Clinical Studies on the Treatment of Cancer Cachexia with Megestrol Acetate plus Thalidomide

Hong-Sheng Wen Xu Li Yu-Zhu Cao Cui-Cui Zhang Fang Yang Yu-Ming Shi
Li-Ming Peng

Oncology Department, Ningbo Development Zone Center Hospital, Ningbo, PR China

Key Words

Cancer-related anorexia/cachexia syndrome · Megestrol acetate · Thalidomide

Abstract

Background: The management of cancer-related anorexia/cachexia syndrome (CACS) is a great challenge in clinical practice. To date, practice guidelines for the prevention and treatment of CACS are lacking. The authors conducted a randomized study to confirm the effectiveness and safety of treatment of CACS utilizing megestrol acetate (MA) plus thalidomide. **Methods:** One hundred and two candidates with CACS were randomly assigned to two treatment groups (trial group and control group): the trial group received MA (160 mg po, bid) plus thalidomide (50 mg po, bid), while the control group received MA (160 mg po, bid) alone. Treatment duration was 8 weeks. **Results:** Analysis of the trial group demonstrated a significant increase from baseline in body weight ($p < 0.01$), quality of life ($p = 0.02$), appetite ($p = 0.01$), and grip strength ($p = 0.01$), and a significant decrease in fatigue, Glasgow Prognostic Score ($p = 0.05$), Eastern Cooperative Oncology Group performance status ($p = 0.03$), IL-6 ($p < 0.01$), and tumor necrosis factor- α ($p = 0.02$). In contrast, in the control group, endpoints with a significant improve-

ment from baseline included body weight ($p < 0.02$) and appetite ($p = 0.02$). The mean changes in the endpoints from baseline in the trial group were significantly greater compared with the control group: in the primary endpoints, body weight ($p = 0.05$), fatigue ($p < 0.01$) and quality of life ($p = 0.01$), and in the secondary endpoints, grip strength ($p = 0.05$), Glasgow Prognostic Score ($p = 0.02$), Eastern Cooperative Oncology Group performance status ($p = 0.02$), IL-6 ($p < 0.01$) and tumor necrosis factor- α ($p = 0.01$). Toxicity was found to be relatively negligible in both groups. **Conclusion:** A combination regimen of MA and thalidomide is more effective than MA alone in the treatment of CACS.

Copyright © 2013 S. Karger AG, Basel

Introduction

‘Cancer-related anorexia/cachexia syndrome (CACS)’ is a common syndrome of advanced cancers characterized by anorexia, tissue wasting and loss of body weight accompanied by a decrease in muscle mass and adipose tissue and by poor performance status that often precedes death [1]. The prevalence of CACS increases from 50 to 80% before death, and in more than 20% of cancer patients, it is the cause of death [1].

The management of CACS is a great challenge in clinical practice. To date, despite several years of coordinated efforts in basic and clinical research, practice guidelines for the prevention and treatment of CACS are lacking. At present, megestrol acetate (MA) is the common medication used in CACS treatment, in spite of the limited effectiveness.

MA, also known as 17 α -acetoxy 6-dehydro 6-methylprogesterone, is a steroidal progestin and progesterone derivative. MA is used mainly as an appetite stimulant in a variety of conditions and as an antineoplastic agent in the treatment of breast, endometrial and prostate cancers [2]. When given in relatively high doses, it can substantially increase appetite in most individuals, even in those with advanced cancer, and is often used to boost appetite and induce weight gain in patients with cancer or HIV/AIDS-associated cachexia [3].

The underlying mechanism of CACS may be a chronic, low-grade, tumor-induced activation of the host immune system, accompanied by the chronic overproduction of cytokines, such as interleukin (IL)-1 β , IL-6 and tumor necrosis factor- α (TNF- α). Chronic administration of the proinflammatory cytokines, both alone and in combination, is capable of reproducing the different features of CACS. High serum levels of these cytokines have been found in cancer patients, which seem to correlate with progression of the tumor [4]. Therapeutic strategies based on either blocking their synthesis or their action was effective in CACS [5].

Thalidomide has numerous effects on the immune system of the body, including potential anticancer and anti-inflammatory activities. At present, this drug is approved for multiple myeloma and currently used experimentally to treat various cancers, dermatological, neurological and inflammatory diseases [6–8]. The clinical use of thalidomide in CACS is still controversial despite some researches indicating that orally administered thalidomide could improve CACS symptoms and patient quality of life (QoL) [9, 10].

