Randomized phase III clinical trial of five different arms of treatment for patients with cancer cachexia: interim results

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Abstract

Objective: In April 2005 a phase III randomized study was started to establish which was the most effective and safest treatment of cancer-related anorexia/cachexia syndrome and oxidative stress in improving identified primary endpoints: increase of lean body mass, decrease of resting energy expenditure (REE), increase of total daily physical activity, decrease of interleukin-6 and tumor necrosis factor-α, and improvement of fatigue assessed by the Multidimensional Fatigue Symptom Inventory–Short Form (MFSI-SF).

Methods: All patients were given as basic treatment polyphenols plus antioxidant agents α-lipoic acid, carbocysteine, and vitamins A, C, and E, all orally. Patients were then randomized to one of the following five arms: 1) medroxyprogesterone acetate/megestrol acetate; 2) pharmacologic nutritional support containing eicosapentaenoic acid; 3) L-carnitine; 4) thalidomide; or 5) medroxyprogesterone acetate/megestrol acetate plus pharmacologic nutritional support plus L-carnitine plus thalidomide. Treatment duration was 4 mo. The sample comprised 475 patients.

Results: By January 2007, 125 patients, well balanced for all clinical characteristics, were included. No severe side effects were observed. As for efficacy, an interim analysis on 125 patients showed an improvement of at least one primary endpoint in arms 3, 4, and 5, whereas arm 2 showed a significant worsening of lean body mass, REE, and MFSI-SF. Analysis of variance comparing the change of primary endpoints between arms showed a significant improvement of REE in favor of arm 5 versus arm 2 and a significant improvement of MFSI-SF in favor of arms 1, 3, and 5 versus arm 2. A significant inferiority of arm 2 versus arms 3, 4, and 5 for the primary endpoints lean body mass, REE, and MFSI-SF was observed on the basis of t test for changes.

Conclusion: The interim results obtained thus far seem to suggest that the most effective treatment for cancer-related anorexia/cachexia syndrome and oxidative stress should be a combination regimen. The study is still in progress and the final results should confirm these data. © 2008 Elsevier Inc. All rights reserved.

Keywords: Cancer-related anorexia/cachexia syndrome and oxidative stress; Proinflammatory cytokines; Lean body mass; Quality of life; Medroxyprogesterone acetate; Combined treatment approach

Introduction

Cachexia is a multifactorial syndrome characterized by tissue wasting, loss of body weight, particularly of lean body (muscle) mass (LBM) and to a lesser extent adipose tissue, metabolic alterations, fatigue, reduced performance

status, very often accompanied by anorexia leading to a reduced food intake; it accompanies the end stage of many chronic diseases and especially cancer and therefore is termed "cancer-related anorexia/cachexia syndrome" (CACS) [1–4].

Key features of CACS are increased resting energy expenditure (REE), increased levels of circulating factors produced by the host immune system in response to the tumor, such as proinflammatory cytokines, or by the tumor itself, such as proteolysis-inducing factor. At the time of cancer diagnosis, 80% of patients with upper gastrointestinal cancers and 60% of patients with lung cancer have already had substantial weight loss. The prevalence of cachexia increases from 50% to >80% before death, and in >20% of patients cachexia is the cause of death [5].

Proinflammatory cytokines interleukin (IL)–1, IL-6, and tumor necrosis factor-α (TNF-α) play a central role in the pathophysiology of CACS [6–10] through long-term inhibition of feeding by negatively acting on hypothalamic orexigenic peptides such as neuropeptide Y and agouti-related protein and/or positively acting on anorexigenic peptides (pro-opiomelanocortin and cocaine- and amphetamine-related transcripts), respectively [11]. There is evidence that a chronic, low-grade, tumor-induced activation of the host immune system, which shares numerous characteristics with the "acute-phase response" found after major traumatic events and septic shock, is involved in CACS [12].

Several mechanisms may lead to oxidative stress (OS) in patients with cancer. First of all is altered energy metabolism, which may be a consequence of symptoms such as anorexia/cachexia, nausea, and vomiting that prevent normal nutrition and thus a normal supply of nutrients such as glucose, proteins, and vitamins, leading eventually to accumulation of free radicals, i.e., reactive oxygen species (ROS), including hydroxyl radicals, superoxide radicals, and others. The second mechanism is a non-specific long-term activation of the immune system with an excessive production of proinflammatory cytokines, which in turn may increase ROS production [13]. The third mechanism leading to OS in patients with cancer may result from the use of antineoplastic drugs; many of them, in particular alkylating agents and cisplatin, are able to produce an excess of ROS and a depletion of critical plasma and tissue antioxidants [14]. Thus, it could be hypothesized that the body redox systems, which include antioxidant enzymes and low-molecular-weight antioxidants, may be dysregulated in patients with CACS/OS and that this imbalance might enhance disease progression.

