

Efficacy and safety of a two drug-combination regimen for cancer-related cachexia in clinical practice

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Disclosure slide

- No Conflicts of Interest to declare

DEFINITION OF CACHEXIA

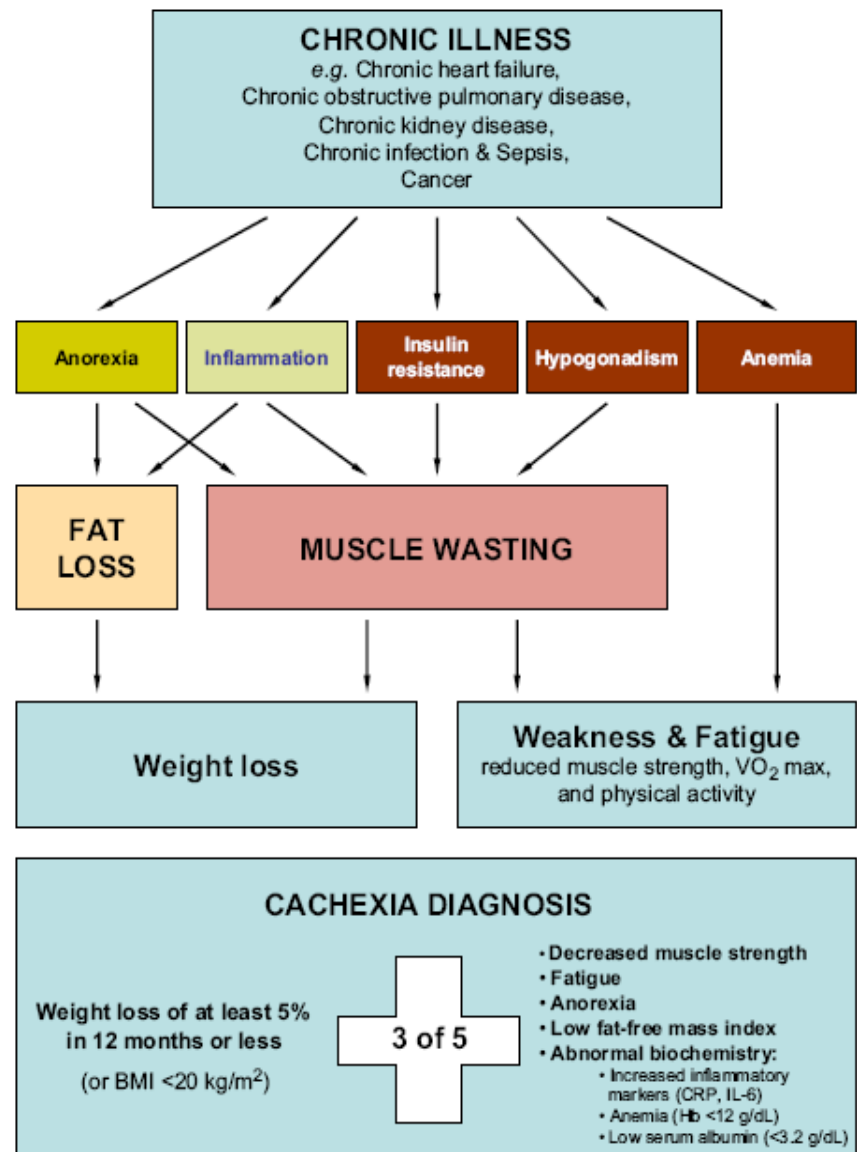
Multi-factorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.

Agreed diagnostic criteria are:

weight loss >5% or >2% in individuals already showing depletion of body weight (BMI <20 kg/m²) or skeletal muscle (sarcopenia).

Assessment for classification and clinical management should include the following domains: anorexia/reduced food intake, catabolic drive, muscle mass and strength, functional and psychosocial impairment.

*Cachexia: a new definition.
Lancet Oncology 2010*



COMBINED APPROACH

To date, attempts at cancer cachexia therapy with a variety of single interventions have had limited success.

