Cancer-Related Anorexia/Cachexia Syndrome and Oxidative Stress: An Innovative Approach beyond Current Treatment

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Abstract

Objective: Cancer-related anorexia/cachexia syndrome and oxidative stress play a key role in the progression and outcome of neoplastic disease. Patients and Methods: On the basis of our previously published studies and clinical experience, we have developed an innovative approach consisting of diet with high polyphenol content (400 mg), p.o. pharmacological support enriched with $n-3$ fatty acids (eicosapentaenoic acid and docosahexaenoic acid) 2 cans (237 mL each) per day, medroxyprogesterone acetate 500 mg/d, antioxidant treatment with $\alpha$-lipoic acid 300 mg/d plus carcobucystine lysine salt 2.7 g/d plus vitamin E 400 mg/d plus vitamin A 30,000 IU/d plus vitamin C 500 mg/d, and selective cyclooxygenase-2 inhibitor Celecoxib 200 mg/d. The treatment is administered for 16 weeks. The following variables are evaluated: (a) clinical variables (stage and Eastern Cooperative Oncology Group performance status); (b) nutritional variables (lean body mass, appetite, and resting energy expenditure); (c) laboratory variables (serum levels of proinflammatory cytokines, C-reactive protein, and leptin and blood levels of reactive oxygen species and antioxidant enzymes); and (d) quality of life variables (European Organization for Research and Treatment of Cancer QLQ-C30, EQ-5D index, and EQ-5D VAS). A phase II nonrandomized study has been designed to enroll 40 patients with advanced cancer at different sites with symptoms of cancer-related anorexia/cachexia syndrome and oxidative stress. Results: As of January 2004, 28 patients have been enrolled: 25 patients were evaluable and 14 of them have completed the treatment (20 patients have completed 2 months of treatment). As for clinical response, five patients improved, three patients remained unchanged, and six patients worsened. The Eastern Cooperative Oncology Group performance status (grade) 1 remained unchanged. As for nutritional/functional variables, the lean body mass increased significantly at 2 and 4 months. As for laboratory variables, reactive oxygen species decreased significantly and proinflammatory cytokines interleukin-6 and tumor necrosis factor-$\alpha$ decreased significantly. As for quality of life, it comprehensively improved after treatment. Conclusions: The treatment has been shown to be effective for clinical response, increase of lean body mass, decrease of reactive oxygen species and proinflammatory cytokines, and improvement of quality of life. The treatment has been shown to be safe with good compliance of patients. The study is in progress (14 further patients will be included).

Introduction

The characteristic clinical picture of anorexia, tissue wasting, loss of body weight accompanied by a decrease in muscle mass and adipose tissue, and poor performance status (PS) that often precedes death has been named cancer-related anorexia/cachexia syndrome (CACS; refs. 1-4). At the time of diagnosis, 80% of patients with upper gastrointestinal cancers and 60% of patients with lung cancer have already experienced substantial weight loss (5). The prevalence of cachexia increases from 50% to $>80\%$ before death, and in $>20\%$ of patients, cachexia is the main cause of death (5). In addition to reduced food intake, important abnormalities in carbohydrate, protein, and lipid biochemistry and metabolism alongside with changes in energy metabolism have been observed, which may account for CACS. CACS may result from circulating factors produced by the tumor, or by the host immune system in response to the tumor, such as cytokines released by lymphocytes and/or monocyte/macrophages. Several proinflammatory cytokines, including interleukin (IL)-1, IL-6, tumor necrosis factor-$\alpha$ (TNF-$\alpha$), IFN-$\alpha$, and IFN-$\gamma$, have been implicated in the pathogenesis of cachexia associated with human cancer (6-10). Additional factors and mechanisms thought to play a central role in CACS are the presence of a chronic systemic inflammatory state, circulating tumor-derived lipolytic and proteolytic factors, increased futile energy-consuming cycles, such as the Cori cycle, and a decreased food intake.

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. Proinflammatory cytokines, proposed as mediators of CACS, may have a central role in long-term inhibition of feeding by mimicking the hypothalamic effect of excessive negative feedback signaling from leptin.

Several mechanisms may lead to oxidative stress (OS) in cancer patients. The first one is the altered energy metabolism, which may be accounted for symptoms such as anorexia/cachexia, nausea, and vomiting that prevent a normal nutrition and thereby a normal supply of nutrients such as glucose, proteins, and vitamins, leading eventually to accumulation of free radicals that are known as reactive oxygen species (ROS), such as hydroxyl radicals, superoxide radicals, and others. The second mechanism is a nonspecific chronic activation of the immune system with an excessive production of proinflammatory cytokines, which in turn may increase the ROS production (11). Indeed, a chronic inflammatory condition associated with increased OS has been suggested as one of the triggering mechanisms of the tumor-induced immune suppression (12). Recently, several studies have reported that the chronic inflammation that occurs in patients with advanced cancer may be attributable to OS, which can adversely affect the immune functions. Indeed, free oxygen radicals produced by macrophages were able to inhibit nonspecific and tumor-specific cytotoxicity and down-regulate signal molecules (13-16). Therapeutic interventions aimed to protect the immune system in cancer patients from OS-induced cell damage may enhance their immune competence. A third mechanism may be the result of the use of antineoplastic drugs: many of them, particularly alkylating agents and cisplatin, are able to produce an excess of ROS and therefore lead to OS (17). Several studies have shown that chemotherapy and radiation therapy are associated with increased formation of ROS and depletion of critical plasma and tissue antioxidants (18).

