Short Communication

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

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Abstract

Purpose: **To test the efficacy and safety of an integrated treatment based on a pharmaconutritional support, antioxidants, and drugs, all given orally, in a population of advanced cancer patients with cancer-related anorexia/ cachexia and oxidative stress.**
Patients and Methods: **An open early-phase II study was designed according to the Simon two-stage design. The integrated treatment consisted of diet with high polyphenols content (400 mg), antioxidant treatment (300 mg/d α-lipoic acid + 2.7 g/d carbocysteine lysine salt + 400 mg/d vitamin E + 30,000 IU/d vitamin A + 500 mg/d vitamin C), and pharmaconutritional support enriched with 2 cans per day (*n*-3)-PUFA (eicosapentaenoic acid and docosahexaenoic acid), 500 mg/d medroxyprogesterone acetate, and 200 mg/d selective cyclooxygenase-2 inhibitor celecoxib. The treatment duration was 4 months. The following variables were evaluated: (*a*) clinical (Eastern Cooperative Oncology Group performance status); (*b*) nutritional [lean body mass (LBM), appetite, and resting energy expenditure]; (*c*) laboratory [proinflammatory cytokines and leptin, reactive oxygen species (ROS) and antioxidant enzymes]; (*d*) quality of life (European Organization for Research and Treatment of Cancer QLQ-C30, Euro QL-5D, and MFSI-SF).**
Results: **From July 2002 to January 2005, 44 patients were enrolled. Of these, 39 completed the treatment and were assessable. Body weight increased significantly from baseline as did LBM and appetite. There was an important decrease of proinflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-α, and a negative relationship worthy of note was only found between LBM and IL-6 changes. As for quality of life evaluation, there was a marked improvement in the European Organization for Research and Treatment of Cancer QLQ-C30, Euro QL-5D$_{VAS}$, and multidimensional fatigue symptom inventory-short form scores. At the end of the study, 22 of the 39 patients were ''responders'' or ''high responders.'' The minimum required was 21; therefore, the treatment was effective and more importantly was shown to be safe.**
Conclusion: **The efficacy and safety of the treatment have been shown by the study; therefore, a randomized phase III study is warranted.** (Cancer Epidemiol Biomarkers Prev 2006;15(5):1030–4)

Introduction

Cancer-related anorexia/cachexia syndrome (CACS), which often precedes death, is complex and characterized by progressive weight loss with depletion of host reserves of skeletal muscle and, to a lesser extent, adipose tissue, anorexia, reduced food intake, poor performance status, and quality of life that often precedes death (1). At diagnosis, 80% of patients with upper gastrointestinal cancers and 60% with lung cancer have already experienced substantial weight loss (2). The prevalence of cachexia increases from 50% to >80% before death, and in >20%, it is the main cause of death (2). However, the mechanisms inducing CACS are not completely understood (3-6), including the dynamics of host response (activation of systemic inflammatory response and metabolic, immune, and neuroendocrine changes) and those tumor characteristics or tumor-derived products that influence expression of the syndrome (e.g., proteolysis-inducing factor).

Several mechanisms may lead to oxidative stress in cancer patients: one might hypothesize that the body redox systems, which include antioxidant enzymes and low molecular weight antioxidants, may be unregulated in cancer patients, and that this imbalance might enhance disease progression. Several evidence has been provided about the mechanisms linking oxidative stress and cancer cachexia (7-11).

CACS/oxidative stress was dealt comprehensively in a number of our previous articles that showed the following: (*a*) CACS is very frequent in advanced disease (12-14). (*b*) A clinically significant oxidative stress takes place in advanced cancer patients (15, 16). (*c*) Both CACS and oxidative stress alone or in combination are highly predictive of clinical outcome and survival (14).

Many single therapies against CACS and oxidative stress have been tested and have met with limited or no success. A combination of therapies addressed to the different pathophysiologic targets will be required to fight the cachectic process.

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Aim of the Study. The aim of this study was to test the efficacy and safety of an integrated treatment based on a pharmaconutritional support, antioxidants, and drugs, all given orally, in a population of advanced cancer patients with CACS/oxidative stress. The efficacy was assessed in terms of clinical response, improvement of nutritional/functional variables, changes of laboratory variable indicators of CACS/oxidative stress, and improvement of quality of life. The interim results of the study have already been published (17).