The main features of cachexia (progressive loss of muscle mass and function) have been shown to be only minimally influenced by the nutritional or pharmacological tools currently available.

However, a combination of dietary, nutritional, and pharmacological approaches to normalize the metabolic milieu may be capable of reversing advanced cancer-related symptoms that affect patient Quality of Life

References:

Support Care Cancer 2010;18:1–9.

Oncologist 2010;15:119–21.

Cancer Epidemiology, Biomarkers & Prevention



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

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

From July 2002 to January 2005, 44 patients were enrolled. Of these, 39 completed the treatment and were assessable.

Body weight, LBM and appetite increased significantly from baseline.

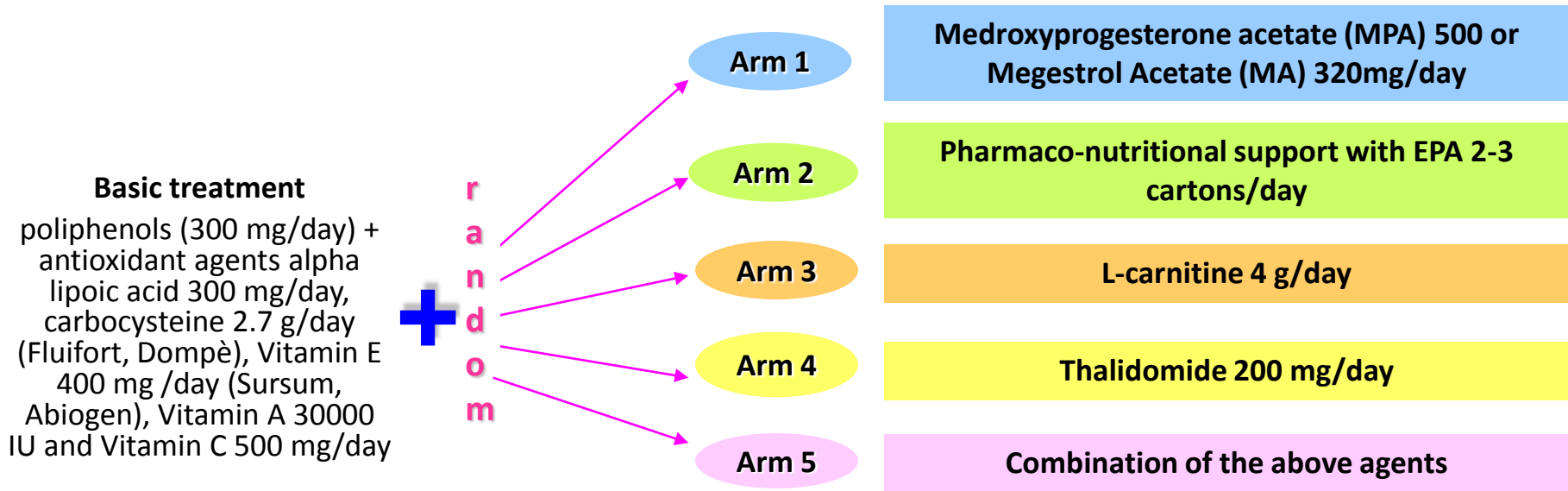
There was an important **decrease of proinflammatory cytokines IL-6 and TNFalpha**

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-5DVAS, 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.

Randomized Phase III Clinical Trial of Five Different Arms of Treatment in 332 Patients with Cancer Cachexia

GIOVANNI MANTOVANI,^a ANTONIO MACCIÒ,^a CLELIA MADEDDU,^a ROBERTO SERPE,^a ELENA MASSA,^a
MARIELE DESSI,^a FILOMENA PANZONE,^a PAOLO CONTU^b



The most effective treatment in terms of all three primary efficacy endpoints, i.e. LBM, REE and fatigue, and the secondary endpoints appetite, IL-6, GPS, and ECOG PS score was the combination regimen that included all selected agents.