Thus, the hypothesis may arise that the body redox systems, which include antioxidant enzymes and low molecular weight antioxidants, may be dysregulated in cancer patients and that this imbalance might enhance disease progression.

Regarding the mechanisms linking OS and cachexia in cancer, the following evidence has been provided: (a) In a murine model of muscle wasting and cachexia, TNF-α has been shown to induce OS and nitric oxide synthase. Moreover, TNF-α-induced cachexia could be prevented with the antioxidants D-α-tocopherol or the nitric oxide synthase inhibitor nitro-l-arginine (19). (b) An enhanced protein degradation is seen in skeletal muscle of cachectic mice given TNF-α, which seems to be mediated by OS. There is some evidence that this may be a direct effect and is associated with an increase in total cellular ubiquitin-conjugated muscle proteins. Another cytokine, IL-6, may play a role in muscle wasting in certain animal tumors, possibly through both lysosomal (cathepsin) and nonlysosomal (proteasome) pathways (20). (c) A high rate of glycolytic activity and lactate production is commonly seen in the skeletal muscle tissue in practically all catabolic conditions, including cancer (21-24). Importantly, it was found even in well-nourished cancer patients (i.e., relatively early in the catabolic process; ref. 25). Because the glycolytic metabolism is normally suppressed by ATP generated by the mitochondrial oxida-
tive energy metabolism, the high glycolytic activity suggests that the capacity of the mitochondrial energy metabolism is too weak to meet the cellular demand for ATP. The mitochondrion is exquisitely sensitive against reactive oxygen intermediates (26, 27) but generates superoxide radicals and hydrogen peroxide, especially if its transmembrane potential (i.e., the energy state) is low (28-30). This generates a potentially vicious circle unless contained by protective mechanisms. In addition, mitochondria were found to produce nitric oxide (31, 32), which is also potentially damaging for mitochondria (19, 32-34). Therefore, it makes sense that mitochondria require normally adequate concentrations of antioxidants and radical scavengers, such as reduced glutathione (35, 36). Spermine is another important scavenger of ROS (37) that was found to exert protective effects on mitochondria (38-40). Among other claims, it was claimed that spermine strongly inhibits the induction of mitochondrial nitric oxide synthase (41). (d) Some characteristic biochemical changes are typically found in all catabolic conditions tested thus far. These changes include a conspicuous increase in the plasma glutamate level (42), which is similarly found in cancer patients (3, 43, 44) and patients with other diseases (45-48). Whether the increase in plasma glutamate is merely an epiphenomenon in the wasting process or directly involved in the pathogenetic mechanism remains to be determined. In addition, the elevated plasma glutamate levels have been shown to be associated with a decreased muscular uptake of glutamate and a corresponding decrease in i.m. glutamate and reduced glutathione levels (42, 47, 49).

Regarding the human cancer, we studied the OS by assessing glutathione peroxidase (GPx), the serum levels of proinflammatory cytokines, which are, according to us, an optimal surrogate marker of clinical cancer cachexia, and correlated them with the most important clinical indices of cancer patients such as stage of disease and Eastern Cooperative Oncology Group (ECOG) PS with the aim of finding the prognostic role for disease outcome in 82 patients with cancer at different sites, mostly in advanced stages (III and IV) of disease (50). We found that GPx was significantly lower in cancer patients than controls and the serum proinflammatory cytokines IL-6 and TNF-α were significantly higher in cancer patients than controls. Moreover, GPx activity decreased significantly in stage IV/ECOG II-III, whereas a direct correlation between stage/ECOG PS and serum levels of IL-6 was observed. In conclusion, our study was the first to show that antioxidant enzymes activity, which is considered a surrogate marker for the body OS, and proinflammatory cytokines, which are considered the most important surrogate marker for cancer cachexia, strictly correlated with the most important clinical variables of cancer disease.

**Aim of the Study.** The aim of the present study was that to test the efficacy and safety of an integrated treatment based on diet, p.o. pharmaconutritional support, and drugs in a population of advanced cancer patients with CACS/OS. The efficacy was assessed in terms of clinical response, improvement of nutritional and functional variables, changes of laboratory variables (considered as indicators of CACS/OS), and improvement of quality of life (QL).
The ultimate goal of our study should be that of translating the results obtained on CACS/OS symptoms found in advanced cancer patients into a prevention trial in a population of individuals at risk of developing CACS/OS.

