European Review for Medical and Pharmacological Sciences 2010; 14: 292-301

Randomised phase III clinical trial of 5 different arms of treatment on 332 patients with cancer cachexia

G. MANTOVANI

Department of Medical Oncology, Schoool of Medicine, University of Cagliari (Italy)

Abstract. – *Background and Objective:* **A phase III randomised study was carried out to establish the most effective and safest treatment to improve the primary endpoints of cancer cachexia: lean body mass (LBM), resting energy expenditure (REE), fatigue; and relevant secondary endpoints: appetite, quality of life, grip strength, Glasgow Prognostic Score (GPS) and proinflammatory cytokines.**

Patients: **Three hundred and thirty-two assessable patients with cancer-related anorexia/cachexia syndrome (CACS) were randomly assigned to one of five arms of treatment: 1 – medroxyprogesterone 500 mg/d or megestrol acetate 320 mg/d; 2 – oral supplementation with eicosapentaenoic acid (EPA); 3 – L-carnitine 4 g/d; 4 – thalidomide 200 mg/d; 5 – a combination of the above. Treatment duration: 4 months.**

Results: **Analysis of variance showed a significant difference between the treatment arms. A post hoc analysis showed the superiority of arm 5 over the others for all primary endpoints. An analysis of changes from baseline showed that LBM (by dual-energy X-ray absorptiometry and by L3 computed tomography) significantly increased in arm 5. REE decreased significantly and fatigue improved significantly in arm 5. Appetite increased significantly in arm 5. IL-6 decreased significantly in arm 5 and 4. GPS significantly decreased in arms 5, 4 and 3. Total daily physical activity showed that total energy and active energy expenditure increased significantly in arm 5. Eastern Cooperative Oncology group-Performance Status (ECOG-PS) significantly decreased in arms 5, 4 and 3. Toxicity was substantially negligible, comparable between treatment arms.**

Conclusions: **The most effective treatment for all three primary efficacy endpoints as well as secondary endpoints appetite, IL-6, GPS and ECOG PS was the combination regimen that included all selected agents.**

Key Words:

Cancer cachexia, Medroxyprogesterone, Megestrol acetate, Eicosapentaenoic acid, L-carnitine, Thalidomide, ECOG-PS, Glasgow prognostic score.

Introduction

Cachexia is a multifactorial syndrome characterized by tissue wasting, body weight loss, substantially due to loss of lean body mass (LBM), increased resting energy expenditure (REE), metabolic alterations, the latter two integrating the framework of the hypermetabolic syndrome, fatigue, reduced performance status, very often accompanied by anorexia leading to a reduced food intake. It accompanies the end stage of several chronic diseases, in particular cancer and therefore it is termed "cancer-related anorexia/cachexia syndrome" (CACS). The prevalence of CACS increases from 50% to >80% before death, and in >20% of cancer patients it is the cause of death[1].

Proinflammatory cytokines interleukin (IL)-1, IL-6 and tumor necrosis factor-α (TNF-α) play a central role in the pathophysiology of CACS. There is evidence that a chronic, low-grade, tumor-induced activation of the host immune system, which shares several characteristics with the ''acute-phase response'', is involved in CACS[2].

Consequently, the management of CACS is a complex challenge, which should address the different causes underlying this clinical event with an integrated or multimodal treatment approach. To date, however, despite several years of co-ordinated efforts in basic and clinical research, practice guidelines for the prevention and treatment of CACS are lacking[3].

On the basis of this rationale we carried out an open early-phase II study according to the Simon two-stage design to test the efficacy and safety of an integrated oral treatment based on pharmaconutritional support, antioxidants and drugs in advanced cancer patients with CACS. Twenty-two out of 39 evaluable patients responded to the treatment achieving a significant improvement of

Corresponding Author: Giovanni Mantovani, MD; e-mail: mantovan@medicina.unica.it

the key endpoint variables LBM, fatigue, appetite, quality of life (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – C30, EORTC QLQ-C30), IL-6 and TNF-α. Body weight increase (1.9 kg) was almost completely sustained by a parallel increase in LBM (1.7 kg) independently correlated to an IL-6 decrease, thus strengthening the role of proinflammatory cytokines. Treatment was safe without any toxic effects[4,5].

These promising results warranted a phase III study. Therefore, in April 2005 we started a phase III randomised study with the aim to establish which was the most effective and safest treatment able to improve the identified "key" variables (primary endpoints) of CACS: increase of LBM, decrease of REE, improvement of fatigue and some relevant secondary endpoints.

Study Design

The study was a phase III randomised trial. The protocol was approved by the reference Ethics Committee. Written informed consent was obtained from all patients. Procedures were in accordance with Good Clinical Practices and the Helsinki Declaration.

Eligibility Criteria

Patients (age ≥18 years) with: histologically confirmed advanced stage tumor at any site, loss of >5% of the ideal or preillness body weight in the previous 3 months with or without abnormal values of proinflammatory cytokines predictive of the onset of clinical cachexia, a life expectancy of ≥4 months, were eligible. Patients could be receiving concomitant antineoplastic chemotherapy or hormone therapy with palliative intent or supportive care.