The main purpose of CACS treatment is to improve the 'core' symptoms. Thus, the authors selected body weight, fatigue and QoL as coprimary endpoints. Appetite, proinflammatory cytokines, Glasgow Prognostic Score (GPS), Eastern Cooperative Oncology Group performance status (ECOG PS) and grip strength were taken as the secondary endpoints.

To the authors' knowledge, few studies address the treatment of CACS with thalidomide combined with MA. On the basis of this, the authors carried out a randomized clinical study to test the efficacy and safety of integrated

oral treatment of CACS with MA and thalidomide. Based on the collective authors' clinical experience, the majority of patients cannot tolerate thalidomide >100 mg/day. Consequently, thalidomide 50–100 mg/day has been found to be effective in clinical practice. Therefore, thalidomide 100 mg/day therapy was adopted in this trial.

Patients and Methods

Study Design

A total of 102 patients were recruited by the Department of Oncology, Ningbo Development Zone Center Hospital (NDZCH) between January 2010 and April 2012. Eligible patients were randomized to receive one of two treatment arms by computer-generated, mixed blocks of 2, 4, 6 and 8 allocation schedules. The protocol was approved by the NDZCH Ethics Committee. Procedures were in accordance with the Helsinki Declaration.

Eligibility Criteria

Eligibility criteria included: (1) patients aged ≥ 18 years, with a histologically diagnosed advanced-stage tumor at any site; (2) loss of >5% of pre-illness or ideal body weight (body mass index) in the previous 3 months; (3) a life expectancy ≥ 4 months; (4) patients could be receiving concomitant chemotherapy and/or palliative supportive care.

Exclusion Criteria

Exclusion criteria were: (1) women of child-bearing age; (2) patients with a mechanical obstruction to feeding; (3) medical treatments inducing significant changes in patient metabolism or body weight; (4) history of thromboembolism; (5) history of hypertension or diabetes mellitus.

Intervention

Patients who met the eligibility criteria were randomly assigned into one of two groups. (1) The clinical trial group: MA (Gerui Pharmaceutical Co. Ltd., Shandong province, PR China) 160 mg per os, twice daily, plus thalidomide (Changzhou Pharmaceuticals, Jiangsu province, PR China) 50 mg per os, twice daily (treatment duration 8 weeks); (2) the control group: MA (Gerui Pharmaceutical Co.) 160 mg per os, twice daily (treatment duration 8 weeks).

Efficacy Endpoints

The efficacy endpoints were evaluated prior to treatment and at 8 weeks, following treatment completion.

Primary Endpoints

Body weight was measured with the RGZ-120-RT body weight scale (Wuxi Weight Co. Ltd., Jiangsu province, PR China). The body weight scale was used in accordance with the directions supplied by the manufacturer. Body weight was measured 3 times a day before meals (breakfast, lunch and dinner). An average value of the 3 body weight measurements was adopted.

Fatigue was evaluated with the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) scale [11]. The MFSI-SF is a 30-item self-report measure designed to assess multidimensional aspects of fatigue. Items are rated on a 5-point scale, and

respondents report on how true each statement was for them during the previous week (0 = not at all; 4 = extremely). Scores are added to obtain subscale scores that included general fatigue, emotional fatigue, physical fatigue, mental fatigue, and vigor. The vigor subscale score was subtracted from the sum of the 4 fatigue subscales to yield a total fatigue score. Subscale scores range from 0 to 24, and MFSI-SF total scores range from 24 to 96, with higher scores indicating increased fatigue.

QoL was assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [12] which includes 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea and vomiting, and pain), 6 single items (dyspnea, insomnia, anorexia, constipation, diarrhea, and financial impact), and 1 global QoL scale.

The questionnaire employs a 1-week time frame and a mix of dichotomous response categories ('yes/no'), 4-point Likert scale type responses (ranging from 'not at all' to 'very much'), and 7-point response scales (numbered visual analogue scales). All scale and single item scores of the QLQ-C30 were linearly transformed to a 0–100 numerical scale.

Secondary Endpoints

Appetite was evaluated with 10-point response scales (numbered visual analogue scales).