Patients and Methods

Study Design. An open early-phase II study was designed according to the Simon two-stage design for $P_1 - P_0 = 0.20$. A response rate value of around 50% was deemed reasonable; therefore, considering P_0 (i.e., noneffective treatment) as a total response of ≤40% of patients and P_1 (i.e., effective treatment) as a total response of at least 60% of patients, the sample should comprise 39 patients, and treatment should be considered effective if at least 21 of these were ''responders.'' The study was approved by the Ethical Committee of the Policlinico Universitario, University of Cagliari, and written informed consent was obtained from all patients before inclusion in the study.

Treatment Plan. The integrated treatment consisted of the following: diet with high polyphenol content (300 mg/d) obtained through alimentary sources or supplemented orally by tablets (one tablet; Quercetix, Elbea Pharma, Milan, Italy); antioxidant treatment: 300 mg/d α-lipoic acid (Tiobec, Laborest, Nerviano, Milan, Italy) orally plus 2.7 g/d carbocysteine lysine salt (Fluifort, Dompè, Milan, Italy) orally plus 400 mg/d vitamin E (Sursum 400, Abiogen Pharma, Pisa, Italy) orally plus 30,000 IU/d vitamin A orally plus 500 mg/d vitamin C orally; oral pharmaconutritional support (ProSure, Abbott Laboratories, North Chicago, IL) enriched with (*n*-3) fatty acids (1.1 g eicosapentaenoic acid and 0.46 g docosahexaenoic acid; 310 kcal per can): 2 cans per day; oral progestagen: 500 mg/d medroxiprogesterone acetate (Provera, Pfizer, Milan, Italy); 200 mg/d selective cyclooxygenase-2 inhibitor celecoxib (Celebrex, Pfizer) orally.

Inclusion and exclusion criteria for patient eligibility have been already reported in our article published in *Cancer Epidemiol Biomarkers and Prevention* (17).

Study End Points. The end points of the study were efficacy and safety. The following were prospectively established as efficacy variables: (*a*) clinical, (*b*) nutritional/functional, (*c*) laboratory, and (*d*) quality of life. The efficacy variables were evaluated before treatment and at 1, 2, and 4 months. A complete list of the efficacy variables and the changes of variables after treatment compared with before treatment considered significant for response to treatment is reported in Table 1. In Table 1, the criteria for considering patients as ''high responders,'' ''responders,'' or ''nonresponders'' are

Table 1. List of efficacy variables and criteria for considering patients as responders, high responders, or nonresponders

Efficacy variables and change considered significant for response to treatment	Criteria defining high responders	Criteria defining responders
Clinical variables		
Performance status (ECOG PS)	Improvement of PS if initial value was ≥1 or stability of PS if initial value was 0	No change of PS < 2 or improvement of PS ≥ 2
Nutritional/functional variables (see reference for methods)		
Body weight (kg) by electronic scale (increase ≥ 5%)	Improvement of at least three nutritional/functional variables with stability of the other variables	Improvement of at least three nutritional/functional variables plus stability of 1 and worsening of 1 or improvement of at least 3 plus stability of the other 2 or improvement of at least 2 plus stability of the other 3
LBM by bioimpedentiometry (increase ≥10%)		
Appetite by VAS (increase ≥2 units)		
REE by indirect calorimetry (decrease ≥10%)		
Grip strength by dynamometer (increase ≥30%)		
Laboratory variables (see reference for methods)		
Serum levels of IL-6 and TNF-α (decrease ≥25%)	Improvement of three or more laboratory variables (including at least proinflammatory cytokines and ROS) independently from the changes of the other variables	Improvement of at least two laboratory variables (including at least proinflammatory cytokines and ROS) independently from the changes of the other variables
Serum levels of leptin (increase ≥100%)		
Blood levels of ROS (decrease ≥80 FORT U)		
Erythrocyte levels of GPx (increase ≥2,000 IU)		
Quality of life questionnaires		
EORTC QLQ-C30 version 3 (score increase ≥25%)	Improvement of the scores of (at least) two or more quality of life questionnaires and no worsening of the others	Improvement of the scores of at least one quality of life questionnaire with no change of the others or worsening of no more than 1
EQ-5D (score increase ≥25%)		
MSFI-SF (score increase ≥25%)		

NOTE: Patients who did not meet the above criteria were considered nonresponders.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; VAS, visual analogue scale; REE, resting energy expenditure; GPx, glutathione peroxidase; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer QLQ-C30; EQ-5D, Euro QL-5D; MSFI-SF, multidimensional fatigue symptom inventory-short form.

also reported. For a detailed description of the methods used, please refer to our article published in *Cancer Epidemiol Biomarkers and Prevention* (17).