Women of child-bearing age, patients with mechanical obstruction to feeding, medical treatments inducing significant changes of patient metabolism or body weight and history of thromboembolism were excluded.

Intervention

All patients included in the study were given as basic treatment polyphenols (300 mg/d) obtained by dietary sources or supplemented by tablets (Quercetix, Elbea Pharma, Milan, Italy) plus lipoic acid 300 mg/d plus carbocysteine 2.7 g/d plus vitamin E 400 mg/d plus vitamin A 30,000 IU/d and vitamin C 500 mg/d, all orally. Patients were then randomized to one of five arms: Arm 1. A progestational agent, i.e., medroxyprogesterone acetate 500 mg/day (MPA) or megestrol acetate 320 mg/d (MA), which we considered equivalent and were prescribed according to specific circumstances. Arm 2. An oral eicosapentaenoic acid (EPA)–enriched (2.2 g/d) nutritional supplement. The prescribed dosages were 2 cartons/day for both ProSure and Resource Support, or 3 cartons/day for Forticare. Arm 3. L-carnitine (Carnitene, SigmaTau, Rome, Italy) 4 g/day. Arm 4. Thalidomide 200 mg/day. Arm 5. MPA or MA plus EPA-enriched nutritional supplement plus L-carnitine plus thalidomide. The planned treatment duration was 4 months.

Efficacy Endpoints

Primary Endpoints

Primary efficacy endpoints were: increase of LBM, decrease of REE and decrease in fatigue symptom. LBM was assessed by conventional bioelectrical impedance analysis (BIA) (Bioelectric Impedance Analyser 101, Akern Spa, Firenze, Italy) in all patients; dual-energy X-ray absorptiometry (DEXA) in 144 patients using a Hologic Delphi W scanner (Hologic Inc., Bedford, MA, USA); regional computed tomography at L3 (L3-CT), currently considered the highest precision method able to provide detail on fat-free mass and specific muscles not provided by DEXA or BIA[6], in 25 patients. REE was assessed by indirect calorimetry (Medgem, SensorMedics Italia Srl, Milan, Italy). Fatigue was assessed by the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF)[7].

Secondary Endpoints

Secondary endpoints were: appetite by visual analog scale (VAS); grip strength by dynamometer (Jamar Hydraulic Hand Dynamometer,Sammons Preston, Bolingbrook, IL, USA); quality of life by the EORTC-QLQ-C30, EuroQol (EQ-5D)$_{index}$, and EQ-5D$_{VAS;}$ serum levels of IL-6 and TNF-a by enzyme-linked immunosorbent assays (Immunotech, Marseille, France); Glasgow Prognostic Score (GPS), currently considered a significant predictive index for

survival in advanced stage cancer patients[8]; blood levels of Reactive Oxygen Species (ROS) (FORT test, Callegari SpA, Parma, Italy) and antioxidant enzyme glutathione peroxidase (GPX) (Randox, Crumlin, UK) by photometer; total daily physical activity and the associated energy expenditure carried out with an appropriate electronic device (SenseWear PRO_2 Armband, SensorMedics Italia, Milan, Italy) able to assess total energy expenditure (TEE), i.e., the sum of REE plus the energy spent in physical activity (Active Energy Expenditure, AEE): it is able to identify the specific type of physical activity (e.g., walking, running, lying down) in such a way as to attribute to it a "functional quality"[9]; performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) scale.

All methods have been reported in detail in our previous papers[4,5]. The endpoints were evaluated before treatment and at 4, 8 and 16 weeks after treatment start.

Safety Endpoints

Adverse events were classified according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events $(CTCAE)_{v3.0}$ criteria.

Statistical Analysis

Differences between groups at baseline were analyzed by the χ^2 test for categoric variables and by Student's t-test (or Wilcoxon rank sum test when appropriate) for continuous variables.The original intention was to compare arms in terms of changes of primary endpoints before and after treatment (16 weeks vs baseline) by conducting one-way analysis of variance (ANOVA) for multiple comparisons using Bonferroni's correction. 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. Analysis was performed on an intent-to treat basis. An interim analysis was planned every 100 randomised patients to test the efficacy (primary efficacy endpoints) and the toxicity of the different arms according to the following "early stopping rules": the arm(s) in which efficacy values resulted signficantly lower ($p<0.05$) by t test for changes vs the other arms would be stopped. Likewise, the arm (s) in which grade 3/4 toxicities values resulted significantly higher ($p<0.05$) by t test for changes vs the other arms would be stopped. Very low significance p values ($p\leq0.001$) were chosen considering that there are 10 possible pairs of between arm comparisons and three endpoints implying 30 possible candidate analyses: p-values are reported including Bonferroni's corrections for multiple comparisons. All analyses were carried out with two-sided tests using a 5% type I error rate. SPSS version 15.0 was used.

Sample Size Calculation

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 should be enrolled for each arm.