Grip strength was assessed using a dynamometer (Tiancheng Hydraulic Hand Dynamometer, Shanghai, PR China). The dynamometer was used according to the manufacturer's directions. Maximal grip strength was measured 3 times using either the patient's right or left hand. The mean value of these 6 maximal grip strength measurements was adopted.

Serum levels of IL-6 or TNF- α were measured by enzyme-linked immunosorbent assay (ELISA) kit (Jingmei Immunotech Co. Ltd., Shenzhen, PR China). A 4-ml venous blood sample was drawn from study participants in the morning before breakfast, centrifuged for 10 min (1,680 rpm) in 4°C and preserved at -20°C. Assessment of serum levels of cytokines (IL-6 and TNF- α) were evaluated by ELISA assay using monoclonal antibodies for two different epitopes of the cytokine molecules. The absorbance of the sample was analyzed by a spectrophotometer at 450 nm.

The GPS was given as follows [13]: albumin >32 g/l and C-reactive protein (CRP) <10 mg/l, GPS 0; albumin <32 g/l or CRP >10 mg/l, GPS 1; albumin <32 g/l and CRP >10 mg/l, GPS 2.

Performance status (PS) was used according to the ECOG PS scale.

Safety Endpoints

Adverse events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTC 3.0).

Statistical Analyses

Differences between groups at baseline were analyzed by the χ^2 test for categorical variables and by Student's *t* test (or Wilcoxon's rank sum test when appropriate) for continuous variables in the stratification factors including age, sex, body weight, weight loss, tumor site, stage, ECOG PS, GPS and palliative chemotherapy. Student's *t* test was conducted to compare both treatment groups in terms of changes in primary endpoints before and after treatment (8 weeks versus baseline). The benefit obtained for endpoints

in each group (difference between baseline values and values after treatment) was assessed using a paired Student's *t* test. The significance of *p* values ($p \leq 0.05$) was chosen. All analyses were carried out with two-sided tests using a 5% type I error rate. SPSS version 17.0 (SPSS Inc., Chicago, Ill., USA) was used.

Sample Size Calculation

Hypothesizing a difference between treatment groups of 10% and considering an α type error of 0.05 and a β type error of 0.10, 46 patients needed to be enrolled in each of the two treatment groups.

Results

Clinical Characteristics

A total of 102 patients were recruited by the Department of Oncology, NDZCH, between January 2010 and April 2012 (fig. 1). The two groups consisted of patients comparable at baseline of the most common stratification factors (table 1). The percentage of dropouts was similar between the two groups; 5 from the trial group and 4 from the control group due to thromboembolism or edema. Ninety-three patients went through the clinical trial, 46 in the trial group and 47 in the control group.

Efficacy Endpoints

Comparison before and after Treatment

For patients in the trial group, comparisons were as follows (table 2): fatigue was significantly improved ($p = 0.01$), appetite significantly increased ($p = 0.01$), body weight increased ($p < 0.01$), both IL-6 and TNF- α decreased ($p = 0.01$ and 0.02 , respectively), GPS and ECOG PS score decreased ($p = 0.05$ and 0.03 , respectively), grip strength increased ($p = 0.01$), and QoL improved ($p = 0.02$). In the control group (table 2), appetite was improved ($p = 0.02$) and body weight increased ($p < 0.05$); however, no significant difference was found in IL-6 and TNF- α levels, GPS-PS scores, grip strength and QoL ($p > 0.05$).

Comparison of the Efficacy between the Two Groups

The mean changes in the efficacy endpoints from baseline in the trial group were significantly greater as compared with the control group, in body weight ($p = 0.025$), fatigue ($p < 0.01$), quality of life ($p = 0.01$), grip strength ($p = 0.05$), GPS ($p = 0.02$), ECOG scale ($p = 0.02$), IL-6 ($p < 0.01$), and TNF- α ($p = 0.01$; table 3). A trend for greater increase in appetite ($p = 0.117$) was found in the trial group as compared with the control group.

Fig. 1. Consort diagram.

Toxicity

Toxicities included thromboembolism, edema, somnolence and constipation at a low occurrence rate and did not necessitate discontinuation of the drug. Patients with thromboembolism or edema were withdrawn from the trial. No significant difference in compliance was found between the control group and the trial group ($p > 0.05$). Overall, patient compliance was good (table 4).