Consequently, the management of CACS/OS is a complex challenge that should address the different causes underlying this clinical event with an integrated or multimodal treatment approach targeting the different factors involved in its pathophysiology.

On the basis of this rationale, we carried out an open early phase II study according to the Simon two-stage design with the aim of testing the efficacy and safety of an integrated treatment based on a pharmacologic nutritional support, antioxidants, and drugs, all given orally, in a population of patients with advanced cancer and CACS/OS. Forty-four patients were enrolled and 39 completed the treatment. At the end of the study, 22 of the 39 patients responded to treatment, achieving a significant improvement of the endpoint variables, i.e., LBM, appetite, IL-6, TNF-α, fatigue, and quality of life (QL; European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30$_{v3}$ [EORTC-QLQ-C30]), and therefore the treatment proved to be effective. As regards safety, it was absolutely well tolerated without any toxic effect [15,16]. Therefore, a randomized phase III study was warranted.

Aim of the study

In April 2005 we started a phase III randomized study with the aim of establishing which was the most effective and safest treatment in improving the identified "key" variables (primary endpoints) of CACS/OS: increase of LBM, decrease of REE, increase of total daily physical activity, decrease of IL-6 and TNF-α, and decrease of fatigue.

Materials and methods

Study design

The study is a phase III randomized two-center trial (Department of Medical Oncology, Policlinico Universitario, and Division of Medical Oncology 2, Ospedale Oncologico Regionale "Businco", Cagliari, Italy). According to the statistical design, the sample comprised 475 patients randomized to one of five arms (95 patients per arm). Random assignment was performed by random-number tables. The protocol was approved by the reference ethics committee. Written informed consent was obtained from all patients. The procedures followed were in accordance with good clinical practices and the Helsinki Declaration.

Endpoints

The efficacy primary endpoints (key variables) were increase of LBM, decrease of REE, increase of total daily physical activity, decrease of IL-6 and TNF-α, and decrease in fatigue symptoms. The secondary endpoints were all other variables studied (see EFFICACY ENDPOINTS). The safety endpoints were classified as adverse events according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0 [17].

Treatment plan

All patients included in the study were given as basic treatment polyphenols (300 mg/d) obtained by alimentary sources (onions, apples, oranges, 150 mL of red wine, green tea) or supplemented by tablets (Quercetix, Elbea Pharma, Milan, Italy; one tablet, 300 mg/d, plus antioxidant agents α-lipoic acid [300 mg/d, included in the Quercetix tablet]

plus 2.7 g/d of carbocysteine [Fluifort, Dompè, Milan, Italy; one sachet per day] plus 400 mg/d of vitamin E [Sursum, Abiogen Pharma, Pisa, Italy; one tablet per day] plus 30 000 IU/d of vitamin A and 500 mg/d of vitamin C [Trocaflu, Laborest, Nerviano (MI), Italy; two sachets per day], all orally). Patients were then randomized to one of the following five treatment arms.

Arm 1. A progestational agent, i.e., 500 mg/d of medroxyprogesterone acetate (MPA; Provera, Pfizer Italia, Borgo San Michele (LT), Italy; one sachet per day) or 320 mg/d of megestrol acetate (MA; Megace, Bristol-Meyers Squibb, Rome, Italy; two tablets, 160 mg/d), was given orally.

Arm 2. Oral supplementation was given with an eicosapentaenoic acid (EPA)–enriched nutritional supplement (2.2 g/d of EPA for ProSure [Abbott, Campoverde di Aprilia (LT), Italy] and Forticare [Nutricia, Milan, Italy], 2 g/d for Resource Support [Novartis, Origgio (VA), Italy]). This supplementation also contained docosahexaenoic acid, with a high-calorie (range 126–160 kcal/100 mL), high-protein (total protein range 6.65–9 g/100 mL) content. As for amino acid content, the content of branched-chain amino acids is reported for two supplements (ProSure contains leucine, isoleucine, and valine; Resource Support contains only leucine; Forticare does not report branched-chain amino acid content). The prescribed dosages were two cartons per day for ProSure, two cartons per day for Resource Support, and three cartons per day for Forticare.