Results

A total of 332 patients were recruited between April 2005 and December 2008 and were all deemed assessable (Figure 1). The five arms consisted of patient groups comparable at baseline on the basis of the most common stratification factors (Table I). Twelve patients withdrew for early death due to progressive disease (PD). The percentage of dropouts was similar between arms.

Primary Efficacy Endpoints (Tables II, III)

According to original intention, i.e. the comparison between arms, the ANOVA test showed a significant difference. The *post-hoc* analysis showed a superiority of arm 5 versus the others as for all primary endpoints as reported in Table II. The analysis of changes from baseline showed that LBM assessed by DEXA significantly increased ($p=0.015$) in arm 5 whilst that assessed by BIA did not change significantly. The L3-CT analysis showed an improvement of the estimated LBM (kgs) ($p=0.001$) and a trend for increase of muscle mass surface (mm^2) in arm 5. REE, which was elevated at enrolment in 85% of patients, decreased significantly ($p=0.044$) in arm 5. Fatigue improved significantly ($p=0.047$) in arm 5. Moreover, the ANOVA test for repeated measures showed a trend across the time points of primary endpoints in arms 3, 4 and 5.

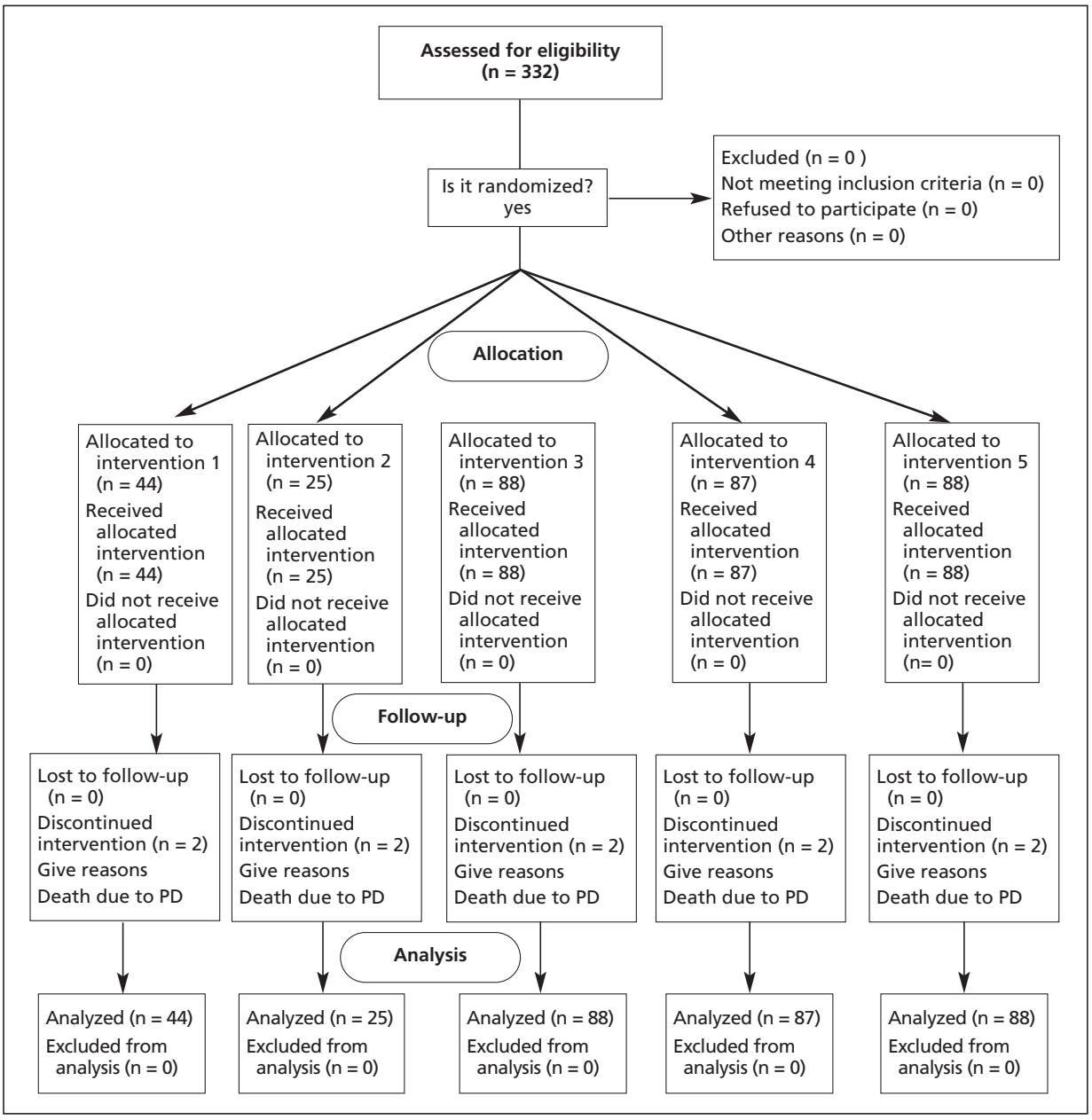

Figure 1. CONSORT diagram. PD: progressive disease.