Statistical Analysis. The benefit obtained by treated patients was evaluated using the paired Student's *t* test or Wilcoxon ranks test when appropriate (baseline versus posttreatment values). Correlations between changes of lean body mass (LBM) and clinical (performance status), nutritional/functional (appetite, grip strength), laboratory variables [interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), leptin, ROS, and glutathione peroxidase], and quality of life questionnaires were tested using two-sided Spearman's rank correlation analysis, using Bonferroni's correction for multiple tests. Moreover, the same correlations were made between changes of fatigue and changes of the variables cited above. Significant relationships were examined by multivariate linear regression analysis. Significance was determined at 5%, 1%, and 0.1% level (two sided).

Results

Patients. From July 2002 to January 2005, 44 patients were enrolled. Of these, 39 completed the treatment and were assessable. Patient clinical characteristics are listed in Table 2.

Study End Points

(a) Efficacy

Clinical Variables. Objective response was evaluated in all 39 patients. After treatment, 16 patients improved (6 patients changed from progression of disease to stable disease, and 10 patients changed from progression of disease to partial response or complete response); seven patients remained unchanged (stable disease); and 16 patients worsened to progression of disease. Performance status remained unchanged (0 or 1) in 22 patients; performance status remained 2 in four patients, whereas it improved (from 2 to 1) in seven patients and worsened in six patients. Performance status was always assessed by the same clinician for all patients to minimize reporter's inherent bias.

Nutritional/Functional Variables. Body weight increased significantly from baseline as did the LBM and appetite, whereas no significant changes in grip strength were noted. A decrease of resting energy expenditure in two of five patients studied was found at the end of treatment.

Laboratory Variables. The results are reported in Table 3. Proinflammatory cytokines IL-6 and TNF-α decreased significantly, whereas leptin increased notably. ROS and glutathione peroxidase dropped and rose, respectively, but the changes were not significant.

Quality of Life Variables. The quality of life variables are reported in Table 3. Overall quality of life and in particular European Organization for Research and Treatment of Cancer QLQ-C30 and Euro QL-$5D_{VAS}$ and fatigue improved after treatment.

Correlations between Changes of LBM and Clinical (Performance Status), Nutritional/Functional (Appetite and Grip Strength), Laboratory (IL-6, TNF-α, Leptin, ROS, and Glutathione Peroxidase), and Quality of Life Variables. A significant negative relationship was only found between LBM and IL-6 changes ($r = -0.40$, $P = 0.013$). Therefore, multivariate regression analysis was not done.

Correlations between Changes of Fatigue and Clinical (Performance Status), Nutritional/Functional (Appetite and Grip Strength), and Laboratory (IL-6, TNF-α, Leptin, ROS, and Glutathione Peroxidase) Variables. No significant relationship was found.

(b) Safety. Overall, the treatment was quite well tolerated by patients. None complained of serious adverse events nor were any withdrawn from the study due to toxicity. One interrupted medroxiprogesterone acetate after 2 months due to deep vein thrombosis of the leg. Thus far, the treatment has shown itself to be safe without significant side effects and has achieved an optimal compliance by patients as assessed by count of both tablets/cans returned.

Assessment of Responders and Nonresponders. At the end of the study, 22 of the 39 patients were responders (17 responders and 5 high responders), whereas the minimum required was 21; therefore, the treatment was effective. It must be taken into account that, as previously reported in Patients and Methods, the response criteria were arbitrary, although very carefully chosen. Two different types of statistical evaluation were used in our study: the first assessed the treatment efficacy comparing the mean ± SD values of the different variables before and after treatment and the second in terms of responders and nonresponders. The second evaluation was used for the final assessment of the treatment efficacy in accordance with the Simon two-stage phase II design selected for this study.

