test. Activities of daily living (ADL) was assessed using the Barthel Index [18]. The ability to perform ten different tasks including bowels and bladder control, grooming, toilet use, feeding, transfer, mobility, dressing, stairs and bathing were rated. Total possible scores range from 0 to 20, with lower scores indicating increased difficulty in performing ADL. Karnofsky Performance Scale Index was used to measure the ability of cancer patients to perform ordinary tasks [19]. The Karnofsky score ranges from 0 to 100, with a higher score indicating the patient is better able to carry out daily activities. The London Handicap Scale (LHS) was used to assess the effect of chronic conditions on a patient's functional ability [20]. Six

dimensions of handicap were assessed: mobility, orientation, occupation, physical independence, social integration and economic self-sufficiency. On a scale of 0 (none) to 6 (extreme), patients selected one category per dimension indicating their perceived level of disadvantage. The total LHS score was calculated as the mean of all the dimension scores. For patients over 65 years old, the Elderly Mobility Scale (EMS) was used to assess their mobility, considering locomotion, balance and key position changes [21]. The EMS includes the assessment of the following tasks: lying to sitting, sitting to lying, sitting to standing, standing, gait, 6- metres timed walk and functional reach. Possible EMS score ranges from 0 (totally dependent) to 20 (independent mobility).

Glutathione level

Venous blood was taken for glutathione (GSH) assay using a standardized kinetic method [22]. Both whole blood and plasma GSH were measured (μmol/L), and the value of whole blood GSH minus plasma GSH was taken as intracellular GSH level for subsequent statistical analysis. Quality control samples were included in every batch of assays to monitor interassay variations.

Ethical consideration

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and was carried out according to the principles set out in the Declaration of Helsinki 1964 and all subsequent revisions, informed consent was obtained, and the relevant institutional review board had approved the study (CRE-2002.127). Written informed consent was obtained from all patients.

Statistical analysis

Characteristics of patients are presented as mean and Standard Deviation (SD) for continuous variables and as numbers and percentages (%) for categorical variables. Independent student's