The Oncologist 2010;15:200–211

A randomized phase III clinical trial of a combined treatment for cachexia in patients with gynecological cancers: Evaluating the impact on metabolic and inflammatory profiles and quality of life

Antonio Macciò ^{a,*}, Clelia Madeddu ^b, Giulia Gramignano ^c, Carlo Mulas ^a, Carlo Floris ^d, Eleonora Sanna ^d, Maria Chiara Cau ^b, Filomena Panzone ^b, Giovanni Mantovani ^b

**A total of 104 advanced-stage gynecological cancer patients were enrolled and randomly assigned to receive either:
megestrol acetate (MA) plus L-carnitine, celecoxib, and antioxidants (arm 1)
or MA alone (arm 2).**

The treatment duration was 4 months.

The combination arm was more effective than arm 2 as regards:
LBM, REE, fatigue, and global QoL.

As for the secondary efficacy endpoints, patient appetite increased, and ECOG PS decreased significantly in both arms.

The inflammation and oxidative stress parameters IL-6, TNF- α , CRP, and ROS decreased significantly in arm 1, while no significant change was observed in arm 2.

Original article

Randomized phase III clinical trial of a combined treatment with carnitine + celecoxib \pm megestrol acetate for patients with cancer-related anorexia/cachexia syndrome

Clelia Madeddu^a, Mariele Dessì^a, Filomena Panzone^a, Roberto Serpe^a, Giorgia Antoni^a, Maria Chiara Cau^a, Lorenza Montaldo^b, Quirico Mela^b, Marco Mura^c, Giorgio Astara^a, Francesca Maria Tanca^a, Antonio Macciò^a, Giovanni Mantovani^{a,*}

Methods: Sixty eligible patients were randomly assigned to: arm 1, L-carnitine 4 g/day + Celecoxib 300 mg/day or arm 2, L-carnitine 4 g/day + celecoxib 300 mg/day + megestrol acetate 320 mg/day, all orally. All patients received as basic treatment polyphenols 300 mg/day, lipoic acid 300 mg/day, carbocysteine 2.7 g/day, Vitamin E, A, C. Treatment duration was 4 months. Planned sample size was 60 patients.

Conclusions: The results of the present study showed a non-inferiority of arm 1 (two-drug combination) vs arm 2 (two-drug combination + megestrol acetate). Therefore, this simple, feasible, effective, safe, low cost with favorable cost-benefit profile, two-drug approach could be suggested in the clinical practice to implement CACS treatment.

AIM of the study: to test in clinical practice the safety and efficacy of a two-drug combination regimen for the treatment of CACS

Primary endpoints:

- **SAFETY;**
- **INCREASE OF LBM;**
- **IMPROVEMENT OF QUALITY OF LIFE**

Secondary endpoints:

- improvement of physical performance (grip strength and 6 min walk test);
- decrease of inflammation (serum levels of IL-6 and Glasgow Prognostic Score)

TREATMENT PLAN

Antioxidants:

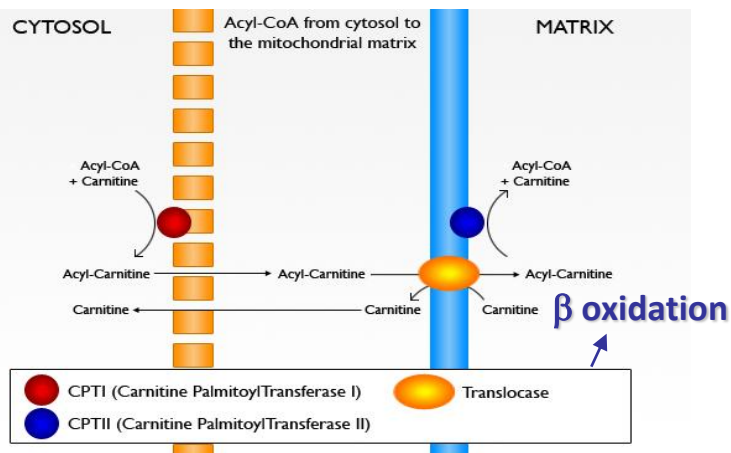
poliphenols (300 mg/d) +alpha lipoic acid 300 mg/d, carbocysteine 2.7 g/d, Vitamin E 400 mg/d, Vitamin A 30000 IU and Vitamin C 500 mg/d