Discussion

The aim of our trial was a possible effective treatment for CACS. In the present study, the more effective treatment for the primary efficacy endpoints (body weight, fatigue and QoL) and for the secondary endpoints (appetite, IL-6, TNF- α , GPS, and ECOG PS score) was the combination regimen, MA plus thalidomide.

The main symptoms of CACS were fatigue, weight loss, anorexia and poor QoL, which were customarily selected as the efficacy endpoints of CACS studies [14, 15]. The 'core' mechanism of CACS was considered a systemic inflammatory response. There is evidence that chronic, low-grade, tumor-induced activation of the host immune system is involved in CACS [16]. The proinflammatory cytokines IL-6 and TNF- α play central roles in the patho-

physiology of CACS [17, 18]. The systemic inflammatory response with an elevated level of CRP is now included in the definition of cancer cachexia. Serum albumin is also closely related to systemic inflammatory response [19]. A cumulative prognostic score based on CRP and albumin, the GPS, as an indicator of the systemic inflammatory response, may reflect the severity of CACS [20–22].

To date, a variety of single interventions to treat CACS have had limited success. Synthetic progestogen medroxyprogesterone or MA are currently the only approved drugs for CACS; their mechanism to treat CACS may be partly related to glucocorticoid activity and the ability to downregulate the synthesis of proinflammatory cytokines and to increase food intake by neuropeptide Y release [23, 24].

Many randomized controlled studies in cancer patients with weight loss have demonstrated that medroxyprogesterone and MA significantly improve appetite, resulting in increased food intake, increased bodyweight and intermittent decline in nausea and/or emesis, whereas in most trials, no definite improvement in QoL was observed [25–27]. A Cochrane database systematic review indicated that MA improves appetite and decreases weight loss in cancer patients, whereas no overall conclusion about QoL or the other could be drawn [28].

Table 1. Clinical characteristics of the control group and the trial group

	Trial group (n = 46)	Control group (n = 47)	p
Age, years	62.1±12.3	61.8±9.8	0.862
Males/females	28/18	27/20	0.737
Body weight, kg	48.0±7.3	47.8±7.3	0.589
Weight loss			
5–10%	38 (82.6)	37 (78.7)	0.64
Tumor site			
Lung	18 (39.1)	16 (34.0)	0.61
Gastric	7 (15.2)	6 (12.8)	0.73
Breast	6 (13.0)	7 (14.9)	0.80
Colorectal	5 (10.9)	6 (12.8)	0.78
Pancreas	4 (8.7)	3 (6.4)	0.67
Esophagus	3 (6.5)	4 (8.5)	0.72
Liver	3 (6.5)	5 (10.6)	0.48
Stage			
III	4 (8.7)	6 (12.8)	0.53
IV	42 (91.3)	41 (87.2)	0.53
ECOG PS			
0	2 (4.3)	1 (2.1)	0.55
1	17 (37.0)	15 (31.9)	0.61
2	21 (45.7)	23 (48.9)	0.75
3	6 (13.0)	8 (17.0)	0.42
GPS			
0, CRP <10 mg/l	5 (10.9)	7 (14.9)	0.56
1, albumin <32 g/l	8 (17.4)	9 (19.1)	0.83
1, CRP >10 mg/l	15 (32.6)	14 (29.8)	0.82
2, CRP >10 mg/l, albumin <32 g/l	18 (39.1)	17 (36.2)	0.77
Palliative chemotherapy			
Yes	30 (65.2)	28 (59.6)	0.57
No	16 (34.8)	19 (40.4)	0.57

Figures in parentheses are percentages. The χ^2 test and Student's t test were used for analysis.

Thalidomide has multiple immunomodulatory and anti-inflammatory properties, mainly by downregulating TNF- α and IL-6 production. Thus, thalidomide has been used for patient treatment of cachexia associated with cancer and AIDS, whereas Davis et al. [29] and Gordon et al. [30] reported that thalidomide was only able to attenuate weight loss and lean body mass loss in CACS patients. Massa and colleagues [31] demonstrated that body weight did not change, whereas appetite improved and IL-6 and TNF- α decreased significantly after 3 months, with thalidomide administered (at a dose of 300 mg/day) to 18 advanced-stage cancer patients. In the present study, thalidomide combined with MA was shown to be effective in terms of the efficacy endpoints fatigue, appetite, body weight, TNF- α , IL-6, and QoL.

