RESEARCH ARTICLE

Editorial Process: Submission:12/02/2021 Acceptance:07/18/2022

A Double-Blind, Placebo-Controlled Randomized Phase IIa Study: Evaluating the Effect of Curcumin for Treatment of Cancer Anorexia–Cachexia Syndrome in Solid Cancer Patients

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Abstract

Objective: We aim to investigate the effect of curcumin on preventing cancer anorexia–cachexia syndrome (CACS) via through mechanism of inhibition on NF-kB signal pathway. Outcome measurement for primary end point was improvement of body tissue composition, and the secondary end points were body weight and body mass index, hand grip muscle strengthening, and safety. **Methods:** This is randomized, double-blind, placebo-controlled phase ll a study, 33 patients with CACS in solid malignancy were enrolled and randomized in 1:1 to receive oral curcumin (at a dose of 800 mg twice daily) or placebo for 8 weeks. **Results:** All parameters of body compositions were not statistically significant different between two groups, which were consist body fat mass [-1.25(SEM 0.87) vs. +0.63(SEM 0.55); p=0.119], skeletal muscle mass [-0.35(SEM 0.60) vs.+0.33(SEM 0.42); p=0.408] and percent body fat [-0.47(SEM 0.95) vs. -0.29(SEM 0.82); p=0.893] including with basal metabolic rate [-13.47(SEM 21.94) vs. +15.30(13.76); p=0.336]. The average of weight loss was also not statistically significant different between two groups. [-1.4 kg(SEM 0.89) in curcumin vs-1.12 kg(SEM 0.73), p=0.810]. Notably, patient with curcumin had less reduction of hand-grip muscle strength on both hands [Rt. handed: -2.47 in curcumin vs. -5.36 in placebo; p=0.318] [Lt. handed: -1.98 vs. -5.43; p=0.317], and basal metabolic rate than placebo group. Most adverse events were grade 1 on both groups similarly. **Conclusion:** Curcumin was not shown to be superior to placebo with regard to increasing the body composition in cancer patients with CACS. However, curcumin might show some clinical benefits, including slow progression of hand-grip muscle strength loss, and basal metabolic rate. Further investigations should be explored.

Keywords: Cancer anorexic cachexia- cancer cachexia- curcumin

Asian Pac J Cancer Prev, **23 (7)**, 2333-2340

Introduction

Cancer anorexia–cachexia syndrome (CACS) is usually found in advanced cancer patients. CACS is a multifactorial process which comprises skeletal muscle and adipose tissue loss which may be compounded by anorexia and a dysregulated metabolic state. Increasing basal energy expenditure and alternating in metabolism of protein, fat and carbohydrate occur after a dysregulated metabolic state. As a result, patients resist to conventional nutritional support, and they will develop progressive weight loss. The sequences of CACS have an effect on poor quality of life, poor physical function, and limited survival in cancer patients.

CACS involves multiple pathways including procachectic and proinflammatory signals from tumor cells, systemic inflammation in the host, and widespread metabolic changes. Tumor produced procachectic factors including proteolysis-inducing (Todorov et al., 1996) and Lipid-mobilizing factors (Hirai et al., 1998). Proteolysis-inducing factors (PIF) have been identified in the urine of weight losing cancer patients such as pancreatic, colon, lung, ovarian, breast, and liver cancer (Skipworth et al., 2007). PIF signals via nuclear factor kappa B (NF kB) and STAT3 pathways were found in animals (Watchorn et al., 2001). Stimulation of these pathways induces proteolysis in muscles via the ubiquitin-proteasome pathway (Whitehouse and Tisdale, 2003) and in hepatocytes, results in production of interleukin-6 (IL-6), interleukin-8 (IL-8) and C-reactive protein (CRP) (Watchorn et al., 2001). Further attempts to correlate PIF levels and outcomes have not shown any correlation (Wieland et al., 2007). Therefore, the proposed mechanisms of PIF have not yet been validated in humans.