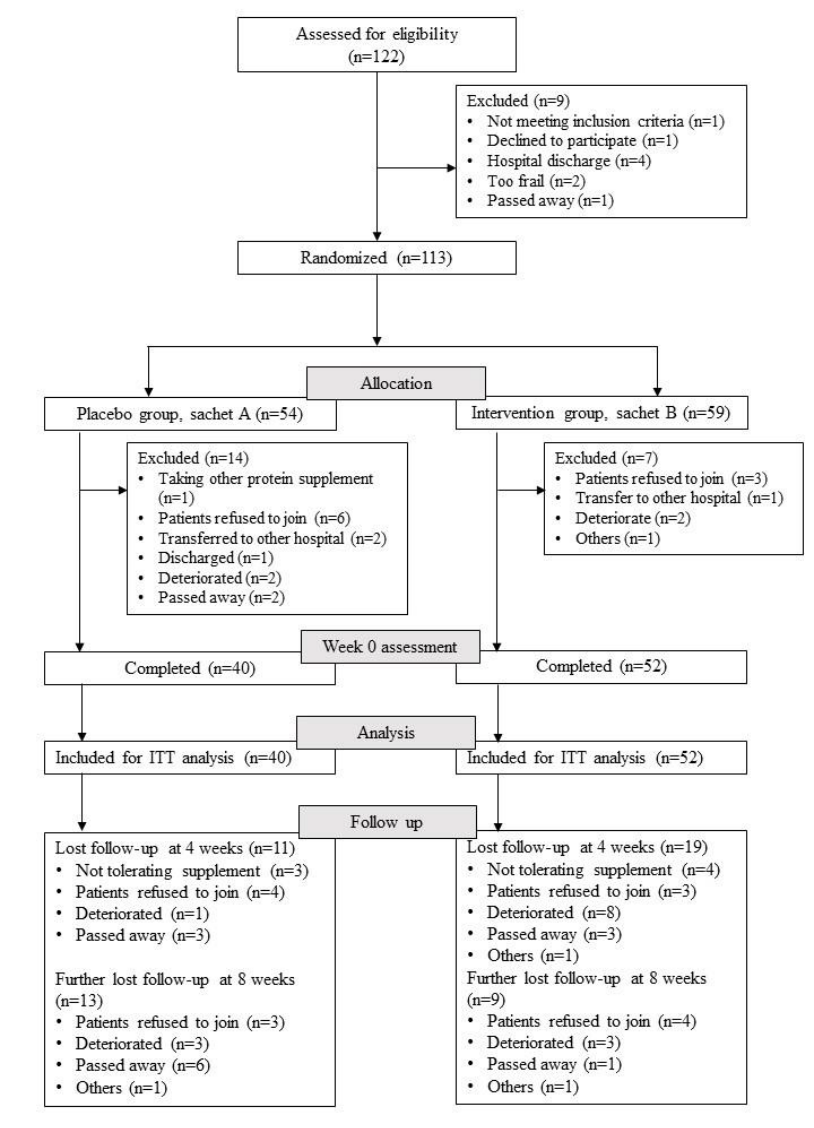

Figure 1 Study flow chart.

t-test and chi-square test were used to examine the differences in characteristics between patients in the intervention group and patients in the placebo group.

Data were analyzed using the Intention-To-Treat (ITT) principle and as Per Protocol (PP). ITT was applied to examine the effects of the intervention on each outcome variable, including all available data from patients who consented to participate in the study. PP was defined as completing the 8-week intervention. Treatment, time, and interaction effects during the 8-week study period were examined with the use of linear mixed-effects model analysis with treatment, time and interactions as fixed effects and patients as random effects. Significant treatment and time interactions in the linear mixed model analysis indicate significant treatment effects. Changes between the baseline and week 4 and week 8 were analyzed accordingly. P values of <0.05 (two-tailed) were considered statistically significant. All data were analyzed using SPSS, version 26.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Patients' characteristics

Figure 1 shows the number of patients at different study stages. A total of 122 patients were approached, however, 9 of them were excluded, while another 21 patients dropped out before completing the assessment at week 0. Out of the 92 patients (40 in the placebo group and 52 in the intervention group) who completed the assessment at week 0, 30 dropped out before the assessment at week 4 and another 22 dropped out before the assessment at week 8.

Table 1 shows the baseline characteristics of the patients. The mean age of the patients at study entry was 60.9 years old (SD 13.7) and the proportion of male patients was 54.3%. The top three primary cancer sites were lung (37.0%), breast (16.3%) and sarcoma (5.4%). Baseline characteristics of the two groups were similar, with no significant differences between the placebo group and the intervention group.

Table 1: Baseline characteristics between placebo group and intervention group.

	Placebo group (n= 40)	Intervention group (n= 52)	P-value[a]
Age, years	63.4 (13.7)	58.9 (13.5)	0.116
Male, n (%)	21 (52.5)	29 (55.8)	0.834
Primary cancer site, n (%)			0.751
Breast	9 (22.5)	6 (11.5)	
Gynecology	1 (2.5)	3 (5.8)	
Colon	1 (2.5)	3 (5.8)	
Lung	12 (30.0)	22 (42.3)	
Lymphoma	1 (2.5)	3 (5.8)	
Multiple myeloma	0	2 (3.8)	
Nasopharyngeal cancer	2 (5.0)	2 (3.8)	
Oral	2 (5.0)	1 (1.9)	
Pancreas	1 (2.5)	1 (1.9)	
Prostate	2 (5.0)	1 (1.9)	
Sarcoma	3 (7.5)	2 (3.8)	
Stomach	1 (2.5)	2 (3.8)	
Others	5 (12.5)	4 (7.7)	
McGill Quality of Life, score			
Physical domain	6.4 (1.7)	6.3 (1.9)	0.771
Psychological domain	8.0 (2.2)	8.1 (1.9)	0.925
Existential domain	6.8 (2.0)	6.5 (1.7)	0.441
Support domain	8.1 (2.0)	7.8 (2.2)	0.524
Sexuality/intimacy	7.2 (3.9)	6.4 (4.1)	0.350
Single item (Overall)	6.3 (2.2)	6.3 (2.0)	0.935
Total quality of life	7.3 (1.5)	7.0 (1.3)	0.310
Weight, kg	53.8 (10.3)	53.9 (11.3)	0.970
Body mass index, kg/m^2	20.9 (3.3)	20.9 (4.0)	0.902
Biceps skinfold, cm	11.0 (7.0)	11.1 (10.0)	0.962
Triceps skinfold, cm	13.8 (7.8)	12.5 (6.9)	0.394
Body fat, %	30.2 (7.5)	27.4 (8.9)	0.166
Waist circumference, cm	76.9 (17.4)	76.0 (20.1)	0.868
Lean muscle mass, kg	36.5 (7.3)	38.1 (8.2)	0.392
Right handgrip, kilopascal	16 (8)	17 (9)	0.949
Left handgrip, kilopascal	15 (7)	16 (9)	0.657
6 min walk test, metres	167 (87)	180 (115)	0.554