Secondary Efficacy Endpoints (Table III)

Appetite increased significantly (p=0.0003) in arm 5. A trend toward an increase in grip strength in arm 4 (p=0.08) and toward an improvement in EQ-5D$_{index}$ in arm 5 (p=0.09) were observed. IL-6 decreased significantly in arm 5 and 4. GPS significantly decreased in arms 5, 4 and 3. TEE and AEE (kcal/d and min/d) increased significantly in arm 5 (p=0.05) (Figure 2 A and B). ECOG-PS significantly decreased in arms 5, 4 and 3.

Interim Analyses

At the first interim analysis on 125 randomised patients a significant inferiority of arm 2 for the primary endpoints LBM (p<0.05 versus arm 4 and 5), REE (p<0.001 versus arm 1, 3 and 5) and fatigue (p=0.002 versus arm 1, p<0.001 versus arm 3, 4 and 5) was observed on the basis of t test for changes. Therefore, arm 2 was withdrawn from the study[10] in accordance with the "early stopping rules". A second interim analysis on 204 patients showed that arm 1 was inferior to

Table I. Baseline patient characteristics.

	Arm 1 (n = 44)	Arm 2 (n = 25)	Arm 3 (n = 88)	Arm 4 (n = 87)	Arm 5 (n = 88)	p*
Male/female	25/19	15/10	47/41	48/39	46/42	*0.959*
Age (yrs)	61.5 ± 9.7	60.6 ± 13.5	62.8 ± 11.5	62.4 ± 11.9	62.4 ± 9.4	*0.866*
Weight (kg)	56.2 ± 11.1	53 ± 9.1	56.9 ± 12.2	58.8 ± 12.4	56.4 ± 10.8	*0.547*
	No. (%)	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	
BMI						
<18.5	8 (18.2)	6 (24)	15 (17)	14 (16.1)	11 (12.5)	
18.5-25	35 (79.5)	18 (72)	66 (75)	67 (77)	71 (80.7)	
>25	1 (2.3)	1 (4)	7 (8)	6 (6.9)	6 (6.8)	*0.863*
Weight loss						
<5%	9 (20.5)	5 (20)	20 (22.7)	20 (23)	22 (25)	
5-10% (3-6 mo)	26 (59)	16 (64)	50 (56.8)	49 (56.3)	47 (53.4)	
>10% (3-6 mo)	9 (20.5)	4 (16)	18 (20.5)	18 (20.7)	19 (21.6)	*0.997*
Tumor site						
Lung	9 (20.4)	5 (20)	17 (19.3)	20 (22.9)	21 (23.9)	
Breast	7 (15.9)	4 (16)	15 (17)	15 (17.2)	14 (15.9)	
Colorectal	5 (11.4)	4 (16)	14 (15.9)	10 (11.5)	12 (13.6)	
Pancreas	3 (6.8)	2 (8)	9 (10.2)	9 (10.4)	9 (10.2)	
Head and neck	3 (6.8)	1 (4)	8 (9.1)	9 (10.4)	7 (8)	
Ovary	4 (9.1)	1 (4)	8 (9.1)	6 (6.9)	7 (8)	
Stomach	4 (9.1)	1 (4)	4 (4.5)	4 (4.6)	4 (4.5)	
Uterus	2 (4.5)	1 (4)	2 (2.3)	2 (2.3)	3 (3.4)	
Kidney	2 (4.5)	1 (4)	2 (2.3)	2 (2.3)	3 (3.4)	
Biliary ducts	1 (2.3)	1 (4)	2 (2.3)	2 (2.3)	2 (2.3)	
Bladder	1 (2.3)	1 (4)	2 (2.3)	2 (2.3)	1 (1.1)	
Prostate	1 (2.3)	1 (4)	2 (2.3)	2 (2.3)	1 (1.1)	
Oesophagus	1 (2.3)	1 (4)	2 (2.3)	2 (2.3)	2 (2.3)	
Liver	1 (2.3)	1 (4)	1 (1.1)	2 (2.3)	2 (2.3)	*1.000*
Stage						
III	2 (4.5)	1 (4)	4 (4.5)	4 (4.6)	4 (4.5)	
IV	42 (95.5)	24 (96)	84 (95.5)	83 (95.4)	84 (95.5)	*1.00*
ECOG PS						
0	1 (2.3)	1 (4)	3 (3.4)	2 (2.3)	3 (3.4)	
1	17 (38.6)	10 (40)	41 (46.6)	44 (50.6)	44 (50)	
2	23 (52.3)	12 (48)	37 (42)	34 (39.1)	35 (39.8)	
3	3 (6.8)	2 (8)	7 (8)	7 (8)	6 (6.8)	*0.992*
Glasgow prognostic score						
0	7 (15.9)	5 (20)	13 (14.8)	14 (16.1)	12 (13.6)	
1-albumin <32 g/l	5 (11.4)	2 (8)	11 (12.5)	11 (12.6)	9 (10.2)	
1-CRP >10 mg/l	12 (27.3)	8 (32)	28 (31.8)	29 (33.4)	30 (34.1)	
2	20 (45.4)	10 (40)	36 (40.9)	33 (37.9)	37 (42.1)	*0.999*
Concomitant palliative chemotherapy						
Yes	36 (81.8)	20 (80)	69 (78.4)	67 (77.1)	68 (77.3)	
No	8 (18.2)	5 (20)	19 (21.6)	20 (22.9)	20 (22.7)	*0.973*

Abbreviations: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; CRP,C-reactive protein. *χ^2 test.