Arm 3. L-carnitine (Carnitene, Biofutura Pharma, Milan, Italy) at 4 g/d (two vials, 2 g/d) was given orally.

Arm 4. Thalidomide (Pharmion S.r.l., Rome, Italy) at 200 mg/d (two tablets, 100 mg/d) was given orally.

Arm 5. Treatment consisted of MPA or MA plus pharmacologic nutritional support plus L-carnitine plus thalidomide.

The planned treatment duration was 4 mo.

A placebo arm was not included as it was not considered ethical because of the results of our phase II study and because an approved drug for the treatment of cancer cachexia is currently available, i.e., MA and MPA.

Eligibility and exclusion criteria

Patient eligibility criteria were an age range of 18–80 y, a histologically confirmed tumor of any site at an advanced stage; loss of ≥5% of the ideal (or preillness) body weight in the previous 3 mo and/or abnormal values of proinflammatory cytokines, ROS and antioxidant enzymes predictive of the onset of clinical cachexia; and a life expectancy of >4 mo. Patients could be receiving concomitant antineoplastic chemotherapy or hormone therapy with curative or palliative intent or supportive care. Exclusion criteria were women of child-bearing age, significant comorbidities, mechanical ob-

struction to feeding, medical treatments inducing significant changes of patient metabolism or body weight, and contraindications to the use of MA/MPA such as a history of thromboembolic events and deep venous thrombosis.

Efficacy endpoints

The following endpoints were evaluated before treatment and at 4, 8, 16, and 24 wk after treatment start.

Primary efficacy endpoints. Lean body mass was assessed by bioelectrical impedance analysis (Bioelectric Impedance Analyser 101, Akern Spa) [15] or dual-energy X-ray absorptiometry from January 2007, which is currently considered the most reliable method. As a complementary assessment to bioelectrical impedance analysis, we calculated the phase angle (derived from reactance and resistance values), which is related to body mass index, fat mass, and LBM. Moreover, the phase angle was shown to have an important prognostic role in

Table 1
Patient clinical characteristics*

Patients enrolled	125
Male/female	74/51
Age (y)	61.9 ± 12.1 (35–81)
Weight (kg)	56.9 ± 11.6 (34–87)
BMI (kg/m^2)	21.3 ± 4 (13.9–31.2)
<18.5	24 (19.2)
18.5–25	91 (72.8)
25–30	10 (8.0)
Weight loss before study entry	
>10%	12 (9.6)
5–10%	66 (52.8)
<5%	47 (37.6)
Tumor site	
Lung	18 (14.4)
Breast	18 (14.4)
Pancreas	16 (12.8)
Colorectal	16 (12.8)
Head and neck	12 (9.6)
Ovary	10 (8.0)
Stomach	8 (6.4)
Uterus	5 (4.0)
Biliary ducts	5 (4.0)
Kidney	5 (4.0)
Bladder	3 (2.4)
Prostate	3 (2.4)
Liver	2 (1.6)
Other	4 (3.2)
Stage	
IIIA	7 (5.6)
IV	118 (94.4)
ECOG PS	
0	5 (4.0)
1	58 (46.4)
2	59 (47.2)
3	3 (2.4)

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status

* Data are presented as number of patients (percentage) or mean ± SD (range).

Table 2
Differences between baseline and post-treatment values of nutritional/functional, laboratory, and quality-of-life variables*