Discussion

CACS and oxidative stress are two of the most important features of advanced cancer and are both predictive of a poor patient clinical outcome (i.e., survival). Moreover, the resulting malnutrition and the loss of LBM worsen the quality of life mainly by negatively affecting the patient's physical activity and recovery by decreasing tolerance to therapy and increasing complications. Thus far, attempts at correcting CACS with enteral nutrition with nasogastric tube or percutaneous gastrostomy or total parenteral nutrition have generally been disappointing (18-22). Likewise, attempts at drug therapy for CACS with a variety of agents have had limited success; consequently, an innovative approach based on a solid background, which at the same time is feasible in an outpatient setting, was designed. In the present phase II study, multiple, feasible, and potentially effective tools available against CACS/oxidative stress to test their efficacy were used: if positive results are achieved, a randomized phase III study will be carried out. The present study shows that the treatment given was effective in inducing a significant increase not only of total body weight but also in LBM: indeed, the body weight increase (1.9 kg) was almost completely sustained by a parallel increase of LBM (1.7 kg). This should translate into a parallel improvement in function, as suggested by our preliminary unpublished results obtained by physical activity assessment and therefore quality of life. The decrease of IL-6 after treatment was the only variable significantly correlated with LBM. This finding further strengthens the role of proinflammatory cytokines in the pathophysiology of CACS/oxidative stress. The increase of leptin after treatment confirms its inverse association with proinflammatory cytokines, which has already been reported in several of our previous articles (13, 14). The quality of life improved significantly after treatment: this was particularly relevant for fatigue. However, it is worth noting that there was no correlation between changes of fatigue and changes of any of the other variables studied.

Two points are to be considered on the sample patients included: (*a*) the tumor site was relatively heterogeneous, thus preventing the likelihood of numerous dropouts inherent to rapidly progressive very poor prognosis tumors, such as pancreatic cancer. (*b*) More than half the patients were in the range of normal body weight (body mass index <25; i.e., were not overtly cachectic), although almost half of them suffered a significant loss of body weight compared with pre-illness.

Table 2. Patient clinical characteristics

	n (%)
Patients enrolled	39
Male/female	23/16
Age	
Mean ± SD	58.9 ± 9.1
Range	42-78
Weight	
Mean ± SD	55.8 ± 10.5
Range	36-76
BMI	
Mean ± SD	21.8 ± 4.4
Range	14.4-32.1
<18.5	9 (23.1)
18.5-25	25 (64.1)
25-30	5 (12.8)
Weight loss before study entry	
>10%	5 (12.8)
5-10%	9 (23.1)
<5%	3 (7.7)
No weight loss	22 (56.4)
Tumor site	
Head and neck	17 (43.6)
Lung	8 (20.5)
Ovary	3 (7.7)
Breast	3 (7.7)
Stomach	2 (5.1)
Pancreas	2 (5.1)
Liver	2 (5.1)
Kidney	1 (2.6)
Uterine sarcoma	1 (2.6)
Stage	
IIIA	1 (2.6)
IV	38 (97.4)
ECOG PS	
0	2 (5.1)
1	27 (69.2)
2	10 (25.7)

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

We shall now try to explain how the different components of our treatment may have acted on the different targets. Regarding the pharmaconutritional support, the main issue is the need to administer an adequate dose. Indeed, in the first of the two large-scale randomized studies (23), LBM did not change significantly in a patient population in which compliance with the experimental supplement averaged 1.4 cans per day, whereas in a substudy, the administration of the supplement enriched with eicosapentaenoic acid was associated with an increase in physical activity, which may reflect improved quality of life (24). Increased activity is particularly beneficial in cachectic patients, as inactivity is a risk factor for muscle atrophy (25). The second study compared the same supplement with megestrol acetate or a combination of the two: however, the combination was not better than megestrol acetate alone (26). Thus, whereas there is much *in vitro* and animal experimental evidence to support the use of (*n*-3) fatty acids, the case for benefit from their supplementation has not yet been definitively proven. The major obstacle is oral delivery of an adequate dose. In addition, the optimum macronutrient/micronutrient supplement mix to accompany (*n*-3) fatty acids remains to be established. Remarkably, in our study, 66.6% of patients consumed 2 cans per day with a mean consumption of 1.5 cans per day. The probable reasons why LBM increased significantly compared with results obtained by Fearon et al. (23), where it did not, were the better compliance of our patients to pharmaconutritional supplement and the longer duration of treatment (4 months versus 8 weeks).

Regarding medroxiprogesterone acetate, notwithstanding the fact that it is currently the only (together with MA) approved drug for CACS, the increased risk of adverse events that therefore entails a careful patient selection must be taken into account when administering it. The dosage of medroxiprogesterone acetate given (500 mg/d) is within the mean range of the currently recommended dosages and has been shown to be safe: indeed, only one patient had to discontinue medroxiprogesterone acetate due to deep vein thrombosis of the leg.