Table II. Comparison of primary efficacy endpoints between arms 3, 4 and 5 by ANOVA test.

Primary efficacy endpoints	Arm 3 Mean ± SD (95% CI)	Arm 4 Mean ± SD (95% CI)	Arm 5 Mean ± SD (95% CI)	p*
LBM				
BIA	–0.52 ± 3.14 (–1.2 to 0.18)	–0.02 ± 3.34 (–0.8 to 0.8)	0.44 ± 3.1 (–0.16 to 1.04)	0.144
DEXA	–0.7 ± 2.2 (–1.2 to -0.2)	–0.8 ± 2.6 (–1.5 to -0.2)	2.1 ± 2.1 (1.6 to 2.7)	0.007
REE	12.08 ± 246 (–47.9 to 72.08)	–21.8 ± 241.9 (–90.6 to 46.9)	–133 ± 259 (–200 to –65.4	0.028
Fatigue	0.85 ± 19.5 (–3.6 to 5.3)	–1.55 ± 15.4 (–5.4 to 2.3)	–7.5 ± 12.8 (–10.4 to –4.6)	0.035

Table II reports the mean changes ± standard deviation of primary endpoints before and after treatment (16 weeks vs baseline). Post hoc analysis showed: LBM (DEXA): arm 5 vs arm 3 and 4: $p<0.001$; REE: arm 5 versus arm 3: $p=0.004$; arm 5 versus arm 4: $p=0.056$; Fatigue: arm 5 versus vs arm 3: $p=0.004$; arm 5 versus arm 4: $p=0.07$. *Abbreviations:* LBM, Lean Body Mass; BIA, bioimpedance analysis; DEXA, dual energy x-ray absorptiometry; REE, resting energy expenditure; n.a., not applicable. *One-way analysis of variance (ANOVA) using Bonferroni's correction for multiple comparisons.

Table III. Primary and secondary endpoints before and after treatment.

Parameter	Arm 1			Arm 2		
	Baseline	After treatment	p*	Baseline	After treatment	p*
Primary endpoints						
LBM (kgs)						
BIA (n = 332)	44.2 ± 8.1	43.8 ± 9.8	0.818	42.4 ± 6.1	40.5 ± 6.8	0.250
DEXA (n = 144)	45.5 ± 7.7	43.3 ± 6.6		43.8 ± 10.6	41.2 ± 9.7	0.652
REE (Kcal/die)	1251 ± 301.9	1428 ± 138	0.493	1150 ± 248	1315 ± 357	0.053
Fatigue (MFSI-SF score)	24.6 ± 19.12	25.9 ± 19.2	0.621	17.3 ± 18.7	27.4 ± 18.6	0.051
Secondary endpoints						
Grip strength (kgs)	25.4 ± 8.1	23 ± 7.9	0.116	24.8 ± 10.2	23.2 ± 8.1	0.14
Appetite (VAS score)	6.1 ± 4.3	7.5 ± 2.7	0.561	5.7 ± 2.6	5.2 ± 2.3	0.46
IL-6 (pg/ml)	46.8 ± 44.5	40.5 ± 39.5	0.499	49 ± 42.8	47.8 ± 43	0.94
TNF alpha (pg/ml)	28.1 ± 46	14.7 ± 18.4	0.883	28 ± 10.1	15.6 ± 21.6	0.28
ROS (FORT U)	432 ± 139	360 ± 201	0.112	347 ± 144	380 ± 114	0.57
GPx (IU/ml)	7144 ± 3162	6528 ± 5150	0.199	5568 ± 3298	6060 ± 2862	0.47
EORTC QLQ-C30 (score)	56.1 ± 12.5	59.4 ± 17.8	0.637	67.7 ± 16.8	61.8 ± 18.4	0.29
EQ-5D-index (score)	0.4 ± 0.32	0.6 ± 0.3	0.579	0.59 ± 0.33	0.33 ± 0.35	0.002
EQ-5D-VAS (score)	44.8 ± 17.5	43.1 ± 21.6	0.378	54.3 ± 18.3	55 ± 18.6	0.79
GPS (score)	1.3 ± 0.75	1.2 ± 0.81	0.056	1.4 ± 0.8	1.3 ± 0.6	0.125
ECOG PS (score)	1.6 ± 0.83	1.7 ± 1.04	0.597	1.5 ± 0.6	1.2 ± 0.4	0.320

Abbreviations: LBM, lean body mass; BIA, bioimpedance analysis; DEXA, dual energy x-ray absorptiometry; REE, resting energy expenditure; IL, Interleukin; TNF, tumor necrosis factor; ROS, reactive oxygen species; GPx, glutathione peroxidase; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire -C30; EQ-5D Euro QL -5D;GPS, Glasgow prognostic score. *Student's t test for paired data.