Up and go test, seconds	24 (24)	21 (25)	0.572
Barthel index, score	16 (3)	16 (3)	0.815
Karnofsky Performance Scale Index, score	63 (8)	63 (9)	0.697
London Handicap Scale, score			
Mobility	3.9 (1.0)	3.7 (1.0)	0.231
Physical independence	3.5 (0.8)	3.4 (0.8)	0.820
Social integration	2.0 (0.8)	2.1 (0.8)	0.680
Occupation	3.6 (0.9)	3.7 (0.7)	0.586
Environmental orientation	1.7 (0.5)	1.9 (0.7)	0.276
Economic sufficiency	3.6 (1.0)	3.4 (1.0)	0.313
Total handicap	3.1 (0.5)	3.0 (0.5)	0.758
Elderly mobility scale	15 (5)	13 (7)	0.495
Intracellular GSH level, μmol	1013 (421)	997 (383)	0.855

Abbreviations: GSH, glutathione.
Values are presented as mean (standard deviation) or otherwise as indicated.
[a]P value by independent t test or chi-square where appropriate

Study outcomes

Figure 2 shows the changes in QOL scores from baseline to week 4 and week 8 in the placebo group and intervention group according to the ITT analysis. Patients in the intervention group showed a consistent improvement in all QOL measures from baseline to week 4. However the inter-group comparison showed no significant group differences in the changes of any domains of QOL scores, single item and total QOL scores (all P for interaction >0.05). There were also no significant group differences in the changes of body weight, BMI, body fat %, lean body mass, biceps and triceps circumferences, waist circumference, handgrip strength, 6-minute walking test, TUG test, Barthel Index, Karnofsky Performance Scale Index, London Handicap Scale, Elderly Mobility Scale and intracellular GSH level over time (all P for interaction >0.05) (Table 2). Similar results were observed for the PP analysis (data not shown).

DISCUSSION

This 8-week double-blind randomized controlled pilot study showed that in Chinese palliative care patients with advanced cancer, there were no significant differences in the changes of QOL, anthropometry, physical function and intracellular GSH level over time between the group that received WP supplementation and the group that received casein supplementation daily.

WP is a rapidly digested, high-quality protein with excellent amino acid profiles, which makes them an important source for sustaining muscle protein anabolism and function, and providing substrates for the synthesis of GSH [8, 23]. However, we did not find a significant group difference in the change of any outcome variables over time. Our results were consistent with a pilot double-blind randomized controlled trial in patients with non-small-cell lung cancer undergoing CT, in which there was no significant effect of 12-week WP supplementation (20 g WP daily) on body weight, body composition, handgrip strength and walking distance [13]. In contrast, a previous study among cancer patients undergoing CT showed that GSH levels significantly improved at week 6 by 6.0% and at week 12 by 11.7% compared with the control after a daily supplementation of 40 g WP with zinc (2.64 mg) and selenium (0.76 mg) [12]. The enhanced immune function from zinc and selenium may improve cell-mediated immunity and antioxidant capacity, and therefore it may explain why the result was in contrast with our study of WP alone. In colorectal cancer patients undergoing CT, 13.5 g WP supplementation for six months improved lean mass compared with the placebo group [11]. The longer duration of the intervention may partly explain the different results compared with our 8-week intervention.