Table 2. Endpoints before and after treatment between the trial group and the control group

	Before treatment	After treatment	p
Trial group (n = 46)			
Fatigue, MFSI-SF score	33.8±23.1	31.3±22.7	0.01
Body weight, kg	48.0±7.3	50.2±7.2	<0.01
Appetite, VAS score	4.5±1.5	5.6±2.0	0.01
IL-6, pg/ml	40.9±20.6	30.1±11.3	0.01
TNF- α , pg/ml	33.0±14.4	27.2±10.3	0.02
GPS	1.5±0.7	1.2±0.8	0.05
ECOG PS	2.0±0.8	1.6±0.7	0.03
Grip strength, kg	20.6±6.6	21.7±7.3	0.01
EORTC QLQ-C30, score	49.0±23.2	56.9±26.3	0.02
Control group (n = 47)			
Fatigue, MFSI-SF score	33.2±21.6	33.0±22.1	0.75
Appetite, VAS score	4.6±1.4	5.5±1.9	0.02
Body weight, kg	47.8±7.3	49.3±7.0	0.02
IL-6, pg/ml	41.8±39.1	39.8±42.0	0.75
TNF- α , pg/ml	31.9±30.2	29.7±32.1	0.66
GPS	1.4±0.8	1.3±0.77	0.71
ECOG PS	1.9±0.6	1.8±0.9	0.76
Grip strength, kg	21.2±11.8	21.8±15.8	0.89
EORTC QLQ-C30, score	50.3±16.6	51.4±19.7	0.79

Student's t test was used for paired data. MFSI-SF = Multidimensional fatigue symptom inventory-short form; VAS = visual analogue scale; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30.

Table 3. Comparison of endpoint changes between the trial group and the control group

Endpoints	Trial group	Control group	p
Primary endpoints			
Fatigue	2.57±4.67	−0.23±5.39	<0.01
Body weight	−2.27±6.62	−1.19±2.57	0.05
QoL	−7.93±13.2	−1.12±2.35	<0.01
Secondary endpoints			
Appetite	−1.07±1.36	−0.85±1.75	0.12
IL-6	10.70±12.3	2.04±3.13	<0.01
TNF- α	5.96±7.34	2.21±2.63	0.01
GPS	0.33±0.57	0.12±0.32	0.02
ECOG PS	0.42±0.8	0.13±0.28	0.02
Grip strength	−1.14±2.36	−0.61±1.13	0.05

The table reports the mean changes $\pm$ standard deviations of the endpoints before and after treatment. Student's t test was used for analysis.

Table 4. Toxicities assessed in the control group and in the trial group

	Original trial group (n = 51)		Original control group (n = 51)		p
	grade 1–2	grade 3–4	grade 1–2	grade 3–4	
Thromboembolism	1/51 (2.0)	0	1/51 (2.1)	1/51 (2.0)	NS
Edema	2/51 (3.9)	0	1/51 (2.1)	1/51 (2.0)	NS
Somnolence	4/51 (7.8)	2/51(3.9)	0	0	
Constipation	4/51 (7.8)	0	0	0	

Figures in parentheses are percentages. The χ^2 test was used for analysis. NS = Not significant.

The dose of thalidomide (50 mg po, bid) that we tested was based largely on the combined clinical experience of the authors and taking into consideration data from previous clinical studies [29]. The thalidomide dose utilized in this study was lower than that used by Gordon et al. [30] and Massa and colleagues [31]. Therefore, we cannot exclude that a regimen of thalidomide >100 mg/day combined with MA could be more efficacious than that which was used in this study. Future trials with thalidomide might incorporate dosing according to drug levels to directly address this concern.

Thromboembolism was the severe side effect of the trial, which necessitated discontinuation of the drugs. Edema could result in an unfavorable body weight gain. Therefore, patients who suffered from thromboembolism or edema were withdrawn from the trial. Patient compliance between the two groups was similar.

One limitation of our study was that lean body mass data were not available as an endpoint. In recent years, lean body mass has been drawn in the evaluation of CACS treatment [32, 33]. However, keeping fat mass within 'healthy' levels is still the aim of intervention in CACS,

which may have a positive impact on QoL, response to treatments and prognosis [34]. Therefore, body weight accompanying the improvement in fatigue and QoL could be utilized as a primary endpoint of the CACS study.

To our knowledge, the present study is the first randomized study of a combination regimen with MA and thalidomide carried out in CACS patients. The combined treatment consists mainly of low-cost drugs, having a favorable cost-benefit profile while achieving optimal patient compliance.