Inconsistencies in the definition of cachexia have limited the epidemiological characterization of the

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condition leading to a poor understanding of the etiology of the condition, and there has been slow progress in identifying therapeutic agents and trialing them in the clinical setting (Maltoni et al., 2005; O'Gorman et al., 1999; Tisdale et al., 2002). Understanding the complex interplay of tumor and host factors may uncover new therapeutic targets. Among orexigenic agents, megestrol acetate is by far the most widely prescribed and at least 15 randomized controlled clinical trials have demonstrated that this drug, at doses ranging from 160–1,600 milligram per day significantly improves appetite with respect to placebo (L´opez et al., 2004). In 2005, there was a Cochrane meta-analysis by E. G. Berenstein and Z. Ortiz reported that megestrol acetate improves weight gain and appetite in cancer patients (Garcia et al., 2013). Although this increase in appetite is very desirable for both patients and their care giver, in most of these trials no definitive improvement in global quality of life was observed (Garcia et al., 2013). Moreover, for example another pharmacological options are corticosteroids, nandrolone decanoate, cannabinoids (dronabinol), cyproheptadine, eicosapentaenoic acid (EPA), melatonin, pentoxifylline and non-steroid anti-inflammatory drugs etc, that those medication not established hypothetical mechanism of action including insufficient evidence to clinical effect (Donohoe et al., 2011).

Currently, research has focused on supplements containing specific, extracted chemicals believed to be the anti-cancer candidates and although some studies have shown benefits (Schroder et al., 2005). Previous data shown efficacy of curcumin (diferuloylmethane) that is derived from turmeric (curcuma longa), in addition curcumin have shown that it suppresses nuclear factor kappa B (NF kB) activation (Singh and Aggarwal, 1995) as well as a multitude of other biological signals pertinent to cancer (Aggarwal et al., 2006). Recent data showed that treatment of human cancer cells with curcumin leads to down-regulation of constitutive nuclear factor kappa B (NF kB)activation, suppression of NF kB-regulated gene products and inhibition of cell growth associated with apoptosis. What is more curcumin can modulate multiple cell signaling pathways.

From various trial in human and animal model about curcumin is shown some efficacy. For in vivo studies, they induced progressive muscle wasting in mice by implanting the MAC16 colon tumor. The result indicates that low doses of curcumin c3 (100 milligrams per kilograms body weight) was able to prevent weight loss in mice bearing MAC16 tumors whereas higher doses of curcumin c3 (250 milligrams per kilograms body weight) resulted in approximately 25 percent weight gain as compared with the placebo-treated animals. Additionally, the effect of curcumin c3 on preventing and reversing cachexia was also evident by gains in the weight of the gastrocnemius muscle about 30–58 percent and with the increased size of the muscle fibers about 30–65 percent (Siddiqui et al., 2009). Furthermore, curcumin inhibited proteasome complex activity and variably reduced expression of muscle-specific ubiquitin ligases: atrogin-1/ muscle atrophy F-box (MAFbx) and muscle RING finger 1(MURF-1) (Sharma et al., 2004).

Another trial Phase I studies of curcumin in human have shown that this agent can be administered safely at oral doses of up to 8-12 grams per day duration 3 months (Cheng et al., 2001; Gupta et al., 2013; Sharma et al., 2001). There was no dose-limiting toxicity. However, the usefulness of curcumin may be attenuated because of its poor oral bioavailability (Thomas et al., 2014). Some data found a significant short-term, favorable effect on the percentage rise in tumor marker in curcumin compare with placebo. There were no significant differences within the predetermined subgroups of age, treatment category or body mass index (Tisdale, 2009).

Although our understanding of cancer anorexia-cachexia syndrome (CACS)has progressed over the past decade, a lack of a definition, diagnostic criteria, classification and standard of care has impeded advancement in both clinical trials and clinical practice.

Therefore, this study will conduct to solve question that evaluating the effect of oral curcumin for treatment of cancer anorexia–cachexia syndrome in solid cancer patients about body composition includes fat, muscle and water composition, weight change, body mass index, hand grip muscle strengthening and including safety and toxicities.