Table III (Continued). Primary and secondary endpoints before and after treatment.

Parameter	Arm 3			Arm 4			Arm 5		
	Baseline	After treatment	p*	Baseline	After treatment	p*	Baseline	After treatment	p*
Primary endpoints									
LBM (kgs)									
BIA (n = 332)	43.3 ± 8.6	44.6 ± 8.7	0.952	43.5 ± 8.3	44.1 ± 8.7	0.846	42.8 ± 8.1	44 ± 7.2	0.609
DEXA (n = 144)	44.8 ± 9.8	45.2 ± 16.7	0.980	45.3 ± 9.8	45.1 ± 9.3	0.897	43.8 ± 9.4	44.9 ± 7.7	0.0148
L3-CT (n = 25)									
Muscle mass (mm^2)	10031 ± 3833	10477 ± 3917	0.148	11419 ± 3802	11831 ± 3074	0.196	10912 ± 3304	11504 ± 3221	0.084
Estimated LBM[a] (kgs)	42.27 ± 29.5	43.5 ± 29.4	0.058	42.4 ± 2.26	42.5 ± 9.1	0.983	42.8 ± 8.1	45.4 ± 23.9	0.001
REE (Kcal/die)	1286 ± 251	1193 ± 324	0.375	1296 ± 445	1169.9 ± 283	0.486	1227 ± 439	1067.1 ± 181	0.044
Fatigue (MFSI-SF score)	26.4 ± 23	26.1 ± 25	0.801	24.2 ± 19.2	27.8 ± 24.6	0.634	26.9 ± 16.8	20 ± 23.1	0.047
Secondary endpoints									
Grip strength (kgs)	5.1 ± 2.6	5.3 ± 3.1	0.607	5 ± 2.5	5.3 ± 2.5	0.351	5.1 ± 2.0	6.1 ± 1.5	0.00037
Appetite (VAS score)	25.9 ± 12.1	25.1 ± 11.9	0.104	23.3 ± 9.4	29.1 ± 8.1	0.086	27.2 ± 13.9	24.2 ± 7.2	0.399
IL-6 (pg/ml)	55.2 ± 18.1	57.1 ± 21	0.832	56.4 ± 19.3	60.3 ± 20	0.188	56 ± 16.1	65.8 ± 18	0.145
TNF alpha (pg/ml)	0.5 ± 0.3	0.4 ± 0.5	0.151	0.5 ± 0.4	0.5 ± 0.38	0.599	0.5 ± 0.3	0.6 ± 0.4	0.092
ROS (FORT U)	45.3 ± 22.6	50 ± 26.8	0.593	46.8 ± 21.7	48.8 ± 22.1	0.712	51.7 ± 21.8	49.2 ± 18	0.950
GPx (IU/ml)	43.8 ± 42.2	31.6 ± 27.9	0.663	40.8 ± 22.9	29.6 ± 25.9	0.0317	41.4 ± 39.9	24.7 ± 23.4	0.0187
EORTC QLQ-C30 (score)	32.2 ± 32.3	37.5 ± 40.7	0.240	30.8 ± 22.9	33.8 ± 30.8	0.649	37.3 ± 35.8	22.5 ± 21.8	0.053
EQ-5D-index (score)	449 ± 128	458 ± 138	0.736	462 ± 138	378 ± 154	0.696	497 ± 121	445 ± 115	0.262
EQ-5D-VAS (score)	6441 ± 4012	7107 ± 3398	0.383	7046 ± 3448	7949 ± 3669	0.203	7434 ± 3125	6676 ± 2542	0.816
GPS (score)	1.2 ± 0.76	0.9 ± 0.86	0.030	1.3 ± 0.8	0.9 ± 0.8	0.006	1.4 ± 0.7	0.9 ± 0.79	0.008
ECOG PS (score)	1.88 ± 0.88	1.5 ± 0.9	0.0001	1.7 ± 0.8	1.5 ± 0.8	< 0.0001	2 ± 0.6	1.5 ± 0.8	< 0.0001

Abbreviations: LBM, lean body mass; BIA, bioimpedance analysis; DEXA, dual energy x-ray absorptiometry; L3-CT, computed tomography at 3rd lumbar vertebra; REE, resting energy expenditure; IL, Interleukin; TNF, tumor necrosis factor; ROS, reactive oxygen species; GPx, glutathione peroxidase; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire -C30; EQ-5D Euro QL -5D;GPS, Glasgow prognostic score. *Student's t test for paired data. [a]Calculated on the basis of the equation as described in reference no. 16.