Patients and Methods

Study Design. An open nonrandomized phase II study was designed. On the basis of the Simon two-stage design for phase II studies, considering P0 (i.e., noneffective treatment) as a total response of ≤40% of patients and P1 (i.e., effective treatment) as a total response of at least 60% of patients, the treatment will be considered effective if at least 18 of 34 patients show a response (“high response” plus “response”; first stage). At the end of the second stage, 21 of 39 “responders” patients will show the effectiveness of treatment. The study was approved by the Ethical Committee of the Policlinico Universitario, University of Cagliari, and written informed consent was obtained by all patients prior to inclusion in the study.

Patient Eligibility

Inclusion criteria

• 18 to 80 years old
• has histologically confirmed tumor of any site at advanced stage, especially cancers inducing early cachexia (head and neck and gastrointestinal cancers);
• had lost at least 5% of their ideal (or pre-illness) body weight in the last 3 months (early “clinical” or overt cachexia);
• and/or with abnormal values of proinflammatory cytokines, ROS, and antioxidant enzymes predictive of the onset of clinical cachexia
• treated with either antineoplastic therapy with curative or palliative intent (chemotherapy or hormone therapy) or supportive care
• has a life expectancy of >4 months.

Exclusion criteria

• pregnancy
• significant comorbidities
• impaired food intake due to mechanical obstruction
• medical treatments inducing significant changes of patient metabolism or body weight such as enteral or parenteral nutrition, corticosteroids, insulin, or any other drug potentially capable of influencing body weight.

Treatment Plan. The integrated treatment consisted of the following:

• diet with high polyphenol content (400 mg) obtained by alimentary sources (onions, apples, oranges, red wine, or green tea) or supplemented o by tablets
• p.o. pharmaconutritional support (ProSure, Abbott Laboratories, North Chicago, IL) enriched with n-3 fatty acids (eicosapentaenoic acid 1.1 g and docosahexaenoic acid 0.46 g, 310 kcal per can): 2 cans per day (eicosapentaenoic acid 2.2 g/d and docosahexaenoic acid 0.92 g/d)
• p.o. progestagen: medroxyprogesterone acetate (Provera, Pharmacia-Pfizer, Milan, Italy) 500 mg/d p.o.
• antioxidant treatment: α-lipoic acid (Tiobec, Laborest, Nerviano, Milan, Italy) 300 mg/d p.o. plus carbocysteine lysine salt (Fluifort, Dompè, Milan, Italy) 2.7 g/d p.o. plus vitamin E (Sursum 400, Abiogen Pharma SpA, Pisa, Italy) 400 mg/d p.o. plus vitamin A 30,000 IU/d p.o. plus vitamin C 500 mg/d p.o.
• selective cyclooxygenase-2 inhibitor Celecoxib (Celebrex, Pharmacia-Pfizer) 200 mg/d p.o.
• with or without anti-TNF-α monoclonal antibody (not yet used).

The polyphenols have been included for their high activity as antioxidants (51): among them, the quercetin is the most effective. The p.o. pharmaconutritional supplement has the objective to integrate the energetic/proteic intake with the supplementation of n-3 fatty acids, which are able to inhibit cytokine production (TNF-α). The treatment with medroxyprogesterone acetate has the objective to inhibit the cytokine production and to act positively on patient cenestesis: our previous experimental and clinical experience with medroxyprogesterone acetate supports this choice (52). The selected antioxidant treatment has been shown to be effective in reducing blood levels of ROS and increasing blood levels of physiologic antioxidant enzymes in a series of our published articles (50, 53, 54). The cyclooxygenase-2 selective inhibitor Celecoxib has been chosen for its ability, shown both in experimental and in clinical studies, to inhibit cancer-related inflammatory mediators (prostaglandin E2), angiogenesis, and therefore cancer progression. The anti-TNF-α monoclonal antibody is now under approval in the United States for the treatment of neoplastic cachexia: a multicenter randomized clinical trial is currently under way to test its effectiveness in cachectic pancreatic cancer patients. The pharmaconutritional support containing n-3 fatty acids and the progestagen have already been found effective when administered alone. The efficacy of the above-cited antioxidant treatment has been already shown in one of our recent studies (54). Clinical data on the efficacy of selective cyclooxygenase-2 inhibitors in the treatment of CACS and OS have not yet been published.

Treatment Duration. The treatment duration was 16 weeks: this period of time was considered sufficient to verify its effects and to meet the patient compliance (i.e., satisfaction, acceptability, and lack of significant side effects).

Study End Points. The end points of this phase II study were efficacy and safety. The following are efficacy variables: (a) clinical, (b) nutritional/functional, (c) laboratory, and (d) QL. The following changes were considered significant for response to treatment:

1. Clinical variables
   • objective clinical response before and after treatment (“complete response,” “partial response,” “stable disease,” or “progressive disease”: an improvement or at least disease stability (stable “complete response” before and after treatment or a change from “partial response” to “complete response” or from “stable disease” to “partial response” or “stable disease” before and after treatment)) (55)
   • PS according to ECOG scale before and after treatment (56): an improvement of 1 unit according to the ECOG PS scale.
2. Nutritional/functional variables
   - weight: an increase of at least 5% of the pretreatment body weight
   - lean body mass (LBM) by bioimpedentiometry: an increase of LBM of at least 10% compared with baseline value
   - appetite evaluated by Visual Analogue Scale ranging from 0 to 10: an increase of at least 2 units after treatment as compared with baseline
   - resting energy expenditure (REE; kcal/d) by indirect calorimetry (calculated only in a subset of patients): a decrease of at least 10% as compared with baseline value
   - grip strength by dynamometer: an increase of at least 30% as compared with baseline value.