	Arm 1. Progestational agent ($n = 21$)			Arm 2. Oral enteral nutrition with EPA ($n = 25$)		
	Baseline	After treatment	P	Baseline	After treatment	P
Nutritional/functional variables						
Body weight (kg)	56.5 ± 8.9	57.2 ± 10	0.29	52.7 ± 9.1	52 ± 9.4	0.39
LBM (kg)	44.5 ± 8.0	44.0 ± 8.3	0.62	41.4 ± 6.1	40.5 ± 6.8	0.25
Appetite	5.3 ± 1.6	6.6 ± 1.5	0.003	5.7 ± 2.6	5.2 ± 2.3	0.46
Phase angle	4.6 ± 2.2	4.1 ± 1.8	0.14	4.3 ± 1.0	4.3 ± 0.9	0.64
Grip strength	25.9 ± 8.4	24.4 ± 7.7	0.52	24.8 ± 10.2	23.2 ± 8.1	0.14
REE (kcal)	1187 ± 244	1099 ± 220	0.19	1150 ± 248	1315 ± 357	0.053
Laboratory variables						
IL-6 (pg/mL)	56 ± 36.9	45.1 ± 33.2	0.85	64 ± 45.8	64.2 ± 59	0.94
TNF-α (pg/mL)	8.8 ± 12.6	15.6 ± 26	0.65	8 ± 10.1	15.6 ± 21.6	0.28
ROS (Fort U)	442 ± 130	325 ± 183	0.26	347 ± 144	380 ± 114	0.57
GPx (U/L)	6184 ± 3617	5814 ± 2585	0.496	5568 ± 3298	6060 ± 2862	0.47
Quality-of-life variables						
EORTC-QLQ-C30	60.4 ± 13.4	64.2 ± 12.7	0.14	67.7 ± 16.8	61.8 ± 18.4	0.29
EQ-5D$_{index}$	0.4 ± 0.3	0.4 ± 0.3	0.67	0.59 ± 0.33	0.33 ± 0.35	0.02
EQ-5D$_{VAS}$	44 ± 16.4	51.1 ± 15.7	0.03	54.3 ± 18.3	55 ± 18.6	0.79
MFSI-SF	19.8 ± 12.1	15.9 ± 13.1	0.17	17.3 ± 18.7	27.4 ± 18.6	0.051

EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; EQ-5D, Euro QL-5D; EPA, eicosapentaenoic acid; GPx, glutathione peroxidase; IL, interleukin; LBM, lean body mass; MFSI-SF, Multidimensional Fatigue Symptom Inventory–Short Form; REE, resting energy expenditure; ROS, reactive oxygen species; TNF, tumor necrosis factor; VAS, visual analog scale

* Data are reported as mean ± SD. Significance was calculated by Student's t test for paired data (baseline versus post-treatment values) for each variable, except for IL-6 and TNF-α (Wilcoxon signed rank test). Results were considered significant if P values were ≤0.05.

patients under surgical, cancer, and intensive care and to be an indicator of function and general health [18].

The REE was assessed by indirect calorimetry (Medgem, SensorMedics Italia Srl, Italy), which measures oxygen consumption per unit time.

Detailed evaluation of daily physical activity and the associated energy expenditure was carried out with an appropriate electronic device (SenseWear, Armband, SensorMedics Italia Srl), which is able to assess total energy expenditure, i.e., REE plus the energy spent in physical activity; its software is able to identify the specific type of physical activity (e.g., walking, running, lying down) in such a way as to attribute a "functional quality" to patient physical activity [19,20].

Serum levels of proinflammatory cytokines (IL-6, TNF-α) were measured by enzyme-linked immunosorbent assays (Immunotech, Marseille, France).

Fatigue by the Multidimensional Fatigue Symptom Inventory–Short Form (MFSI-SF) was calculated by a numerical score, with possible total fatigue scores ranging from −24 to 96 [21,22]. Results are reported as mean scores.

Secondary endpoints

- Objective clinical response before and at the end of treatment (complete response, partial response, stable disease, progressive disease) according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria [23];
- Progression-free survival at the end of the study;

- Performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) PS scale [24];
- Appetite by visual analog scale (VAS);
- Grip strength by dynamometer;
- Blood levels of ROS (FORT test, Callegari SpA, Italy) and antioxidant enzyme glutathione peroxidase by photometer (Randox, Crumlin, UK);
- Quality of life assessed by the EORTC-QLQ-C30, EuroQol (EQ-5D)$_{index}$, and EQ-5D$_{VAS}$.

The methods have been reported in detail in our previous reports [15,16].

Statistical design

Hypothesizing a difference between arms of 20% and considering an α type error of 0.05 and a β type error of 0.20, 95 patients had to be enrolled for each arm. Analysis was performed on an intention-to-treat basis. The most effective arm for the primary endpoint variables were assessed by one-way analysis of variance for repeated measures (or the Kruskal-Wallis test for non-parametric variables). In addition, the arms were compared for the mean change (of primary endpoints) by t test for changes. Moreover, the benefit obtained for primary and secondary endpoints in each arm (changes between baseline and after-treatment values) was assessed using paired Student's t test or Wilcoxon signed-rank test when appropriate. Significance was determined at the 5% level. Progression-free survival was evaluated starting from the date of randomization in the study using the Kaplan-Meier method.