Acknowledgments

The authors wish to express their appreciation to Dr. Nan Li and Dr. Wu Yong from Ningbo Health Biomedical Inc., and Dr. Dennis Middleton (NZ), Hospital Consultant and Director, Foreigners Medical Clinic, NDZCH, for their critical review.

Disclosure Statement

No competing financial interests exist.

References

- 1 Tazi E, Errihani H: Treatment of cachexia in oncology. *Indian J Palliat Care* 2010;16:129–137.
- 2 Neumann F: The physiological action of progesterone and the pharmacological effects of progestogens – a short review. *Postgrad Med J* 1978;54:11–24.
- 3 Becker KL: Principles and Practice of Endocrinology and Metabolism. New York, Lippincott, Williams and Wilkins, 2001.
- 4 Mantovani G, Macciò A, Massa E, Madeddu C: Managing cancer-related anorexia/cachexia. *Drugs* 2001;61:499–514.
- 5 Argiles JM, Lopez-Soriano FJ, Busquets S: Counteracting inflammation: a promising therapy in cachexia. *Crit Rev Oncog* 2012;17:253–262.
- 6 Jazieh AR, Komrokji R, Gupta A, Patil S, Flora D, Knapp M, Issa M, Abdel Karim N: Phase II trial of thalidomide, irinotecan and gemcitabine in chemonaive patients with advanced non-small cell lung cancer. *Cancer Invest* 2009;27:932–936.
- 7 Ott PA, Chang JL, Oratz R, Jones A, Farrell K, Muggia F, Pavlick AC: Phase II trial of dacarbazine and thalidomide for the treatment of metastatic melanoma. *Chemotherapy* 2009;55:221–227.
- 8 Teo SK, Stirling DI, Zeldis JB: Thalidomide as a novel therapeutic agent: new uses for an old product. *Drug Discov Today* 2005;10:107–114.
- 9 Reid J, Mills M, Cantwell M, Cardwell CR, Murray LJ, Donnelly M: Thalidomide for managing cancer cachexia. *Cochrane Database Syst Rev* 2012;4:CD008664.
- 10 Davis M, Lasheen W, Walsh D, Mahmoud F, Bicanovsky L, Lagman R: A phase II dose titration study of thalidomide for cancer-associated anorexia. *J Pain Symptom Manag* 2012;43:78–86.