3. Laboratory variables
   - serum levels of proinflammatory cytokines (IL-6 and TNF-α): a decrease of at least 25% as compared with baseline values
   - serum levels of leptin: an increase of at least 100% as compared with baseline values
   - blood levels of ROS by FORT test: a decrease of at least 80 to 100 FORT units as compared with baseline values
   - evaluation by photometer of the erythrocyte levels of the antioxidant enzyme GPx: an increase of at least 2,000 units (or 50%) as compared with baseline values.

4. Evaluation of QL by the following questionnaires:
   - European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 version 3: an increase of at least 25% of the score as compared with baseline values
   - Euro QL EQ-5D: The Euro QL EQ-5D is a generic, single index measure of health status developed by a collaborative research network with participants in different European countries. EQ-5D defines health in terms of five dimensions: mobility, self/care, usual activity, pain/discomfort, and anxiety/depression. Each dimension is divided into three levels. The resulting scale values give a weight of 1 to “full health” and 0 to “death.” EQ-5D was designed for self-completion and consists of a two-page questionnaire. The first page records the respondent’s level of problem on each of the EQ-5D dimensions: this information can then be converted into a single index score and is named EQ-5Dindex. The second page questionnaire records the respondent’s assessment of the overall health state on a 10 cm Visual Analogue Scale (from 0 to 100) and is named EQ-5DVAS. An increase of at least 25% of the scores of both EQ-5Dindex and EQ-5DVAS as compared with baseline values.
   - Multidimensional Fatigue Symptom Inventory—Short Form is a 30-item questionnaire evaluating the principal manifestations of fatigue (57). The vigor subscale was assessed independently. An increase of at least 25% of the scores as compared with baseline values.

Timing of Evaluation of Above Variables. The clinical, nutritional/functional, laboratory, and QL variables were evaluated before treatment and at 4, 8, and 16 weeks (1, 2, and 4 months).

Criteria for Considering the Patients as “Responders,” “High Responders,” or “Nonresponders.” The patients were to be considered as “high responders” if the following changes occurred after treatment:
   - improvement of clinical response plus improvement of ECOG PS or improvement of clinical response plus stability of ECOG PS or stability of clinical response plus improvement of ECOG PS
   - improvement of at least three nutritional/functional variables with stability of the other variables
   - improvement of at least three laboratory variables (including proinflammatory cytokines and ROS) independently from the changes of the other variables
   - improvement of the scores of at least two QL questionnaires and no worsening of the others.

The patients were to be considered as “responders” if the following changes occurred after treatment:
   - no change or even slight worsening of the clinical response such as “stable disease” for >3 months plus no change for ECOG PS < 2 or Karnofsky > 60 and improvement for ECOG PS ≥ 2/Karnofsky ≤ 60
   - improvement of at least three nutritional/functional variables plus stability of one and worsening of one or improvement of at least three plus stability of the other two or improvement of at least two plus stability of the other three
   - improvement of at least two laboratory variables (i.e., proinflammatory cytokines and ROS) independently from the changes of the other variables
   - improvement of the scores of at least one questionnaire plus worsening of no more than one.

The patients were to be considered as “nonresponders” if the following changes occurred after treatment:
   - worsening of clinical response reaching “progressive disease” by 3 months or stable “progressive disease” before and after treatment or no improvement for ECOG PS ≥ 2/Karnofsky ≤ 60 or worsening for ECOG PS < 2/Karnofsky ≥ 60
   - worsening of more than one nutritional/functional variable independently from the changes of the other variables or improvement of one and no change of the other four or no change of at least four variables
   - improvement of only one laboratory variable or no change of all variables or worsening of more than three variables
   - no change of the scores of all QL questionnaires or worsening of the score of more than one QL questionnaire.

Methods

Evaluation of LBM by Bioimpedentiometry. The impedance measurements were conducted with a bioelectric impedance analyzer series 101 (using the standard four-electrode arrangement at 800 mA and 50 kHz). Body composition data analyzed by bioelectric impedance analyzer are derived from correlations of resistance (R) and reactance (Xc). During the bioelectric impedance analyzer measurement, the subjects lay supine with arms and legs angled outward so that the medial surface of the limbs do not touch the rest of the body. For conventional whole body measurement, the electrodes will be placed between the hand and the foot of the dominant side.
REE by Indirect Calorimetry. The REE includes the basal energy expenditure plus the energy required for eating, minimal physical activity, and thermogenic effect of food. We used a Deltatrac metabolic monitor (Datex Ohmeda, Helsinki, Finland) that evaluates oxygen consumption and carbon dioxide production by applying the Harris-Benedict formulas.