Materials and Methods

Patients

Patients with a histologically confirmed locally advanced/ advanced stage solid malignancy at any site, weight loss of at least 5% in 12 months or body mass index (BMI) < 20 kg/m^2, and were contained 3 of the following; which were deceased muscle strength, fatigue, anorexia, low fat-free muscle index, and abnormal biochemistry (increased inflammatory markers; CRP or IL-6, Anemia; Hb <12 g/dL, low serum albumin; <3.2 g/ dL), were eligible. Patients were receiving concomitant systemic treatment with chemotherapy or targeted therapy or radiotherapy with palliative intent.

Patients had to be at least 18 years of age, have an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 2, and have adequate hematologic, hepatic, and renal function. The preserved hepatic function was defined as serum total bilirubin less than 2.0 mg/dL, serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) less than 3 times of upper normal limit, except patient with Gilbert's disease and liver metastasis keep serum total bilirubin less than 4.0 mg/dL and serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) less than 5 times of upper normal limit. An adequate renal function was defined as serum creatinine less than 2.0 mg/dL.

Patients with an unstable medical condition or undercurrent illness, including active infections requiring treatment with systemic antibiotics, unstable coagulation disorders, high risk of clinical bleeding, history of hypersensitivity to curcumin, obstructive jaundice were excluded. In addition, pregnant and breast-feeding women were excluded.

Complete eligibility criteria are provided in the study protocol, and all subjects have to giving their written

informed consent before enrollment.

Study design and treatment

This study was a double-blind, placebo-controlled randomized phase lla study. From August 2016 through February 2017, we enrolled 46 patients, of whom 33 underwent 1:1 block of four randomizations by programmed computer-generated (www.randomization.com); 17 patients were randomly assigned to received curcumin at dose of 800 mg twice daily orally and 16 patients were randomly assigned to received placebo. Patients were treated for 8 weeks or discontinuation of treatment owing to adverse effects or for other reasons.

Curcumin and placebo

Curcumin and placebo were provided from THAI HERBAL PRODUCTS CO., LTD in 400 mg per caplet form. Each capsule was contained 240 mg of curcuminoids. The corn starch was ingredient in placebo capsule. The Good Manufacturing Practice (GMP) and quality control standards by mean of International Organization for Standardization (ISO) 9002 were used for all products.

End points and assessments

The primary end point was the body tissue composition consisting of body fat mass, skeletal muscle mass, and percentage of body fat. The hypothesis was higher body tissue composition in patients with curcumin than placebo group. The secondary end points included body weight, body mass index (BMI), hand grip muscle strengthening, and basal metabolic rate. All the patients who underwent randomization were followed for body tissue composition, body weight, body mass index, hand grip muscle strengthening, basal metabolic rate at baseline (week 0) and at the end of treatment (week 8). Safety was assessed by an evaluation of the incidence of clinical adverse events and laboratory variables, which were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 at baseline (week 0) and every 4 weeks until the end of treatment (week 8).

Statistical analysis

Baseline and clinical characteristics were summarized using descriptive statistics. For continuous variable under the normality assumptions were met, means and standard error of means were calculated. For categorical variables, frequency and percentage were used.

All clinical variables were considered statistical significance if p–value was less than 0.05 and statistical tests were chosen as follows:

1. To compare the differences in mean between the two groups, the unpaired t–test was applied.

2. To compare the differences in proportion between the two groups, the z–test was used.

3. To compare the results before and after receiving the treatment under one method in the quantitative variables, the paired t–test was applied.

4. To compare the results before and after receiving the treatment under different methods in the quantitative variables, the general linear model was used.

Demographic and outcome analysis included all the patients who underwent randomization. Safety analysis included all the treated patients (those who received at least one dose of study drug). At the time of the interim, 6 patients had die (18% of the 33 patients' deaths required for the final analysis). The boundary for declaring superiority with respect to the number of body tissue composition at the interim analysis was a p-value of less than 0.05. The protocol specified that if superiority with respect to the number of body tissue composition was shown, the body weight, the body mass index, and hand grip muscle strengthening would then be tested hierarchically at the 5% alpha level. All statistical analysis in this study were performed by using SPSS version 19.