L-carnitine 4 g/day
+ Celecoxib 300 mg/day

Treatment duration: 4 months

RATIONALE FOR SELECTED AGENTS



L-carnitine, a trimethylated amino acid is a co-factor required for transformation of the free long-chain fatty acids into acyl-carnitines and for their subsequent transport into the mitochondrial matrix, where they undergo beta oxidation for cell energy production: thus, it is crucial for cell energy metabolism. **It was shown to be effective in improving fatigue as well as appetite and LBM in one of our recently published studies.**

(Gramignano G et al, Nutrition. 2006 22:136-45).

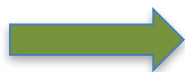
Oxidative stress is closely correlated to both chronic inflammation and metabolic disorders. In previous studies, we clearly demonstrated in vivo and in vitro the efficacy of **specific antioxidants**, such as reduced lipoic acid and cysteine, which are the most important precursors of cell-reduced glutathione.



[Mantovani G](#), [Macciò A](#), [Madeddu C](#), et al. The impact of different antioxidant agents alone or in combination on reactive oxygen species, antioxidant enzymes and cytokines in a series of advanced cancer patients at different sites: correlation with disease progression. [Free Radic Res](#). 2003 Feb;37(2):213-23.

Phase II nonrandomized study of the efficacy and safety of COX-2 inhibitor celecoxib on patients with cancer cachexia

Giovanni Mantovani • Antonio Macciò •
Clelia Madeddu • Roberto Serpe • Giorgia Antoni •
Elena Massa • Mariele Dessì • Filomena Panzone

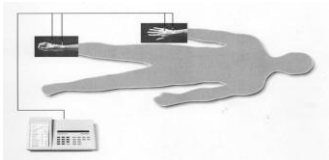


Significant increase in weight and BMI as well as the QoL score in patients receiving celecoxib (200 mg twice daily) compared those receiving the placebo

PRIMARY EFFICACY ENDPOINTS

1 LEAN BODY MASS

a) BIA



2 Quality of life

a) **FATIGUE** by the Multidimensional Fatigue Symptom Inventory–Short Form (MFSI-SF)

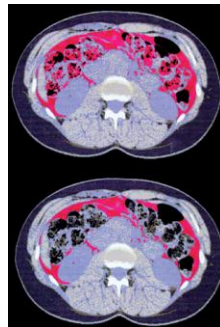
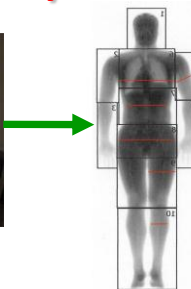
Stein KD, et al. Cancer Pract 1998;6:143-152

b) **Overall QL** by the EORTC-QLQ-C30

c) **regional computed tomography at L3 (L3-CT)**

Slice O' Matic

currently considered the
highest precision method able
to provide detail on fat-free
mass and specific muscles not
provided by DEXA or BIA



Muscle mass (mm²)

Estimated LBM (kgs)

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SECONDARY EFFICACY ENDPOINTS

1

PHYSICAL PERFORMANCE

by 6 MIN WALK TEST

2

GRIP STRENGTH

by Jamar Hydraulic Hand
Dynamometer



3

PROINFLAMMATORY CYTOKINE

by enzyme-linked immunosorbent assays



serum samples

4

GLASGOW PROGNOSTIC SCORE

→ An inflammation-based score

C-reactive protein \leq 10 mg/ml and albumin \geq 35 g/l

0

C-reactive protein \leq 10 mg/ml and albumin $<$ 35 g/l

1

C-reactive protein $>$ 10 mg/ml and albumin \geq 35 g/l

1

C-reactive protein $>$ 10 mg/ml and albumin $<$ 35 g/l

2

5

PERFORMANCE STATUS

by ECOG PS scale

Forrest LM, et al. Br J Cancer 2005;92:1834-1836

Patients and Methods

Eligibility criteria:

- Patients (aged 18-85 years) with histologically confirmed advanced stage tumor at any site, loss of at least 5% of ideal or preillness body weight in the previous 6 months and a life expectancy ≥ 4 months, were eligible. Patients could be receiving concomitant antineoplastic chemotherapy or hormone therapy in the palliative medicine setting or supportive care only. Opioids were allowed for the treatment of cancer pain.

Exclusion criteria:

- Childbearing age, impaired food intake due to mechanical obstruction, medical treatments inducing significant changes of patient metabolism or body weight, history of thromboembolism, cardiac disease, such as congestive heart failure or left ventricular ejection fraction $<35\%$, uncontrolled hypertension, previous myocardial infarction, unstable angina, uncontrolled arrhythmia, positive history for cerebrovascular events, inflammatory bowel diseases, gastrointestinal ulcers.

Statistical analysis

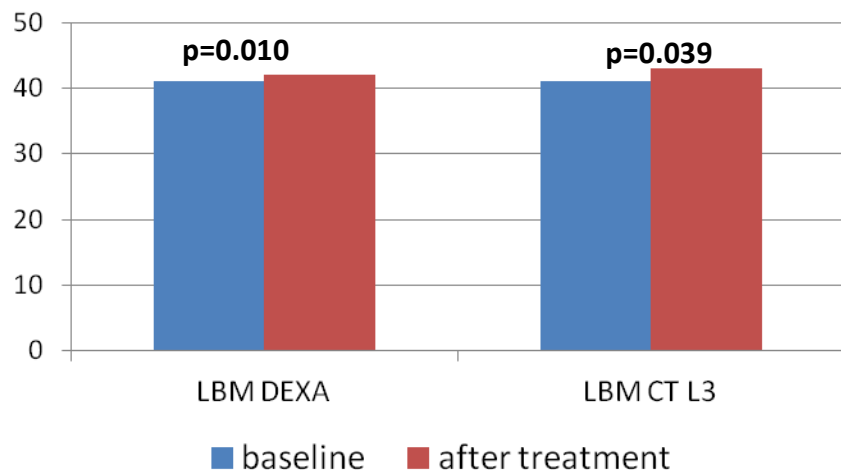
The statistical objectives of the study were to analyze for statistically significant differences the changes (the mean pre intervention versus post intervention values) in treated patients for each primary and secondary efficacy endpoint. One way analysis of variance was used for all comparisons and the Wilcoxon sum rank test was used where appropriate. Statistical significance was established at $p < 0.05$. SPSS version 15.0 was used.

Patient clinical characteristics

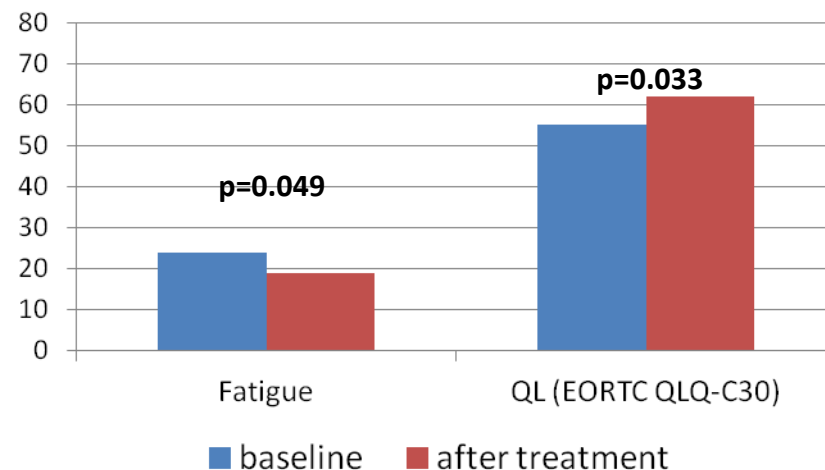
	N.	%
Male/female	51/22	70/30
Age (years)	65±9.6	Range 32-82
Weight (kgs)	56.2±11.5	Range 32-79
BMI	21.1±3.7	Range 13-29.9
Weight loss		
<5%	3	4
5-10% (3-6 mo)	41	56
>10% (3-6 mo)	29	40
Stage		
III	3	4
IV	70	96
Tumor site		
Head and neck	21	28
Lung	11	16
Colorectal	10	14
Pancreas	7	9
Stomach	7	9
Ovary	6	8
Other	11	16
Concomitant palliative chemo, No. (%)		
Yes	59	81
No	14	19