As for cyclooxygenase-2 inhibitors, notwithstanding their potential interest also in the treatment of cancer cachexia, some concerns have recently arisen on the clinical use of these agents because of their toxicity and particularly cardiovascular risks (http://www.fda.gov). We believe that at the dosage (200 mg/d) and for the duration (4 months) used in our study, the treatment can be considered completely safe. In a recent study carried out on 15 patients with CACS treated with medroxiprogesterone acetate (500 mg twice daily) and celecoxib (200 mg twice daily) plus oral food supplementation for 6 weeks, an increase of body weight and an improvement in fatigue, appetite, and performance status (27) were observed.

Among the potentially useful agents not used in this study, anti-TNF-α and anti-IL-6 monoclonal antibodies, although promising, have not yet obtained the approval for CACS treatment.

Table 3. Nutritional/functional, laboratory, and quality of life variables evaluated after 1, 2, and 4 months of treatment on 39 patients

Variables	Baseline	1 mo	*P*	2 mo	*P*	4 mo	*P*
Body weight (kg)	55.1 ± 10	56.5 ± 10.5	0.001	56.4 ± 9.7	0.036	57 ± 9.8	0.031
LBM (kg)	38 ± 9	38.9 ± 9	0.059	39.4 ± 8.9	0.045	39.7 ± 8.7	0.024
Grip strength (kg)	28.0 ± 10.4	27.8 ± 9.5	0.879	27.9 ± 9.3	0.673	28.1 ± 9.5	0.827
Appetite	5.5 ± 2.5	6.6 ± 2.2	0.005	6.8 ± 1.9	0.001	7.0 ± 1.6	0.004
IL-6 (pg/mL)	12.5 ± 9.9	8.8 ± 8.7	0.002	7.5 ± 8.6	0.003	7.4 ± 8.5	0.007
TNF-α (pg/mL)	22.2 ± 16.6	19.5 ± 16	0.204	15.8 ± 13	0.020	14 ± 11.7	0.015
Leptin (ng/mL)	5.9 ± 6.1	8.9 ± 10.6	0.008	10.2 ± 13.3	0.031	13.6 ± 13.3	<0.001
ROS (FORT U)	468.5 ± 97.2	436.6 ± 92.5	0.033	437.7 ± 89.6	0.087	444.1 ± 93.6	0.162
GPx (units/L)	8,206.6 ± 2,322.3	8,339.3 ± 2,411.8	0.726	8,295.9 ± 2,314.1	0.848	8,849.2 ± 2,629	0.211
Quality of life questionnaires							
EORTC QLQ-C30	65.9 ± 16.3	72.4 ± 15.6	0.008	71.8 ± 14.6	0.020	70.9 ± 14.6	0.044
EQ-5D$_{index}$	0.50 ± 0.4	0.58 ± 0.4	0.175	0.56 ± 0.4	0.340	0.59 ± 0.4	0.114
EQ-5D$_{VAS}$	49.4 ± 21.4	58.9 ± 22.7	0.016	58.6 ± 20.6	0.015	58.7 ± 19.4	0.009
MSFI-SF	20.1 ± 22.1	14.4 ± 20.3	0.125	11.8 ± 17.2	0.022	10.8 ± 14.4	0.004

NOTE: Data are reported as mean ± SD. As for EORTC QLQ-C30, EQ-5D index, and EQ-5D$_{VAS}$, the increasing of score corresponds to improvement of quality of life, whereas for MSFI-SF, the decrease of quality of life score corresponds to amelioration of fatigue. Significance was considered for $P < 0.05$ as calculated with Student's *t* test for paired data (posttreatment values versus baseline values). Significance for IL-6, TNF-α, and leptin was calculated using Wilcoxon ranks test.
Abbreviations: GPx, glutathione peroxidase; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer QLQ-C30; EQ-5D, Euro QL-5D; MSFI-SF, multidimensional fatigue symptom inventory-short form.

The methodologic issues to be considered aside from the combined approach used in the present study include the best way to assess the degree of CACS, its appropriate characterization by measuring all possible contributing factors (a ''CACS staging system''), and the best ways to assess caloric intake, nutrition status, patient functioning, and well-being. Considering that both CACS and oxidative stress are clinically relevant in terms of their effect on both patient quality of life and survival, the search for a potentially effective treatment on both these end points must be considered critical among the not yet available oncologic treatments with a high effect.

It must also be taken into account that the treatment tested is simple, easy to administer, and based mainly on alimentary sources, relatively low-cost pharmaconutritional support, and low-cost drugs: therefore, it may be considered as having a favorable cost-benefit profile while achieving an optimal patient compliance.

The results of the present study are very encouraging, although they should be considered with some caution taking into account that this is an uncontrolled study. Therefore, a phase III randomized study will begin very soon as a multicenter trial.

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