Results

Patients and treatment

Of the 33 patients who underwent randomization, 17 were treated with curcumin and 16 were treated with placebo. The minimum follow-up for assessment was 8 weeks. Eight of 33 patients (24%) were excluded from analysis due to loss to 2nd follow-up, drug intolerance, and no clinical benefit, which were 6 patients, 1 patient, and 1 patient, respectively. Therefore, twenty five patients had completed the study protocol.

The median age of the patients was 58 years. Most patients were men, had an ECOG performance status score of 1, had advanced stage, and were primary lung cancer. All the patients had received systemic treatment on each specific cancer type. The demographic and clinical characteristics of the patients were well balanced between both groups, with slight between group imbalances in the percentages of primary site of cancer, stage of disease, and route of nutrition support. The patients with placebo group had more percentages for using enteral feeding via nasogastric tube, and diagnosis of primary head and neck cancer than patient with curcumin group (Table 1).

Body tissue composition

Eight weeks of follow up to evaluate efficacy of curcumin by using InBody machine, there were slightly decreased in body fat mass, the percentage of fat, and basal metabolic rate in patients with curcumin. All parameters were slightly increased in patients with placebo, except the percentage of body fat that was slightly decreased. When we compared on each parameter between two groups either baseline or last follow up period, all parameters were not statistically significant difference between two groups on both period of measurements (Table 2).

In addition, there were no statistically significant difference in all parameters of body compositions between baseline and follow-up measurement on both treatment groups, which were slightly increased in changing of body fat mass, skeletal muscle mass, and basal metabolic rate in placebo group; meanwhile; there were slightly decreased of all parameters in patients with curcumin group (Table 3).

Table 1. Baseline Characteristics, and Stratification Factors

	Treatment (n*=17)	Placebo (n*=16)	p-value
Age (years) [mean, (SEM**)]	59.3 (3.0)	57.0 (1.9)	0.54
Male Gender (n, %)	12 (70.6)	14 (87.5)	0.4
Primary site of cancer (n, %)			
Lung	8 (47.0)	5 (31.2)	0.48
Head and neck	2 (11.8)	4 (25)	0.40
Other gastroenterology	2 (11.8)	6 (37.5)	0.12
Colorectal	1 (5.9)	0	1.00
Breast	1(5.9)	1(6.2)	1.00
Other	3 (17.6)	0	0.23
Stage of disease (n, %)			
Stage 3	5 (29.4)	3 (18.7)	0.69
Stage 4	11 (64.7)	13 (81.2)	0.44
Other (T1S1I1)	1 (5.9)	0	1.00
ECOG Performance Status (n, %)			
1	13 (76.47)	8 (50)	0.11
2	4 (23.53)	8 (50)	0.11
Route of nutrition support (n, %)			
Oral	13 (76.5)	8 (50)	0.16
Nasogastric tube	3 (17.6)	4 (25)	0.69
Other tube feeding	1 (5.9)	4 (25)	0.17
Enteral nutrition (n, %)			
No	11 (64.7)	9 (56.2)	0.73
Add	6 (35.3)	7 (43.7)	0.73
Palliative surgery (n, %)			
No	17 (100)	13 (81.2)	0.10
Yes	0	3 (18.7)	0.10
Systemic treatment (n, %)			
Yes	15 (88.2)	15 (93.7)	1.00
No	2 (11.8)	1 (6.2)	1.00
Line of chemotherapy			
First line	6 (35.3)	9 (56.2)	0.30
Second line	3 (17.6)	0	0.23
Third line	0	0	NA
Other	1(5.9)	1 (7.2)	1.00
Concurrent chemo radiotherapy	6 (35.3)	5 (31.2)	1.00
No	1 (5.9)	1 (6.2)	1.00
Radiotherapy (n, %)			
Concurrent chemotherapy	5 (29.4)	5 (31.2)	1.00
Palliative	2 (11.8)	2 (12.5)	1.00
Definitive	0	0	NA
No	10 (58.8)	9 (56.2)	1.00

*n, number of patients; **SEM, Standard Error of means; **ECOG, Eastern Cooperative Oncology Group

Body weight (BW) and body mass index (BMI)

Changing in body weight and body mass index (BMI) between baseline and follow up period on each group was summarized in Table 4. An average of two evaluations per patient, patients with curcumin had weight loss for 1.4 kgs and lost 1.12 kgs in 8 weeks for patients with placebo, which there was not statistically significance different between both groups (p-value=0.810). Similarly, the body mass index (BMI) was declined in 8 weeks on both groups, which were 0.5 kg/m^2 in curcumin group, and 0.44 kg/m^2 in placebo group.