RESULTS: PRIMARY ENDPOINTS

LBM (kg)



Quality of life (QL)



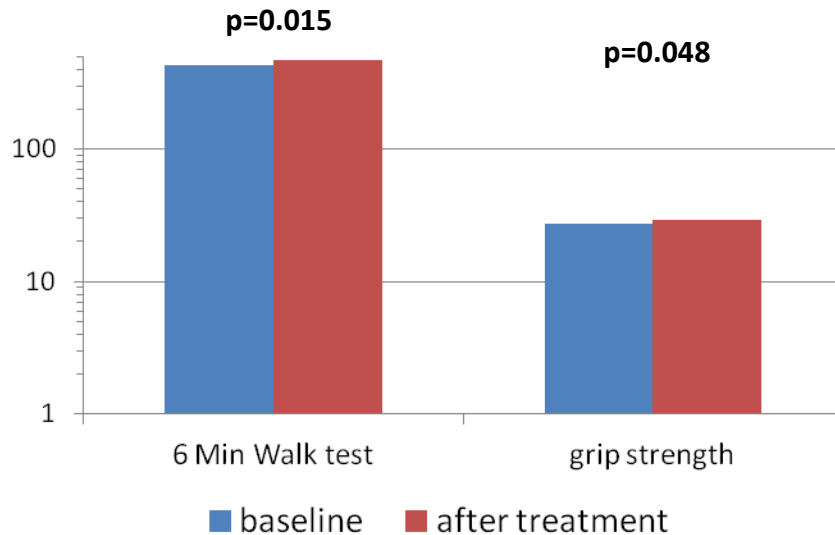
Specific treatment-related toxicity was quite negligible. No grade 3-4 toxicities occurred and no patient had to discontinue the treatment due to severe adverse events.

Toxicity assessed as the worst toxicity per patients

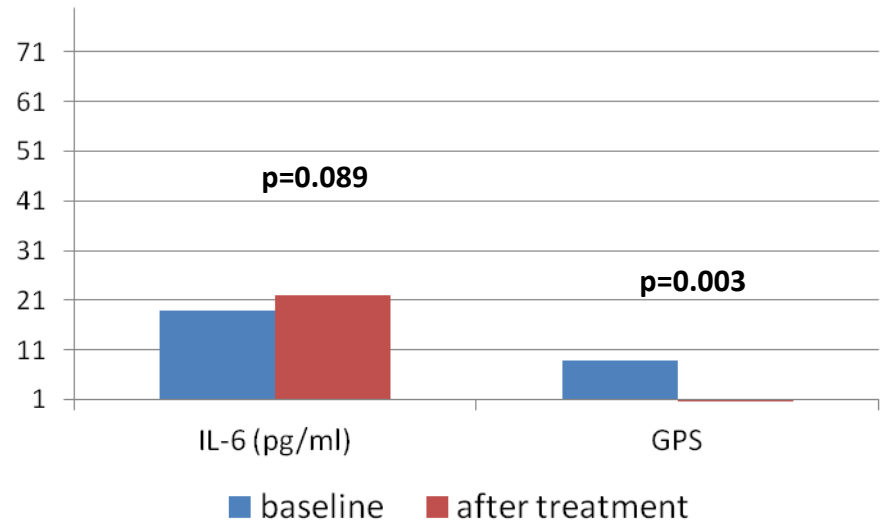
	Grade	
	1/2	3/4
Diarrhea	1	0
Epigastralgia	1	0
Thromboembolism/ Deep vein thrombosis	0	0

RESULTS: SECONDARY ENDPOINTS

Physical performance



Inflammatory markers



The assessment of physical performance by 6MWT test and grip strength showed an improvement ($p = 0.015$ and $p = 0.048$, respectively).