Assessment of Serum Levels of Proinflammatory Cytokines and Leptin. Proinflammatory cytokines (IL-6 and TNF-α) were evaluated by ELISA assay using monoclonal antibodies to two different epitopes of the cytokine molecules. The absorbance of the sample was analyzed by a spectrophotometer at 450 nm. Serum leptin levels were determined with an ELISA assay using a monoclonal antibody specific for human leptin. The absorbance was measured by a spectrophotometer at 450 ± 10 nm. More details about the techniques are reported in our previous studies (58, 59).

Blood Levels of ROS and Erythrocyte Levels of GPx. Blood levels of ROS were determined using the FORT test: the radical species produced by the reaction that are directly proportional to the quantity of lipid peroxides present in the sample interact with an additive (phenylenediamine derivative) that forms a radical molecule evaluable by spectrophotometer at 505 nm (Form CR 2000, Callegari, Parma, Italy). Results are expressed as FORT units where 1 FORT unit corresponds to 0.26 mg/L of H2O2 (60). Erythrocyte GPx was measured by photometer using a commercially available kit (Ransod, Randox Lab, Crumlin, United Kingdom).

Statistical Analysis. The benefit obtained by treated patients will be evaluated using the paired Student’s t test or Wilcoxon signed rank test when appropriate for all patients at all times to minimize reporter’s bias. The benefit obtained by treated patients was evaluated using the paired Student’s t test or Wilcoxon signed rank test when appropriate for all patients at all times to minimize reporter’s bias. The benefit obtained by treated patients was evaluated using the paired Student’s t test or Wilcoxon signed rank test when appropriate for all patients at all times to minimize reporter’s bias.

Results

Patients. From July 2002 to December 2003, 28 patients were enrolled: 25 were evaluable. Patient clinical characteristics are listed in Table 1. It is to be noted that 13 patients were clearly underweight (body mass index < 18.5 kg/m2) and 12 were normal weight. Of 25 evaluable patients were clearly underweight (body mass index < 18.5 kg/m2) and 12 were normal weight. Of 25 evaluable patients, whereas three patients improved (from ECOG PS 2 to 1). ECOG PS was evaluated by the same clinician for all patients at all times to minimize reporter’s bias.

Study End Points

1. Efficacy.

Clinical variables. Objective response was evaluated in 14 patients who completed 4 months of treatment: after treatment, 5 patients improved (3 patients changed from ‘‘progressive disease’’ to ‘‘stable disease’’) and 2 patients changed from ‘‘stable disease’’ to ‘‘partial response’’, 3 patients remained unchanged (‘‘stable disease’’), and 6 patients worsened (from ‘‘stable disease’’ to ‘‘progressive disease’’). ECOG PS remained unchanged (1) in most patients, whereas three patients improved (from ECOG PS 2 to 1). ECOG PS was evaluated by the same clinician for all patients at all times to minimize reporter’s bias.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
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<tbody>
<tr>
<td>Patients enrolled (n)</td>
<td>28</td>
</tr>
<tr>
<td>Patients evaluable (n)</td>
<td>25*</td>
</tr>
<tr>
<td>Male/female (n)</td>
<td>12/16</td>
</tr>
<tr>
<td>Age (y)</td>
<td>58.2 ± 9.0</td>
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<tr>
<td>Mean ± SD</td>
<td>36-76</td>
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<tr>
<td>Weight (kg)</td>
<td>51.4 ± 11.0</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>36-76</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.59 ± 0.07</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>145-175</td>
</tr>
<tr>
<td>Body mass index (kg/m2)</td>
<td>20.5 ± 4.7</td>
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<tr>
<td>Mean ± SD</td>
<td>14.4-31.6</td>
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<tr>
<td>Range</td>
<td>13 (46.4)</td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>12 (42.9)</td>
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<tr>
<td>18.5-25</td>
<td>3 (10.7)</td>
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<tr>
<td>&gt;25</td>
<td>3 (10.7)</td>
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<tr>
<td>Tumor site [n (%)]</td>
<td>Head and neck 14 (50)</td>
</tr>
<tr>
<td>Breast 4 (14.3)</td>
<td></td>
</tr>
<tr>
<td>Lung 3 (10.7)</td>
<td></td>
</tr>
<tr>
<td>Stomach 2 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Ovary 2 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Uterine sarcoma 1 (3.6)</td>
<td></td>
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<tr>
<td>Colon 1 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Pancreas 1 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Stage [n (%)]</td>
<td>II 1 (3.6)</td>
</tr>
<tr>
<td>IIA 1 (3.6)</td>
<td></td>
</tr>
<tr>
<td>IV 26 (92.8)</td>
<td></td>
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<tr>
<td>ECOG PS [n (%)]</td>
<td>0 1 (3.6)</td>
</tr>
<tr>
<td>1 16 (57.1)</td>
<td></td>
</tr>
<tr>
<td>2 11 (39.3)</td>
<td></td>
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</tbody>
</table>

*Two patients were withdrawn from the study for noncompliance due to severe comorbidities and one patient died of ‘‘progressive disease’’ before 1 month of treatment was completed.