According to the current guidelines, oral nutritional supplementation plus individual nutritional counseling is recommended as the standard care for all cancer patients at nutritional risk [7]. In malnourished patients with different cancer types and receiving CT, personalized nutritional counseling with 40 g WP supplementation for three months resulted in improved body composition, body weight and muscle strength compared to nutritional counseling alone [24]. The lack of treatment effect in our study may emphasize the need for personalized nutritional counseling in addition to nutritional supplementation to educate patients, or provide strategies to support patient convenience/compliance [25]. However, similar to our study, QOL scores were not significantly different between the group receiving WP supplementation and the control group [12, 24]. It should be noted that QOL is a subjective construct which is influenced by various factors. It has been suggested that the stage of disease was the major determinant of patients' QOL, followed by deterioration in nutritional status and dietary intake [26, 27]. This may explain why there was no treatment effect on QOL over time in our sample of palliative care patients with advanced cancer.

There are other reasons which may explain the lack of group difference in the changes of any outcomes in our study. First, the effectiveness of WP supplementation would depend on patients' baseline nutritional status and habitual protein intake [28]. However, it is not known if there was any group difference in terms of baseline nutritional status and protein intake in our study. Literature has suggested that losses in lean body mass were ~40% lower in older adults in the highest quintile than those in the lowest quintile of energy-adjusted protein intake [29]. In patients with advanced cancer, malnutrition is often associated with chronic cancer-induced systemic inflammation resulting in anorexia, insulin resistance, anabolic resistance and