Table 2
(continued)

Arm 3. L-Carnitine (n = 24)			Arm 4. Thalidomide (n = 20)			Arm 5. Combination of all (n = 20)		
Baseline	After treatment	P	Baseline	After treatment	P	Baseline	After treatment	P
59.2 ± 11.6	59.9 ± 11.8	0.79	58.2 ± 13.6	57.9 ± 13.2	0.51	54.6 ± 8.9	56 ± 8.2	0.03
45.7 ± 7.7	46.4 ± 8.4	0.57	43.7 ± 8.2	44.7 ± 7.7	0.04	44 ± 8.0	45.1 ± 8.6	0.135
5.8 ± 3.0	6.4 ± 2.4	0.44	5.1 ± 2.3	5.4 ± 2.4	0.44	5.2 ± 2.7	6.7 ± 1.8	0.004
3.93 ± 1.1	3.99 ± 1.3	0.28	4.1 ± 0.8	4.0 ± 0.9	0.73	4 ± 1.3	4.2 ± 1.1	0.141
24.6 ± 8.7	26.6 ± 8.1	0.09	25.7 ± 6.8	25.3 ± 7.2	0.58	25.9 ± 12.1	25.9 ± 10.3	0.98
1226 ± 273	1016 ± 90	0.07	1000 ± 250	1090 ± 247	0.77	1343 ± 464	1264 ± 383	0.022
37.8 ± 29.3	25.7 ± 25.3	0.29	43.4 ± 37.9	26.2 ± 19.3	0.03	36.1 ± 19.1	22.6 ± 23.1	0.29
26.2 ± 22	22.7 ± 37.9	0.91	11.9 ± 7.7	26.7 ± 41.1	0.39	29.8 ± 37.2	37.8 ± 38.4	0.59
451 ± 165	339 ± 142	0.52	505 ± 99	451 ± 150	0.39	483 ± 153	425 ± 125	0.66
6823 ± 3766	5603 ± 3215	0.56	5371 ± 2087	6151 ± 4253	0.96	5806 ± 2217	7415 ± 2494	0.23
67.6 ± 11.7	72.7 ± 11.0	0.36	60.6 ± 9.6	68.4 ± 10.7	0.01	53.4 ± 17.2	58.7 ± 13.6	0.117
0.59 ± 0.3	0.57 ± 0.4	0.76	0.5 ± 0.2	0.6 ± 0.3	0.11	0.33 ± 0.3	0.4 ± 0.3	0.217
62.5 ± 16.5	62.4 ± 15.2	0.94	46.4 ± 19.5	53.6 ± 15	0.09	52.3 ± 16.6	57 ± 19.8	0.25
15.5 ± 14.3	7.9 ± 14.9	0.04	24.8 ± 14.6	21.1 ± 8.5	0.39	28.3 ± 18.4	19.3 ± 17.6	0.015

Results

From April 2005 to January 2007, 125 patients were evaluable (male/female ratio 74/51, mean age 61.9 y, range 35–80). Fourteen of 149 enrolled patients (9%) died during treatment, and 10 patients were not evaluable because they had not completed the treatment at the time of the interim analysis. Patient clinical characteristics are listed in Table 1. Most patients had stage IV disease. Approximately 83% of patients had >5% weight loss (20% were clearly underweight), and 17% of patients were enrolled on the basis of abnormal values of proinflammatory cytokines, ROS, and antioxidant enzymes predictive of the onset of clinical cachexia. At baseline 50.4% of patients had an ECOG PS score of 0–1 and 49.6% had an ECOG PS score of 2–3. In general, the five treatment arms were comparable for all variables (age, weight, body mass index, stage of disease, ECOG PS). The distribution of different cancer sites and disease stages (almost all stage IV) was well balanced over the five study arms.

Compliance to treatment was good. In general, patients had to record daily the assumption and quantity of prescribed treatment. For some treatments, such as nutritional support containing EPA, a patient had to return the empty packages to the investigator. The actual daily mean consumption of EPA-containing nutritional support was 1.5 ± 0.53 cartons/d for ProSure and Resource Support and 2.3 ± 0.46 cartons/d for Forticare.

In detail, eight, eight, and nine patients received ProSure, Resource Support, and Forticare, respectively. Provided that we considered the three nutritional supplements equivalent in terms of effectiveness, the choice to administer one nutritional supplement rather than another was determined by what was made available by the producers free of charge.