Nutritional/functional variables. The results are reported in Table 2. The body weight increased significantly from baseline at all times (1, 2, and 4 months). The LBM increased significantly at 2 and 4 months (Fig. 1), the appetite increased significantly at 1 and 2 months, whereas the grip strength did not show significant changes. A decrease of REE in two patients at the end of treatment was found.

Laboratory variables. The results are reported in Table 2. ROS decreased significantly after 1 and 2 months, whereas GPx activity did not show significant changes. Proinflammatory cytokines IL-6 and TNF-α decreased significantly at all (but one) times, whereas leptin did not show significant changes.

QL variables. The QL variables are reported in Table 3 and Fig. 2: overall, the QL improved after treatment. EORTC QLQ-C30 improved at 1 and 2 months, whereas GPx activity did not show significant changes. Proinflammatory cytokines IL-6 and TNF-α decreased significantly at all (but one) times, whereas leptin did not show significant changes.

Overall, the treatment was quite well tolerated by patients. No patient was withdrawn from the study due to toxicity. One patient interrupted medroxiprogesterone acetate after 2 months for leg deep vein thrombosis and one patient interrupted the treatment after 2 months due to toxicity. One patient interrupted medroxiprogesterone acetate after 2 months for leg deep vein thrombosis and one patient interrupted the treatment after 2 months due to toxicity. One patient interrupted medroxiprogesterone acetate after 2 months for leg deep vein thrombosis and one patient interrupted the treatment after 2 months due to toxicity.
Table 2. Nutritional/functional and laboratory variables evaluated after 1, 2, and 4 months of treatment

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>After 1 mo (25 patients)</th>
<th>P</th>
<th>After 2 mo (20 patients)</th>
<th>P</th>
<th>After 4 mo (14 patients)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Weight (kg)</td>
<td>51.3 ± 10.1</td>
<td>52.7 ± 11.1</td>
<td>0.009</td>
<td>55.3 ± 10.6</td>
<td>0.013</td>
<td>58.1 ± 12.4</td>
<td>0.019</td>
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<tr>
<td>LBM (kg)</td>
<td>35.1 ± 8.6</td>
<td>35.9 ± 8.8</td>
<td>0.067</td>
<td>37.6 ± 8.2</td>
<td>0.045</td>
<td>40.5 ± 9.1</td>
<td>0.023</td>
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<td>Appetite</td>
<td>4.79 ± 2.7</td>
<td>6.71 ± 2.1</td>
<td>0.004</td>
<td>7.2 ± 1.8</td>
<td>0.050</td>
<td>8.0 ± 2.0</td>
<td>0.074</td>
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<tr>
<td>Grip strength</td>
<td>24.9 ± 8.9</td>
<td>24.7 ± 7.5</td>
<td>0.723</td>
<td>27.8 ± 6.1</td>
<td>0.831</td>
<td>30.5 ± 9.0</td>
<td>0.977</td>
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<tr>
<td>ROS (FORT units)</td>
<td>496.2 ± 91.9</td>
<td>442.3 ± 96.2</td>
<td>0.029</td>
<td>425.9 ± 89.4</td>
<td>0.037</td>
<td>434.6 ± 108.1</td>
<td>0.108</td>
</tr>
<tr>
<td>GPx (units/L)</td>
<td>8,837.2 ± 3,176</td>
<td>7,857.5 ± 2,563</td>
<td>0.131</td>
<td>8,047.7 ± 3,069.6</td>
<td>0.137</td>
<td>8,944.1 ± 4,035.1</td>
<td>0.606</td>
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<tr>
<td>IL-6 (pg/mL)</td>
<td>14.9 ± 7.5</td>
<td>10.7 ± 7.7</td>
<td>0.030</td>
<td>8.5 ± 6.9</td>
<td>0.020</td>
<td>7.0 ± 4.9</td>
<td>0.004</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>32.5 ± 21.8</td>
<td>21.8 ± 18.8</td>
<td>0.018</td>
<td>19.4 ± 16.6</td>
<td>0.084</td>
<td>14.5 ± 9.0</td>
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</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>3.9 ± 4.3</td>
<td>5.6 ± 7.2</td>
<td>0.211</td>
<td>7.3 ± 7.8</td>
<td>0.306</td>
<td>18.7 ± 19.5</td>
<td>0.027</td>
</tr>
</tbody>
</table>

NOTE: Data are reported as means ± SD. P < 0.05, Student’s t test for paired data (post-treatment values versus baseline). Significance for leptin values before and after treatment was calculated with Wilcoxon rank sum test.

to supervening pancreatitis. Thus far, the treatment has been shown to be safe without significant side effects and achieved an optimal compliance by patients. The patient’s compliance was assessed by count of tablets/cans returned by patients.

Assessment of “Responders” and “Nonresponders”. Our interim analysis on 14 patients who have completed the treatment showed 7 patients “responders”: consequently, our interim results may allow the study to proceed to the end of the first stage to include 34 patients. At the end of the second stage, 21 of 39 “responders” patients will show the efficacy of treatment. It is to be taken into account the arbitrary nature of the response criteria, cited under Patients and Methods, although they were built up by us carefully.