Hand-grip muscle strength

At baseline and follow up period, an average of hand-grip muscle strength in kilograms on both right-handed and left-handed in patients with curcumin showed slightly decreased in 8 weeks, which the different number on right-handed and left-handed were minus 2.47 kgs -, and minus 1.98 kgs decrease at follow up peroid, respectively. In placebo group, hand-grip muscle strength on both hands were more declined than patients with curcumin, but it was not statistically significant different in kilograms (p-value=0.32) (Table 5).

Safety

Treatment-related adverse events, including both nonhematologic and hematologic adverse events were similar between two groups. In the curcumin group, 11.8% of the patients had only events of grade 1, which were 5.9% had grade 1 nausea/vomiting, and another 5.9% had grade 1 asthenia. In placebo group, 18.7% of the patients had events of grade 1, which were asthenia (in 12.5% of the patients), and nausea/vomiting (6.2%), respectively. There were no any events of grade 2 to grade 5 or serious adverse event in both groups (Tables 6-7). Adverse events of special interest based on prior studies of curcumin, irrespective of attribution to study treatment, none had event of any grade of gall bladder problem, bile duct obstruction, bleeding disorder, and skin reaction.

Treatment-related adverse events led to treatment interruption, and discontinuation were not statistically significant different between two groups (for dose interruption; 29.4% in curcumin group vs 31.2% in placebo, p-value=1), (for treatment discontinuation; 5.9% in curcumin group vs 12.5% in placebo group, p-value=0.6). Treatment-related events leading to discontinuation was modest between two groups (1 patient in curcumin group, 2 patients in placebo group). The most common treatment-related events leading to discontinuation were nausea/ vomiting and asthenia in curcumin group (in 5.8% and 5.8%, respectively). Two additional patients in placebo group discontinued treatment owing to asthenia (one of whom had drug insoluble problem which was difficult to feed via through NG tube).

Two deaths in the curcumin-treated patients, including one patient died from cancer progression, and another died from septic shock without neutropenia. All of four patients in control group died from disease progression.

Complete blood count, renal and liver function

Table 2. Body Composition Parameters between Both Groups at Baseline and Follow up Period

Parameters	Baseline measurements		p-value	Follow-up measurements		p-value
	Curcumin mean, (SEM***)	Placebo mean, (SEM***)		Curcumin mean, (SEM***)	Placebo mean, (SEM***)	
Body fat mass (kgs*)	52.3 (2.7)	54.2 (3.1)	0.65	51.6 (2.8)	56.5 (4.6)	0.35
Skeletal muscle mass (kgs*)	22.2 (0.9)	23.7 (1.2)	0.32	22.2 (1.2)	25.3 (1.6)	0.13
Body fat (percent)	19.3 (2.4)	17.4 (2.2)	0.58	18.5 (2.4)	15.0 (2.7)	0.36
Basal metabolic rate (kcals**)	1270.4 (35.3)	1326.7 (44.5)	0.32	1268.0 (43.0)	1388.1 (61.2)	0.11

*kgs, kilograms; **kcals, kilocalories; ***SEM, Standard Error of means

Table 3. The Difference of All Body Composition Parameters between Baseline and Follow up Period on each Group

Different (calculated by pre-post)	Body fat mass (kgs*) mean,(SEM***)	Skeletal muscle mass (kgs*) mean, (SEM***)	Body fat (percent) mean, (SEM***)	Basal metabolic rate (kcals**) mean, (SEM***)
Treatment	-1.25 (0.87)	-0.35 (0.60)	-0.47 (0.95)	-13.47 (21.94)
Controls	+0.63 (0.55)	+0.33 (0.42)	-0.29 (0.82)	+15.30 (13.76)
P-value	0.119	0.408	0.893	0.336