The comparison between baseline and post-treatment values showed the following results (Table 2):

> Significant increases in appetite ($P = 0.003$) and EQ-5D$_{VAS}$ score ($P = 0.03$) and an improvement in ECOG PS score ($P = 0.03$) in arm 1
> Significant increases in MFSI-SF score ($P = 0.05$) and REE ($P = 0.05$), a decrease in EQ-5D$_{index}$ score ($P = 0.02$), and an improvement in ECOG PS score ($P = 0.004$) in arm 2
> Significant improvements in MFSI-SF score ($P = 0.039$) and ECOG PS score ($P = 0.0003$) in arm 3
> Significant increases in LBM ($P = 0.043$) and EORTC-QLQ-C30 score ($P = 0.011$), a decrease in serum IL-6 levels ($P = 0.033$), and an improvement of ECOG PS score ($P = 0.03$) in arm 4
> Significant increases in total body weight ($P = 0.033$) and appetite ($P = 0.004$) and improvements in MFSI-SF score ($P = 0.015$), REE ($P = 0.022$), and ECOG PS score ($P = 0.041$) in arm 5

Analysis of variance comparing the different treatment arms (for changes between baseline and post-treatment values) showed (Table 3):

> A significant improvement of REE score in favor of arm 5 versus arm 2
> A significant improvement of MFSI-SF score in favor of arms 1, 3, and 5 versus arm 2

Table 3
Comparison between arms for the primary endpoint variables by analysis of variance*

	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	P
LBM (kg)	−0.425 ± 3.726	−0.912 ± 3.901	0.363 ± 2.732	0.953 ± 1.913	1.080 ± 3.094	0.1857
REE (kcal)	−54.80 ± 79.86	135.43 ± 149.62	−139.5 ± 131.87	90 ± 465.08	−178.83 ± 132.84	0.0412[†]
IL-6 (pg/mL)	5.17 ± 19.75	−6.1 ± 62.1	−12.58 ± 39.19	−18.75 ± 21.86	−11.3 ± 29.98	0.8316
TNF-α (pg/mL)	6.856 ± 31.67	18.9 ± 55.1	−8.1 ± 74.5	196.7 ± 435.3	−116 ± 314.6	0.1921
MFSI-SF (score)	−2.444 ± 7.205	10.400 ± 17.020	−7.118 ± 13.071	−3.667 ± 12.329	−8.933 ± 12.418	0.0007[‡]

IL, interleukin; LBM, lean body mass; MFSI-SF, Multidimensional Fatigue Symptom Inventory–Short Form; REE, resting energy expenditure; TNF, tumor necrosis factor

* Data are presented as mean difference ± SD. The most effective arm for the primary endpoint variables were assessed by one-way analysis of variance. Results were considered significant if P values were ≤0.05. Between-arm analysis was assessed by Tukey's post hoc test.

[†] For REE, arm 5 is significantly different from arm 2 (confidence interval 1.00–627.52).

[‡] For MFSI-SF, arm 1 is significantly different from arm 2 (confidence interval −25.236 to 0.453), arm 2 from arm 3 (confidence interval 4.962–30.073), and arm 2 from arm 5 (confidence interval 6.391–32.276).

A significant increase in EQ-5D$_{index}$ score in favor of arms 1, 4, and 5 versus arm 2

A significant inferiority of arm 2 versus arms 3, 4, and 5 for the primary endpoints LBM, REE, and MFSI-SF was observed on the basis of t test for changes. Consequently, arm 2 will be withdrawn from the study.

The average times to death in the different arms were 5.3 ± 2 mo for arm 1 (range 4–9), 8.2 ± 6.8 mo for arm 2 (range 4–24), 8.0 ± 5.7 mo for arm 3 (range 4–27), 7.5 ± 2.4 mo for arm 4 (range 4–10+, i.e., one patient was still alive 10 mo after enrollment), and 8.6 ± 5.4 mo for arm 5 (range 4–18).

Discussion

The CACS and OS are two of the most important features of advanced cancer and are clinically relevant for their impact on patient QL, outcome, and survival. Moreover, CACS, mainly through the loss of LBM, worsens QL by negatively affecting patient physical activity. The predominant features of CACS, i.e., progressive loss of muscle mass and function, have been shown to be only minimally affected by the nutritional or pharmacologic tools currently available.

Unfortunately, although much progress has been made in the understanding of the pathophysiologic mechanisms leading to CACS/OS, the development of early and effective interventions aimed at preventing and/or reversing the metabolic changes ultimately leading to muscle wasting is far from being attained [25]. Therefore, the search for a potentially effective treatment of CACS/OS must be considered critical among the as yet unavailable oncologic treatments with high impact. Thus far, attempts at CACS/OS therapy with a variety of interventions have had limited success. Conversely, a combination of dietary, nutritional, and pharmacologic approaches to normalize the metabolic environment may have the potential to reverse CACS and improve the associated symptoms that affect QL [26].