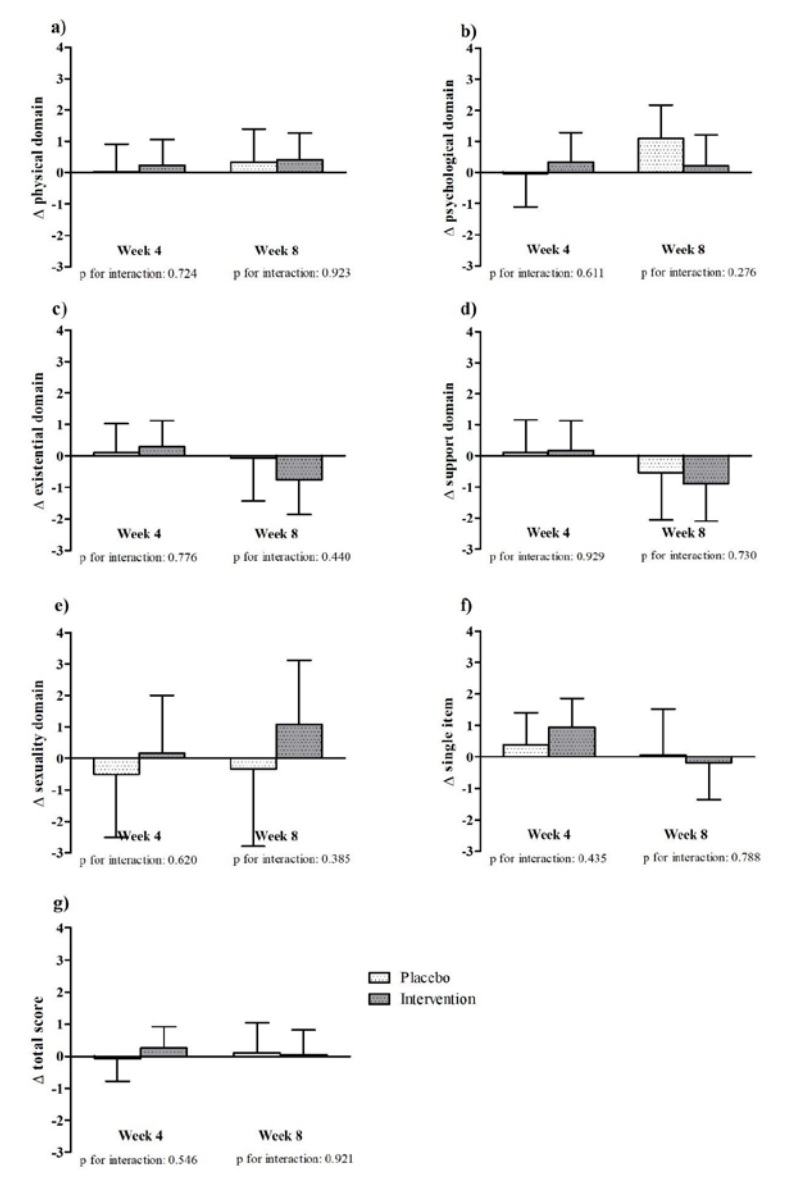

Figure 2 Mean changes of QOL from baseline to week 4 and week 8 in placebo group (n=40) and intervention group (n=52): a) physical domain, b) psychological domain, c) existential well-being, d) support domain, e) sexuality domain, f) single item, g) total score. Data are presented as mean ± 95% confidence interval. Mean change was calculated as: week 4/week 8 value minus baseline value.

Table 2: Comparison of the changes of anthropometry, physical function and glutathione level among the placebo group (n=40) and the intervention group (n=52).

	Mean (SD)			Change after 4 weeks		Change after 8 weeks	
	Week 0	Week 4	Week 8	Mean change[a] (95% CI)	P value of interaction[b]	Mean change[a] (95% CI)	P value of interaction[b]
Anthropometry Weight, kg							
Placebo	53.8 (10.3)	54.0 (12.0)	51.2 (10.4)	0.12 (-5.61, 5.86)	0.459	-2.70 (-9.62, 4.23)	0.180
Intervention	53.9 (11.3)	57.0 (13.1)	57.4 (13.0)	3.06 (-2.27, 8.39)		3.46 (-2.40, 9.32)	
Body mass index, kg/m^2							
Placebo	20.9 (3.3)	21.0 (3.8)	20.5 (3.6)	0.10 (-1.81, 2.01)	0.688	-0.41 (-2.84, 2.02)	0.472
Intervention	20.9 (4.0)	21.5 (4.4)	21.6 (4.7)	0.63 (-1.15, 2.41)		0.74 (-1.32, 2.80)	
Biceps skinfold, cm							