*kgs, kilograms; **kcals, kilocalories; ***SEM, Standard Error of means

Table 4. Weight and BMI Values for Patients in Both Study Groups at the 2 Time Points

		Weight (Kgs***)			BMI (kgs/m^2****)		
		mean	(SEM)	p-value	mean	(SEM)	p-value
Treatment	Baseline	52.29	(2.70)		19.06	(0.86)	
	Follow up	50.89	(2.64)	0.137*	18.56	(0.86)	0.134*
	Variation	-1.40	(0.89)		-0.50	(0.31)	
Control	Baseline	54.25	(2.83)	0.145*	19.51	(0.72)	
	Follow up	53.13	(3.21)		19.07	(0.84)	0.113*
	Variation	-1.12	(0.73)	0.810**	-0.44	(0.26)	0.886**

* p values for the comparison between baseline and follow up at same group; ** p values for the comparison between the variations in the Treatment and Control groups; ***kgs, kilograms; **** kgs/m^2, kilograms per meter square

test were evaluated, which there were no statistically significant different of values at baseline and follow up period between two groups, except serum creatinine. Serum creatinine was significantly increased at 8 weeks in patient with curcumin when compared to placebo group, however, an elevated serum creatinine level in curcumin group was not even adverse event of grade 1 acute kidney injury.

Table 5. Hand-Grip Muscle Strength Alterable in both Groups at Baseline and Follow up.

	Treatment	Control	P-value
Right-sided, mean, (SEM)			
Baseline	26.62 (1.92)	24.25 (2.25)	0.428
Follow up	24.44 (2.37)	19.39 (3.77)	0.269
Different value	-2.47 (1.46)	-5.36 (2.54)	0.318
Left-sided, mean, (SEM)			
Baseline	23.62 (1.66)	23.38 (2.19)	0.928
Follow up	21.97 (2.41)	18.07 (3.59)	0.365
Different value	-1.98 (1.24)	-5.43 (3.11)	0.317

Table 6. Adverse Events in the As-Treated Population*

Events	Curcumin number of patient (percent)	Placebo number of patient (percent)	p-value
Treatment-related event			
Event leading to dose interruption	5 (29.4)	5 (31.2)	1
Event leading to dose reduction of treatment	0	1 (6.25)	0.485
Event leading to discontinuation of treatment	1 (5.9)	2 (12.5)	0.601
Event occurring in patients in either group			
Nausea and vomit	1 (5.9)	1 (6.2)	1
Asthenia	1 (5.9)	2 (12.5)	0.601
Diarrhea	0	0	NA
Rash or allergic	0	0	NA
Event of interest			
Skin reaction	0	0	NA
Gall bladder problem	0	0	NA
Bile duct obstruction	0	0	NA
Bleeding disorder	0	0	NA

* The as-treated population included all the patients who received at least one dose of study treatment

Table 7. The Different of Laboratory Values at Baseline and Follow up Period in the As-Treated Population on each Treatment Group

Different of value (at baseline and follow up)	Curcumin mean, (SEM*)	Placebo mean, (SEM*)	p-value
Hematologic			
Hemoglobin (gram per deciliter)	-0.79 (0.46)	-0.14 (0.37)	0.274
White blood cell count **(per cubic millimeter)	+664.71(2012.79)	+951.88 (2006.05)	0.92
Platelet count (per cubic millimeter)	-18705.88 (34106.32)	-14062.50 (40446.62)	0.93
Nonhematologic			
Serum creatinine (milligram per deciliter)	+0.04 (0.06)	-0.14 (0.06)	0.045***
Serum total bilirubin (milligram per deciliter)	+0.09 (0.18)	+0.26 (0.30)	0.622
Serum aspartate aminotransferase (AST) (international units per liter)	+8.59 (10.27)	+3.13 (8.01)	0.68
Serum alanine aminotransferase (ALT) (international units per liter)	+13.12 (18.06)	+1.31 (5.82)	0.549
Serum albumin (gram per deciliter)	-0.26 (0.17)	-0.78 (0.35)	0.186

*SEM, Standard Error of means; **Events were attributed to treatment by the investigator and are listed as indicated by the investigator on the case-report form. Although decreased or increased white blood cell count may reflect some condition such as post-chemotherapy or infection process. ***p-value less than 0.05 statistically significant.