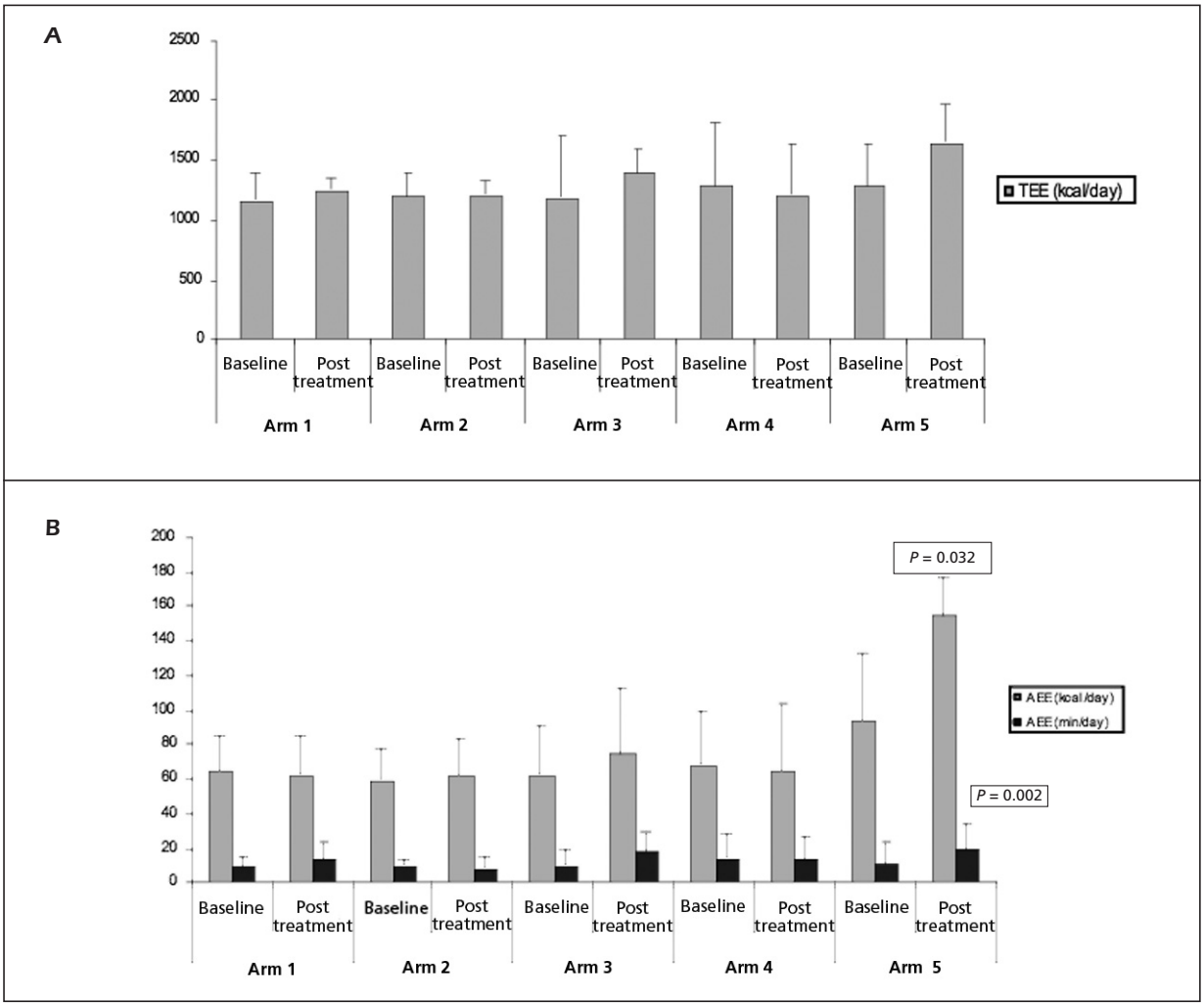

Figure 2. Assessment of total daily physical activity and the associated energy expenditure. Total Energy Expenditure (TEE) ***(A)*** as well as Active Energy Expenditure (AEE) ***(B)*** increased significantly in arm 5. Bars in Figure A report Total Energy Expenditure (TEE) calculated as kcal/24h consumption. Bars in Figure B report Active Energy Expenditure (AEE) expressed as number of kcal/24h consumed beyond the limit of 3.0 METs and number of minutes of activity higher than 3.0 METs (MET = Metabolic Equivalent). 1 MET equals to oxigen consumption equal to 3.5 ml O_2/kg/min, or 1 kcal/ kg/hour, both equal to Resting Energy Expenditure (REE).

the others as for primary efficacy endpoints LBM (p=0.02 versus arm 5), REE (p=0.03 versus arm 5), fatigue (p=0.02 versus arm 4 and p=0.002 versus arm 5) and therefore it was withdrawn from the study in accordance with the "early stopping rules".

Toxicity

Toxicity was substantially negligible, comparable between treatment arms. Only 2 patients with grade 3/4 diarrhea were reported in arm 3 and 5. Overall, patient compliance was very good (Table IV).

Discussion

The aim of our trial was to search for a potentially effective treatment of CACS, which must be considered critical among the as yet unavailable oncologic treatments with high impact. Among the selected efficacy endpoints, we have highlighted as primary endpoints LBM, REE and fatigue, considered the "core" symptoms of CACS, and, among the secondary endpoints, appetite, proinflammatory cytokines and a scoring system based on the systemic inflammation, i.e. GPS: its prognostic value is independent of tu-

Table IV. Toxicity assessed as the worst toxicity per patient.