Discussion

CACS/OS are two of the most important features of advanced cancer and are both predictive of the patient clinical outcome. In recent years, we have come to a better understanding of cancer cachexia: it may be considered as a multifactorial complication of cancer resulting from a complex interaction of major central nervous system and metabolic abnormalities attributable to a combination of tumor-byp products and host cytokine release, comorbidities, and psychological factors rather than a simple increase in energy consumption by the tumor and malnutrition on the part of the patient. Under normal circumstances, both humans and animals respond to malnutrition with a complex neuroendocrine mechanism that eventually leads to an increase in appetite, a relative sparing of LBM and consuming of fat stores, and an overall decrease in the normal REE (61-65). Cachexia refers instead to a pathologic state of malnutrition where appetite diminishes in conjunction with an increase in REE and a relative wasting of LBM. The resulting malnutrition and the loss of LBM worsens the QL and also affects recovery by decreasing tolerance to therapy and increasing complications. Therefore, it would be best to concentrate the efforts on early therapeutic intervention and consider the severity of clinical features as ranging from mild anorexia to severe cachexia. Thus far, attempts at drug therapy for cachexia with a variety of agents have had limited success. The most widely used agents, megestrol/medroxyprogesterone acetate, have been successful to a certain extent in reversing weight loss, although this occurs as a result of an increase in the fat mass and water retention rather than the preservation of LBM.

Megestrol/medroxyprogesterone acetate are generally recommended for long-term (>2-3 months) use, whereas glucocorticoids may be considered useful for a shorter period for appetite stimulation (66, 67). Glucocorticoids have been shown to act rapidly on appetite, and they also show an improvement in fatigue and general sense of well-being. Furthermore, there also seems to be evidence for recommending antiserotonergic drugs, prokinetic agents, branched-chain amino acids, eicosapentaenoic acid, and thalidomide, which act on the feeding regulatory feedback to increase appetite and inhibit tumor-derived and host-derived catabolic factors such as cytokines. Most of these second-line drugs have different sites and/or mechanisms of action. Therefore, these agents could be used to replace first-line drugs in case of failure depending on the cause of cachexia or the patient’s general conditions. Appetite stimulants could remove anorexia with mild side effects at doses that would be able to stabilize weight loss for a certain period of time (66). A prokinetic agent should be used in case of early satiety or opioid-induced nausea. Branched-chain amino acids and eicosapentaenoic acid could be used for the nutritional support (68). Most of the treatments suggested above have not received enough evaluation as...
yet to be recommended as any more than second-line treatments; nevertheless, they could be used not only on an individual basis but also in randomized controlled studies. Furthermore, several new promising drugs are soon to be tested in clinical trials (69-76): they include melanocortin antagonists, growth hormone secretagogues (synthetic agonists of ghrelin, a newly identified orexigenic peptide), and cytokine antagonists or inhibitors. These agents could lead to the development of a combined drug therapy that may, at the same time, address the different aspects of cancer cachexia and target more specific pharmacologic interventions, an approach that has been shown to be highly effective in the management of other cancer-related symptoms such as chemotherapy-induced nausea and cancer pain.

The issues to be considered methodologically for this combined approach include the best way to assess the degree of CACS, the appropriate characterization by measuring all possible contributing factors (a CACS staging system), and the best ways to assess caloric intake, nutrition status, function, and patient well-being.

In a series of our previous articles, we have dealt with CACS/OS and have provided the following evidence: (a) A clinically significant OS takes place in advanced cancer patients, as shown by increased levels of ROS and decreased levels of GPx (50, 54). (b) CACS is a very frequent symptom in advanced disease and is associated with high levels of proinflammatory cytokines (11, 58, 59). (c) Both CACS and OS alone and in combination are highly predictive of clinical outcome and survival (59). (d) The antioxidant agents α-lipoic acid, carbocysteine lysine salt, amifostine, reduced glutathione, and vitamins A, C, and E administered to cancer patients alone or in combination were able to reduce ROS levels and increase GPx activity while reducing serum levels of proinflammatory cytokines (i.e., they were effective on OS; ref. 54). (e) α-Lipoic acid and N-acetyl cysteine were able to correct in vitro the most significant functional defects of peripheral blood mononuclear cells isolated from advanced stage cancer patients (i.e., the defective response to anti-CD3 monoclonal antibody and the defective membrane expression of CD25 and CD95; ref. 53).

Considering that both CACS and OS are clinically relevant in terms of their impact on both patient QL 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 impact. The rationale for including the specific components of our integrated treatment was reported under Patients and Methods. Moreover, we would like to remark the specific role of the pharmaconutritional support based on several previously published clinical trials, which showed its effectiveness in patients with CACS. A clinical study carried out by Barber et al. (77) on 20 patients with pancreatic cancer showed that after administration of the p.o. nutritional supplement enriched with fish oil, patients had significant weight gain, dietary intake increased significantly, REE failed significantly, and PS and appetite were significantly improved. In a study carried out by Fearon et al. (78), 200 patients were randomized to consume the same nutritional supplement without C0 n 3 fatty acids: the results suggested that, if taken in sufficient quantities, only the n 3 fatty acid–enriched supplement resulted in net gain of weight, LBM, and improved QL. Further clinical trials carried out on smaller number of advanced cancer patients with weight loss using the same nutritional supplement showed a stop in weight loss and a slight increase of body weight (79, 80).