Placebo	11.0 (7.0)	10.7 (6.9)	9.1 (6.0)	-0.31 (-4.10, 3.48)	0.803	-1.91 (-6.15, 2.33)	0.683
Intervention	11.1 (10.0)	11.4 (7.3)	10.3 (6.4)	1.11 (-2.55, 4.76)		-0.76 (-4.36, 2.83)	
Triceps skinfold, cm							
Placebo	13.8 (7.8)	13.1 (7.9)	12.8 (7.1)	-0.70 (-4.37, 2.97)	0.391	-0.92 (-5.13, 3.30)	0.547
Intervention	12.5 (6.9)	13.9 (7.7)	13.2 (7.5)	1.48 (-1.92, 4.87)		0.77 (-2.87, 4.42)	
Body fat, %							
Placebo	30.2 (7.5)	29.6 (7.2)	29.7 (8.9)	-0.55 (-5.24, 4.15)	0.399	-0.52 (-6.42, 5.39)	0.498
Intervention	27.4 (8.9)	29.5 (8.5)	29.6 (8.6)	2.11 (-1.98, 6.20)		2.16 (-3.09, 7.41)	
Waist circumference, cm							
Placebo	76.9 (17.4)	79.9 (8.9)	77.6 (3.3)	2.99 (-7.45, 13.4)	0.829	0.74 (-10.4, 11.9)	0.478
Intervention	76.0 (20.1)	80.5 (13.1)	81.8 (12.0)	4.48 (-4.35, 13.3)		5.78 (-2.85, 14.4)	
Lean body mass, kg							
Placebo	36.5 (7.3)	37.1 (9.4)	34.2 (7.4)	0.56 (-4.60, 5.72)	0.937	-2.30 (-8.20, 3.60)	0.349
Intervention	38.1 (8.2)	38.4 (9.5)	39.5 (9.8)	0.29 (-4.21, 4.79)		1.40 (-3.84, 6.65)	
Physical function							
Right handgrip, kilopascal							
Placebo	16 (8)	15 (8)	17 (8)	-0.84 (-5.04, 3.37)	0.416	0.78 (-4.28, 5.83)	0.750
Intervention	17 (9)	18 (9)	16 (9)	1.50 (-2.29, 5.29)		-0.28 (-4.56, 3.99)	
Left handgrip, kilopascal							
Placebo	15 (7)	15 (9)	16 (9)	-0.86 (-4.94, 3.22)	0.941	0.25 (-4.42, 4.92)	0.623
Intervention	16 (9)	15 (9)	15 (7)	-1.07 (-4.80, 2.67)		-1.27 (-5.22, 2.69)	
6 min walking test, metres							
Placebo	167 (87)	189 (128)	236 (127)	22.5 (-33.8, 78.8)	0.761	69.5 (-1.34, 140)	0.359
Intervention	180 (115)	214 (118)	206 (118)	34.5 (-19.6, 88.6)		26.7 (-33.1, 86.5)	
Up & go test, seconds							
Placebo	24 (24)	21 (23)	15 (15)	-3.48 (-14.0, 7.01)	0.620	-8.71 (-19.1, 1.64)	0.782
Intervention	21 (25)	15 (11)	16 (11)	-7.05 (-16.6, 2.52)		-6.81 (-15.7, 2.06)	
Barthel Index, score							
Placebo	16 (3)	16 (4)	17 (4)	0.07 (-1.74, 1.88)	0.989	0.96 (-1.45, 3.38)	0.609
Intervention	16 (3)	16 (4)	16 (5)	0.09 (-1.58, 1.75)		0.16 (-1.84, 2.16)	
Karnofsky Performance Scale Index, score							
Placebo	63 (8)	66 (11)	69 (13)	2.77 (-2.07, 7.61)	0.960	6.63 (-0.67, 13.9)	0.371
Intervention	63 (9)	66 (11)	66 (14)	2.60 (-1.85, 7.05)		2.37 (-3.64, 8.39)	
London Handicap Scale, score							
Mobility							
Placebo	3.9 (1.0)	3.6 (1.0)	3.4 (1.2)	-0.30 (-0.79, 0.18)	0.990	-0.49 (-1.10, 0.13)	0.464
Intervention	3.7 (1.0)	3.4 (1.0)	3.5 (1.0)	-0.30 (-0.74, 0.14)		-0.19 (-0.70, 0.31)	
Physical independence							
Placebo	3.5 (0.8)	3.4 (1.0)	3.3 (1.2)	-0.05 (-0.48, 0.39)	0.790	-0.15 (-0.80, 0.50)	0.876
Intervention	3.4 (0.8)	3.5 (0.9)	3.2 (1.2)	0.03 (-0.37, 0.43)		-0.22 (-0.75, 0.32)	
Social integration							
Placebo	2.0 (0.8)	2.1 (0.7)	1.9 (0.9)	0.08 (-0.29, 0.45)	0.418	-0.09 (-0.61, 0.43)	0.229
Intervention	2.1 (0.8)	2.0 (0.7)	2.4 (0.9)	-0.13 (-0.46, 0.21)		0.32 (-0.11, 0.75)	
Occupation							
Placebo	3.6 (0.9)	3.5 (1.0)	3.4 (1.1)	-0.05 (-0.46, 0.36)	0.997	-0.13 (-0.67, 0.42)	0.846
Intervention	3.7 (0.7)	3.6 (0.8)	3.5 (0.9)	-0.05 (-0.42, 0.33)		-0.20 (-0.65, 0.26)	