Discussion

This study presented constitutes the first clinical evaluation of curcumin in regulating cancer anorexia-cachexia syndrome (CACS). Theoretically, the pathophysiology of cancer cachexia is complex, including decreased secretin of host anabolic hormones, altered host metabolic response with abnormalities in protein, lipid, and carbohydrate metabolism (Aoyagi et al., 2015). Additionally, pro-inflammatory cytokines and cachectic factors such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), IL-6, interferon-gamma, and NF-kappa B, have been postulated to play role in the etiology of cancer cachexia via through transporting across the blood brain barrier at the luminal surface of brain endothelial cells causing release of substances that affect appetite. Therefore, CACS induced by pro-inflammatory cytokines and cachectic factors can be blocked by inhibitors of cyclooxygenase, suggesting that a curcumin, may be the direct mediator of appetite suppression (Ireson et al., 2001).

This study was randomized phase II study involving all kinds of solid cancer patients with cancer anorexia–cachexia syndrome (CACS). The hypothesis was that curcumin will increase body compositions and body weight in patients with solid malignancy and CACS when compared to placebo after adjusting by age, gender, primary site of cancer, stage of cancer, performance status, and supplementary nutrition support. The results from the study allowed three conclusions, which will help to optimize the design of future clinical study of curcumin: (1) curcumin was not statistically significant improve in body compositions and body weight comparing to placebo; (2) curcumin may cause clinical benefit in term of hand grip muscle strength and slow progress of CACS by decreasing in basal metabolic rate and preventing the decline in serum albumin (3) oral administration of curcumin for two months at dose of up to 2 grams daily appeared safe and no serious adverse event.

Our first conclusion for an efficacy of curcumin in patients with CACS, the body compositions including body fat mass, skeletal muscle mass were slightly decreased in curcumin group; meanwhile, their parameters were slightly increased in placebo group. Regarding to low systemic bioavailability of curcumin and unknown disposition of hepatobiliary system for curcumin in human (Dhillon et al., 2008), the optimum dose of curcumin requires to increase to achieve therapeutic target, which our study used total dose of curcumin at 1.6 grams per day. Attenuation of weight loss by curcumin in the setting of pancreatic cancer was previously described in animal models only. An in vivo study for cancer cachexia model, MAC16 colon tumor was injected in bearing mice, which the result showed administration of 100 or 250 milligrams per kilogram dose of curcumin attenuated weight loss in the animals (Siddiqui et al., 2009). However, in fact, the animal models are not able to translate to human clinical practice perfectly (Dhillon et al., 2008). Although, many clinical studies of oral curcumin incorporating larger enrolled populations will be required to establish the safety of chronic administration, but some published clinical studies showed achieved targeted dosage of curcumin up to range 4 - 8 grams per day for cancer treatment (Shoba et al., 1998; Epelbaum et al., 2008). Another study demonstrated curcumin levels at 2 grams were transiently detectable in serum of healthy enrolled population, and coingestion with pepper constituent l-piperroylpiperidine increased curcumin serum AUC by factor of 20 (Kotler, 2000). Therefore, each curcumin analogue might have different activities and potencies. Additionally, patients with curcumin group in this study had 50% less for insertion of tube feeding than patients with placebo group (4 patients in curcumin vs 8 patients in placebo), which patients with placebo may be sufficiently received total calories and nutrition support more than patients with curcumin. Some studies showed that nutrition support either via parenteral route alone or tube feeding are able to increase fat mass but did not impact on survival (Khal et al., 2005).