- 11 Prue G, Rankin J, Cramp F, Allen J, Gracey J: Fatigue in gynaecological cancer patients: a pilot study. *Support Care Cancer* 2006;14:78–836.
- 12 Masika GM, Wettergren L, Kohi TW, von Esen L: Health-related quality of life and needs of care and support of adult Tanzanians with cancer: a mixed-methods study. *Health Qual Life Outcomes* 2012;10:133.
- 13 McMillan DC: An inflammation-based prognostic score and its role in the nutrition-based management of patients with cancer. *Proc Nutr Soc* 2008;67:257–262.
- 14 Madeddu C, Macciò A, Panzone F, Tanca FM, Mantovani G: Medroxyprogesterone acetate in the management of cancer cachexia. *Expert Opin Pharmacother* 2009;10:1359–1366.
- 15 Mantovani G, Macciò A, Lai P, Massa E, Ghiani M, Santona MC: Cytokine involvement in cancer anorexia/cachexia: role of megestrol acetate and medroxyprogesterone acetate on cytokine downregulation and improvement of clinical symptoms. *Crit Rev Oncog* 1998;9:99–106.
- 16 Mantovani G, Macciò A, Lai P, Massa E, Ghiani M, Santona MC: Cytokine activity in cancer-related anorexia/cachexia: role of megestrol acetate and medroxyprogesterone acetate. *Semin Oncol* 1998;25:45–52.
- 17 Argiles JM, Lopez-Soriano FJ, Busquets S: Counteracting inflammation: a promising therapy in cachexia. *Crit Rev Oncog* 2012;17:253–262.
- 18 Kim HJ, Kim HJ, Yun J, Kim KH, Kim SH, Lee SC, Bae SB, Kim CK, Lee NS, Lee KT, Park SK, Won JH, Park HS, Hong DS: Pathophysiological role of hormones and cytokines in cancer cachexia. *J Korean Med Sci* 2012;27:128–134.
- 19 McMillan DC, Elahi MM, Sattar N, Angerson WJ, Johnstone J, McArdle CS: Measurement of the systemic inflammatory response predicts cancer-specific and non-cancer survival in patients with cancer. *Nutr Cancer* 2001;41:64–69.
- 20 Partridge M, Fallon M, Bray C, McMillan D, Brown D, Laird B: Prognostication in advanced cancer: a study examining an inflammation-based score. *J Pain Symptom Manage* 2012;44:161–167.
- 21 El-Mowafy AM, El-Mesery ME, Salem HA, Al-Gayyar MM, Darweish MM: Prominent chemopreventive and chemoenhancing effects for resveratrol: unraveling molecular targets and the role of C-reactive protein. *Chemotherapy* 2010;56:60–65.
- 22 Shimoda M, Katoh M, Kita J, Sawada T, Kubota K: The Glasgow Prognostic Score is a good predictor of treatment outcome in patients with unresectable pancreatic cancer. *Chemotherapy* 2010;56:501–506.
- 23 Mantovani G, Macciò A, Esu S, Lai P, Santona MC, Massa E, Dessì D, Melis G, Del Giacco S: Medroxyprogesterone acetate reduces the production of cytokines and serotonin involved in anorexia/cachexia and emesis by peripheral blood mononuclear cells of cancer patients. *Biochem Soc Trans* 1997;25:296.
- 24 Yeh SS, Schuster MW: Megestrol acetate in cachexia and anorexia. *Int J Nanomed* 2006;1:411–416.
- 25 Tomíška M, Tomisková M, Salajka F, Adam Z, Vorlíček J: Palliative treatment of cancer anorexia with oral suspension of megestrol acetate. *Neoplasma* 2003;50:227–233.
- 26 De Conno F, Martini C, Zecca E, Balzarini A, Venturino P, Groff L, Caraceni A: Megestrol acetate for anorexia in patients with far-advanced cancer: a double-blind controlled clinical trial. *Eur J Cancer* 1998;34:1705–1709.
- 27 Macciò A, Madeddu C, Gramignano G, Mulas C, Floris C, Sanna E, Cau MC, Panzone F, Mantovani G: A randomized phase III clinical trial of a combined treatment for cachexia in patients with gynecological cancers: evaluating the impact on metabolic and inflammatory profiles and quality of life. *Gynecol Oncol* 2012;124:417–425.
- 28 Berenstein EG, Ortiz Z: Megestrol acetate for the treatment of anorexia-cachexia syndrome. *Cochrane Database Syst Rev* 2005;CD004310.
- 29 Davis M, Lasheen W, Walsh D, Mahmoud F, Bicanovsky L, Lagman R: A phase II dose titration study of thalidomide for cancer-associated anorexia. *J Pain Symptom Manage* 2012;43:78–86.
- 30 Gordon JN, Trebble TM, Ellis RD, Duncan HD, Johns T, Goggin PM: Thalidomide in the treatment of cancer cachexia: a randomised placebo controlled trial. *Gut* 2005;54:540–545.
- 31 Mantovani G, Macciò A, Madeddu C, Gramignano G, Serpe R, Massa E, Dessì M, Tanca FM, Sanna E, Deiana L, Panzone F, Contu P, Floris C: Clinical trial with thalidomide in patients with tumors at different sites in progression of disease after previous treatments. *Support Palliat Cancer Care* 2004;1:21–28.
- 32 Madeddu C, Dessì M, Panzone F, Serpe R, Antoni G, Cau MC, Montaldo L, Mela Q, Mura M, Astara G, Tanca FM, Macciò A, Mantovani G: Randomized phase III clinical trial of a combined treatment with carnitine + celecoxib ± megestrol acetate for patients with cancer-related anorexia-cachexia syndrome. *Clin Nutr* 2012;31:176–182.
- 33 van der Meij BS, Schoonbeek CP, Smit EF, Muscaritoli M, van Leeuwen PA, Langius JA: Pre-cachexia and cachexia at diagnosis of stage III non-small-cell lung carcinoma: an exploratory study comparing two consensus-based frameworks. *Br J Nutr* 2012;16:1–9.
- 34 Coronha AL, Camilo ME, Ravasco P: The relevance of body composition in cancer patients: what is the evidence? *Acta Med Port* 2011;24:769–778.