	Arm 1		Arm 2		Arm 3		Arm 4		Arm 5		
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	*p**
Diarrhea	0	0	1	0	2	2	0	0	3	2	N.S.
Epigastralgia	1	0	2	0	0	0	0	0	1	0	N.S.
Peripheral sensorial neurotoxicity	0	0	0	0	0	0	0	0	0	0	N.S.
Somnolence	0	0	0	0	0	0	2	0	0	0	N.S.
Thromboembolism/ Deep vein thrombosis	1	0	0	0	0	0	0	0	1	0	N.S.

Abbreviations: N.S., not significant. *χ^2 test.

mor stage and conventional scoring systems, superior to PS and to other markers of the systemic inflammatory response.

In the present study the most effective treatment for both all three primary efficacy endpoints and the secondary endpoints appetite, IL-6, TNF-α, GPS and ECOG PS was the combination regimen: this is perfectly in keeping with the assumption that CACS is a multifactorial process and therefore an effective approach should be multitargeted.

The present study is, to our knowledge, the first randomized study with such a high number of patients enrolled and an ample range of treatments carried out in CACS. The results require some considerations:

1. The selected primary endpoints were very well chosen: indeed, the combination arm demonstrated to successfully target them as well as some important secondary endpoints;
2. The efficacy of the combined treatment on the inflammatory response symptoms (cytokines, GPS) and on primary efficacy endpoints adds further evidence to the assumption that the core symptoms of cachexia are systemic inflammation-driven;
3. We do not have an indisputable explanation as to why the different single agents, ineffective or little effective alone, become effective when combined together: thus, an additive or even a synergistic effect may be hypothesised;
4. The combined treatment consists mainly of diet, low-cost pharmacologic nutritional support and low-cost drugs, having a favorable cost-benefit profile while achieving optimal patient compliance.

The promising results of our study should suggest a wide clinical application of the combined treatment. However, we are aware that our results may not be easily translated into current practice as the treatment may appear at first not simple to administer and to attain an adequate compliance in cachectic cancer patients who often have a huge drug burden. To overcome these issues proper patient communication and motivation are paramount.

The results of the present study, showing the efficacy of a combined treatment approach, seem to confirm the basic assumption that the treatment of cancer cachexia, a multifactorial syndrome, is more likely to yield success with a multitargeted approach.

As for future trends, on which experimental research has been focused recently, it can be suggested that drugs or treatments currently tested in animal models and in phase I and II clinical studies may be shortly translated into clinical phase III trials: namely, drugs downregulating the production and/or release of proinflammatory cytokines, particularly IL-6, ghrelin, ghrelin mimetics or antagonists, and steroid androgen-receptors modulators (SARMs) such as ostarine.

References

1) Bruera E. ABC of palliative care. Anorexia, cachexia, and nutrition. Br Med J 1997; 315: 1219-1222.

2) Mantovani G, Maccio A, Massa E, Madeddu C. Managing cancer-related anorexia/cachexia. Drugs 2001; 61: 499-514.

3) Boddaert MS, Gerritsen WR, Pinedo HM. On our way to targeted therapy for cachexia in cancer? Curr Opin Oncol 2006; 18: 335-340.

4) Mantovani G, Madeddu C, Macciò A, Gramignano G, Lusso MR, Massa E, Astara G, Serpe R. Cancer-related anorexia/cachexia syndrome and oxidative stress: an innovative approach beyond current treatment. Cancer Epidemiol Biomarkers Prev 2004; 13: 1651-1659.

5) Mantovani G, Maccio A, Madeddu C, Gramignano G, Lusso MR, Serpe R, Massa E, Astara G, Deiana L. A phase II study with antioxidants, both in the diet and supplemented, pharmaconutritional support, progestagen, and anti-cyclooxygenase-2 showing efficacy and safety in patients with cancer-related anorexia/cachexia and oxidative stress. Cancer Epidemiol Biomarkers Prev 2006; 15: 1030-1034.

6) Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab 2008; 33: 997-1006.

7) Stein KD, Martin SC, Hann DM, Jacobsen PB. A multidimensional measure of fatigue for use with cancer patients. Cancer Pract 1998; 6: 143-152.

8) Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dagg K, Scott HR. A prospective longitudinal study of performance status, an inflammation-based score (GPS) and survival in patients with inoperable non-small-cell lung cancer. Br J Cancer 2005; 92: 1834-1836.

9) Dahele M, Skipworth RJ, Wall L, Voss A, Preston T, Fearon KC. Objective physical activity and self-reported quality of life in patients receiving palliative chemotherapy. J Pain Symptom Manage 2007; 33: 676-685.

10) Mantovani G, Maccio A, Madeddu C, Gramignano G, Serpe R, Massa E, Dessì M, Tanca FM, Sanna E, Deiana L, Panzone F, Contu P, Floris C. Randomized phase III clinical trial of five different arms of treatment for patients with cancer cachexia: interim results. Nutrition 2008; 24: 305-313.