Table 3. QL variables evaluated after 1, 2, and 4 months of treatment

<table>
<thead>
<tr>
<th>Questionnaires</th>
<th>Baseline</th>
<th>After 1 mo (25 patients)</th>
<th>P</th>
<th>After 2 mo (18 patients)</th>
<th>P</th>
<th>After 4 mo (12 patients)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC QLQ-C30</td>
<td>56.1 ± 16.7</td>
<td>65.9 ± 17.6</td>
<td>0.003</td>
<td>70.2 ± 13.5</td>
<td>0.019</td>
<td>62.0 ± 14.1</td>
<td>0.459</td>
</tr>
<tr>
<td>EQ-5D&lt;sub&gt;index&lt;/sub&gt;</td>
<td>0.33 ± 0.4</td>
<td>0.45 ± 0.3</td>
<td>0.128</td>
<td>0.59 ± 0.3</td>
<td>0.144</td>
<td>0.54 ± 0.3</td>
<td>0.029</td>
</tr>
<tr>
<td>EQ-5DVAS</td>
<td>44.1 ± 2.2</td>
<td>55.8 ± 2.2</td>
<td>0.022</td>
<td>62.1 ± 2.0</td>
<td>0.038</td>
<td>61.9 ± 1.9</td>
<td>0.089</td>
</tr>
<tr>
<td>MFSI-SF (fatigue)</td>
<td>37.0 ± 19.7</td>
<td>21.4 ± 18.1</td>
<td>0.019</td>
<td>20.1 ± 14.9</td>
<td>0.006</td>
<td>25.0 ± 16.0</td>
<td>0.179</td>
</tr>
<tr>
<td>MFSI-SF (subscale “vigor”)</td>
<td>4.57 ± 3.0</td>
<td>7.0 ± 5.1</td>
<td>0.054</td>
<td>7.0 ± 3.0</td>
<td>0.077</td>
<td>8.50 ± 6.4</td>
<td>0.195</td>
</tr>
</tbody>
</table>

Note: Global QL score for each questionnaire (mean ± SD). For EORTC QLQ-C30, EQ-5D<sub>index</sub>, and EQ-5DVAS the increasing of score corresponds to improvement of QL; for Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF), the decrease of QL score corresponds to amelioration of fatigue. *, P < 0.05, Student’s t test for paired data (post-treatment values versus baseline).
The results obtained in the present study may be considered very encouraging; in fact, LBM increased significantly at 2 and 4 months; the weight increased at 1, 2, and 4 months; the appetite increased at 1 and 2 months; the proinflammatory cytokines decreased at all (but one) time points; the QL (EORTC QLQ-C30, EQ-5D, and EQ-5Dv2) improved; and the “fatigue” improved. It is worth noting that all the patients who showed an improvement in the laboratory variables also showed an improvement in functional variables. As for objective response evaluated in 14 patients who completed 4 months of treatment, 5 patients improved, 3 patients remained unchanged, and 6 patients worsened. ECOG PS remained unchanged in most patients, whereas three patients improved.

The assessment of the “responder” patients showed seven responders. It is to be taken into account the arbitrary nature of the response criteria, cited under Patients and Methods, although they were built up by us carefully. Having selected for our study the Simon two-stage design for phase II studies, we were compelled to consider the patients as responders or nonresponders. On the basis of these interim results, the study may be allowed to proceed to the end of the first stage to include 34 patients. We are confident that the innovative treatment approach of CACS tested in the present study and based on multiple components, each targeted at different factors involved, will confirm its efficacy at the study end in both improving objective clinical symptoms such as LBM and subjective symptoms such as QL. It is also to be taken into account that the treatment consists mainly of diet, relatively low-cost pharmacological support, and low-cost drugs: therefore, it may be considered as having a favorable cost-benefit profile, whereas achieving an optimal patient compliance. As shown in previous studies, both physicians and patients look for more effective treatments for the most important clinical problems of CACS. Caregivers report that it is difficult to cope with patients who progressively lose weight and strength while persistently refusing adequate food intake. Selection criteria for cachexia need to be carefully defined and not only in terms of tumor type and extent but also in terms of the mechanism inducing cachexia, with the hope that the clearly defined patient subgroups will help to better identify those more likely to benefit from the available therapies. Cancer cachexia treatment should also address and focus on the symptomatic advantages in terms of QL rather than just on nutritional aspects, because the survival of these patients may be very short at this stage of disease.

The results of the present study are very encouraging, although they should be considered with some caution taking into account that this represents an uncontrolled study, reported at an interim phase. The ultimate goal should be that of translating the results obtained in advanced cancer patients into a prevention trial in a population of individuals at risk of developing CACS/OS.

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References

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Cancer-Related Anorexia/Cachexia Syndrome and Oxidative Stress: An Innovative Approach beyond Current Treatment

Giovanni Mantovani, Clelia Madeddu, Antonio Macciò, et al.


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