According to this rationale, we previously demonstrated in a phase II study [16] the efficacy of an integrated treatment against CACS/OS. In that study we demonstrated that the body weight increase (1.9 kg) was almost completely sustained by a parallel increase in LBM (1.7 kg) that was independently correlated to a decrease in IL-6, thus strengthening the role of proinflammatory cytokines in the pathophysiology of CACS/OS. QL, particularly fatigue symptoms, improved significantly after treatment.

The positive results achieved thus far warranted us to start a randomized phase III study with the aim of comparing the different single agents for CACS/OS versus their combination and to test which was the most effective in improving the identified primary endpoints.

The different single agents were selected on the basis of the following rationale. The antioxidant agents were shown to be effective in our previous studies [27–32]. The polyphenols, in particular quercetin, were included for their high activity as antioxidants [33]. Synthetic progestogens, MA/MPA, are currently the only approved drugs for CACS in Europe. Their mechanism of action has not been as yet fully understood and may be partly related to glucocorticoid activity and an ability to downregulate the synthesis and release of proinflammatory cytokines by peripheral blood mononuclear cells [34] and to increase food intake by neuropeptide Y release [35]. Several randomized studies in mixed groups of weight-losing patients with cancer have suggested that MA/MPA improves appetite and stabilizes weight to an extent greater than placebo [36–40]. The ω-3 polyunsaturated fatty acids (EPA and docosahexaenoic acid) have been shown to inhibit the production of proinflammatory cytokines and thereby to act positively on cancer cachexia. In experimental tumor models EPA has demonstrated antitumor and anticachectic effects. Studies on weight-losing patients with pancreatic cancer receiving EPA have shown suppression of IL-6 production by peripheral blood mononuclear cells [41–43]. Barber et al. [44] demonstrated that an EPA-enriched supplement added to the diet may reverse cachexia in patients with advanced pancreatic cancer. A double-blinded randomized study [45]

in 200 patients with pancreatic cancer demonstrated a significant positive correlation between the assumption of the nutritional supplement and the increase of weight and LBM, provided that EPA supplementation was ≥1.5 cartons a day. Carnitine is a cofactor required for transforming the free long-chain fatty acids into acyl-carnitine and for their subsequent transport into the mitochondrial matrix to produce acetyl-coenzyme A through the β-oxidation pathway. The relation between coenzyme A and carnitine is pivotal for cell energy metabolism: coenzyme A is required for β-oxidation, metabolism of several amino acids, pyruvate dehydrogenase synthesis, and thus for triggering the tricarboxylic acid cycle [46,47]. Patients with cancer are especially at risk for carnitine deficiency; they frequently present with decreased caloric intake and numerous antineoplastic drugs can interfere with the absorption and synthesis of carnitine. Thalidomide has multiple immunomodulatory and antiinflammatory properties; its inhibitory effect on TNF-α and IL-6 production may be responsible for its anticachectic activity. Thus, thalidomide has been used for treatment of cachexia associated with acquired immunodeficiency syndrome, tuberculosis, and cancer.

With regard to the present phase III study, we report the interim results on 125 patients enrolled up to now. The safety data did not show any side effect due to anticachectic treatment and no patients had to be withdrawn from the study; no toxicity of any grade according to NCI common terminology criteria was found. As for efficacy, this interim analysis showed an improvement of at least one primary endpoint in arms 3, 4, and 5, whereas arm 2 showed no benefit for the primary endpoints LBM, REE, and MFSI-SF. In detail, arm 3 was effective in inducing an improvement in fatigue symptoms, arm 4 an increase in LBM and a decrease in IL-6, and arm 5 a decrease in REE and fatigue symptoms. With regard to the secondary endpoints, we observed increases in appetite and EQ-5D$_{VAS}$ and a decrease in ECOG PS score in arm 1, a decrease in ECOG PS score in arm 2, an increase in EORTC-QLQ-C30 and a decrease in ECOG PS score in arm 4, and an increase in total body weight and appetite and improvement of ECOG PS score in arm 5. Moreover, analysis of variance showed an improvement in fatigue in favor of arms 1, 3, and 5 versus arm 2 and an improvement of REE in favor of arm 5 versus arm 2. On the basis of this interim analysis, we plan to exclude arm 2 from future randomization.

With regard to a possible different effectiveness among the three nutritional supplements due to their possible different compositions in nutrients, calorie contents, and presence of branched-chain amino acids, we consider the three supplements absolutely comparable for the purposes of our study.