Environmental orientation							
Placebo	1.7 (0.5)	2.0 (0.8)	2.3 (1.2)	0.28 (-0.06, 0.62)	0.158	0.53 (0.04, 1.02)	0.266
Intervention	1.9 (0.7)	1.8 (0.7)	2.0 (0.6)	-0.05 (-0.36, 0.26)		0.18 (-0.23, 0.58)	
Economic sufficiency							
Placebo	3.6 (1.0)	3.5 (1.1)	3.8 (1.0)	-0.12 (-0.62, 0.39)	0.701	0.19 (-0.40, 0.77)	0.725
Intervention	3.4 (1.0)	3.4 (1.1)	3.7 (1.0)	0.02 (-0.45, 0.48)		0.32 (-0.17, 0.81)	
Total handicap							
Placebo	3.0 (0.5)	3.0 (0.6)	3.0 (0.8)	-0.03 (-0.30, 0.24)	0.789	-0.03 (-0.43, 0.38)	0.817
Intervention	3.0 (0.5)	2.9 (0.6)	3.0 (0.7)	-0.08 (-0.33, 0.17)		0.04 (-0.30, 0.37)	
Elderly mobility score							
Placebo	15 (5)	14 (6)	16 (6)	-0.84 (-5.12, 3.44)	0.495	1.44 (-3.35, 6.23)	0.784
Intervention	13 (7)	15 (7)	16 (7)	1.20 (-2.90, 5.29)		2.32 (-2.00, 6.64)	
Intracellular GSH, µmol							
Placebo	1013 (421)	954 (286)	992 (412)	-59.2 (-240, 121)	0.352	-21.2 (-224, 181)	0.773
Intervention	997 (383)	1054 (415)	937 (267)	57.0 (-110, 224)		-60.6 (-241, 120)	

Abbreviations: SD, standard deviation; CI, confidence interval; GSH, glutathione
[a]Mean change was calculated as the week 4/week 8 value minus the baseline value.
[b]P value of interaction (time x treatment) was tested using linear mixed models.

muscle loss [30]. These metabolic derangements may interfere and limit the effect of WP supplementation in this subgroup of patients. Second, included patients may be at different phases of cachexia, namely pre-cachexia, cachexia and refractory cachexia. It has been suggested that cachexia cannot be treated with nutrition alone but rather a combination of physical exercise to counteract inactivity atrophy and catabolism, pharmacological agents affecting metabolism, and nutritional intervention to secure adequate energy intake [31, 32]. Therefore, the benefits of WP supplementation alone may be limited in extent due to the multifactorial etiology of cancer cachexia. In addition, the advanced stage of the disease and its catabolic effects may have counteracted the positive effect of the WP supplementation [33]. The insignificant effect of WP on our outcome measures may also be explained by a heterogeneous group of patients with different types of cancer and treatments in our study as compared with a homogeneous group of patients with similar types of cancer and treatments [11, 12].

To the best of our knowledge, the present study was the first trial examining the effect of WP supplementation in palliative care patients with advanced cancer. Several limitations should be acknowledged. First, the low statistical power due to the small sample size may reduce the chances of detecting the significant differences in outcome measures. However, the high drop-out rate as a result of progressive disease and clinical deterioration has been reported in other palliative oncology trials [34]. Second, the duration of the intervention was 8-week, which was relatively short compared with other studies. Third, we did not have strict inclusion criteria in terms of anorexia, cachexia, nutritional status, type of cancer and current therapy in this study as we wanted to test the effectiveness of WP supplementation in a broad population of palliative cancer patients. Therefore, a heterogeneous group of patients may be resulted and dilute the treatment effect [35]. Fourth, lean mass was measured using BIA which may lack the accuracy to detect small changes in body composition over time compared with computerized tomography [36].

CONCLUSION

In conclusion, the present study did not show an improvement in QOL, anthropometry, physical function and intracellular GSH level through an 8-week WP supplementation in Chinese palliative care patients with advanced cancer. It appears that current findings did not support the use of WP supplementation in advanced cancer patients. In light of the small sample size, larger trials with a more homogeneous population are warranted to clarify its effectiveness in this population.

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