For hand-grip muscle strengthening assessment, we found that the reduction of hand-grip muscle strengthening both hands in patients with placebo had estimated 2.5

times lower than patients with curcumin. Curcumin may decrease protein catabolism led to slow down on net loss of muscle mass, and alleviate process of proteolysis via through inhibit the ATP ubiquitin-dependent pathway (Strasser, 2008). Decreased muscle strength may help distinguish between cancer cachexia from other causes in cancer patients, which it could be used as a diagnostic criterion with higher sensitivity and specificity for cancer cachexia (Ni and Zhang , 2020). Generally, CACS is often associated with an elevated basal metabolic rate, despite a decrease in physical and total energy expenditure (Deodhar et al, 1980). Interestingly, the basal metabolic rate in patients with curcumin was more declined than patients with placebo, which may determine that curcumin could stop toward process of cancer cachexia.

Our last conclusion regarding to the safety of curcumin is consistent with many previous publications of curcumin in clinical studies. For example, two clinical trials studied on the efficacy of curcumin in patients with arthritis, which results showed that daily dosages of 1.2-2.1 grams of curcumin for 2-6 weeks did not cause adverse effects (Satoskar et al., 1986; Cheng et al., 2001). Moreover, a pilot study found that tablets of turmeric extract containing 99.8% curcumin did not cause any treatment-related adverse event at 8 grams per day. In our study, some patients with curcumin had mild adverse events (grade I) such as abdominal discomfort, nausea and vomiting. Patients with curcumin had statistically significant increase in serum creatinine compared to placebo, however, no one got worse to impaired kidney function or acute kidney injury and discontinued (or interrupted) the primary treatment.

This study was, to our knowledge, the first randomized phase II study with such a small number of enrolled patients and wide range of specific treatment on each primary cancer. A small sample size in this study increased the likelihood of a type II error skewing the results, which decreased the power of the study. However, there was some evidence of an effect, but the results had just lacked statistical significance. There required to be a careful balance between not dismissing outright what could be a real effect and also not making undue claims about the effect. Moreover, this study might produce false-positive results, or overestimating the magnitude of an association. The results required some considerations as followings; (1) there was heterogeneity of enrolled population such as site of primary cancer, specific on cancer treatment, (2) It was difficult to control total calories intake or nutrition status between both groups equally, and imbalance for route of feeding between two groups, (3) there are factors affecting the results of body composition such as older age group trends to get more fat and muscle loss than younger age group, poor performance status.

In conclusion, In spite of lacking significant in clinical benefit of curcumin on increasing of body compositions and body weight, this pilot study of curcumin in all kinds of solid cancer patients with CACS demonstrated that curcumin inhibited process of CACS via reduction of basal metabolic rate and slow down the progression of hand-grip muscle strength loss. Doses of up to 1.6 grams per day of curcumin can be administered to patients with CACS for up to 8 weeks safely. Moreover, this study provided information that may help optimize the clinical trial design of curcumin, including studying on the systemic effects of higher dose levels as potential agent for cancer cachexia treatment in the future. Nuclear factor kappa B (NF-kB) levels merit further exploration as potentially suitable predictive biomarker for CACS treatment with curcumin.

Author Contribution Statement

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Aornchuma Chaiworramukkul and Naiyarat Prasongsook. The first draft of the manuscript was written by Aornchuma Chaiworramukkul and Naiyarat Prasongsook, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

General

The authors are grateful to the Office of research Development, Phramongkutkao Hospital, Division of Medical Oncology, Department of Medicine, Phramongkutklao Hospital, and PMK Cancer Center for supporting this study.

Funding Statement

This study received funding from Department of Medicine, Phramongkutklao Hospital, Bangkok, Thailand.

Approval

This study was conducted according to ICH-GCP guidelines and the Declaration of Helsinki. The study protocol was approved by Institutional Review Boards Royal Thai Army Medical Department, Phramongkutklao College of Medicine (protocol number: R008h/63).

Ethical Declaration

Institutional Review Boards Royal Thai Army Medical Department, Phramongkutklao College of Medicine, Phramongkutklao College of Medicine, Bangkok, Thailand.

Data Availability

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Study Registration

This study was registered with Thai clinical Trials Registry (TCTR) (www.thaiclinicaltrials.org), number TCTR20220521003, and was completed.

Conflict of Interest

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other

equity interest; and expert testimony or patent-licensing arrangement), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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