In our study EPA has demonstrated no benefit on the primary endpoints of CAS/OS. The results of a recently published large multicenter study [48] that compared two different dosages (2 and 4 g) of a novel diester preparation of EPA versus placebo in cachectic patients with cancer showed no statistically significant improvement in established primary endpoints, which were very similar to those selected for our study; however, it has to be taken into account that the large multicenter study compared only the effect of EPA at two different dosages, whereas in our study the EPA was included in an EPA-enriched nutritional supplementation. In conclusion, we agree with Fearon et al. [48] that the benefit of ω-3 fatty acids by themselves is at best marginal and it may be that future studies should concentrate on other agents or combination regimens. Moreover, a recently published meta-analysis including randomized controlled trials that assessed oral EPA versus placebo or control in patients with advanced cancer and CACS provided no evidence that EPA improves symptoms associated with CACS [49].

The present study suggests a limited efficacy of 500 mg/d of MPA and 320 mg/d of MA (arm 1), which is by far the most widely prescribed regimen and the only one approved in Europe for CACS.

To date, ≥15 randomized controlled studies have demonstrated that MPA/MA significantly improves appetite, food intake, body weight, and sometimes nausea and emesis, whereas in most trials no definite improvement in global QL was observed [12,25]. The weight gain observed with progestogen administration consists mainly of water and fat mass, but they have virtually no influence on the increase of LBM and therefore on functional activity [50].

Two of our studies [34,51] demonstrated a beneficial effect of MA/MPA in patients with CACS and their ability to downregulate synthesis and release of key cytokines involved in CACS. In the first study [51], we demonstrated in a population of patients with advanced stage head and neck cancer who were treated with cisplatin-based neoadjuvant chemotherapy the ability of MA (320 mg/d) to improve appetite, bodyweight, and the Spitzer QL index and to induce a reduction of serum levels of proinflammatory cytokines and IL-6 production in vitro. The second study [34] showed that MPA, at doses that are pharmacologically active in vitro (0.1, 0.2, and 0.4 mg/L), was able to significantly reduce the in vitro production and/or release of cytokines IL-1, IL-6, and TNF-α and serotonin in patients with advanced stage cancer at different sites.

Moreover, it is to be taken into account that MPA/MA may give rise to some important side effects such as thromboembolism, hyperglycemia, hypertension, peripheral edema, alopecia, and adrenal insufficiency.

Carnitine may be considered a very intriguing drug; in the present study it was found to be effective in improving fatigue and performance status. Indeed, in one of our recently published studies L-carnitine administration (6 g/d for 30 d) proved its efficacy by improving fatigue and increasing LBM and appetite in a population of 12 patients with advanced cancer [52]. These concurrent positive results would seem to suggest that carnitine could become a very interesting and novel approach in the treatment of CACS/OS.

Thalidomide induced an improvement of LBM and a decrease of IL-6. These findings strengthen those previously

reported by us in a small sample of cachectic patients with cancer (an increase of appetite and a decrease of TNF-α) [53]. In the current literature there are two studies that have assessed the anabolic effects of thalidomide in gastrointestinal cancer cachexia. Gordon et al. [54] recently published a randomized placebo-controlled study that demonstrated that treatment with 200 mg/d of thalidomide for 24 wk was well tolerated and effective at attenuating loss of body weight and LBM in patients with cachexia due to advanced pancreatic cancer [54]. Khan et al. [55] demonstrated a gain of LBM after a short treatment with thalidomide in cachectic patients with esophageal cancer.

The interim results obtained so far seem to suggest that the most effective treatment for CACS/OS should be a combination regimen including all treatments potentially considered effective. This is in keeping with the general consensus that CACS/OS is a multifactorial process and, hence, the effective approach should be multimodal. Alternatively, in the single-agent approach, the most interesting are carnitine and thalidomide.

Due to the brevity of the present report, which presents only interim results, we have not considered methodologic issues such as the best way to assess the degree of CACS, the appropriate characterization measuring all possible contributing factors (a CACS staging system), and the best ways to assess function and patient well-being.

It is also to be taken into account that the treatment consists mainly of diet, relatively low-cost pharmacologic nutritional support, and low-cost drugs. Therefore it may be considered as having a favorable cost–benefit profile while achieving optimal patient compliance.

The study is still in progress. The ultimate goal should be of translating the results obtained in patients with advanced cancer into a prevention trial in a population of patients at risk of developing CACS/OS.

Acknowledgments

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