The Glasgow Prognostic Score (GPS) decreased significantly, whilst serum IL-6 remained unchanged.

CONCLUSIONS

The results of the present study confirmed the safety and efficacy of the two-drug combination regimen. Therefore, this simple, feasible, effective, safe, low cost with favorable cost-benefit profile, two-drug approach could be suggested in the clinical practice to implement CACS treatment.

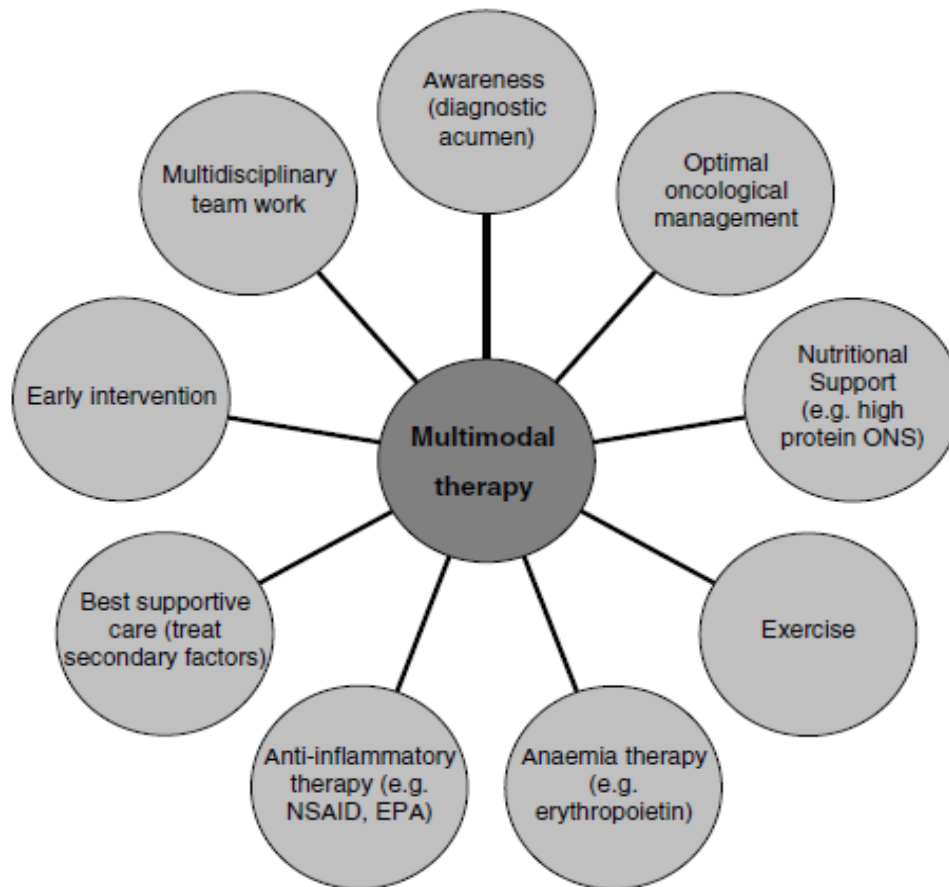
It must be pointed out that the majority of patients during treatment were subjected to palliative chemotherapy protocols that may have positively affected the results.

The efficacy of the combined treatment in terms of the modulation of inflammatory response with the amelioration of the primary endpoints confirms our assumption that the main symptoms of cachectic cancer patients are systemic inflammation-driven.

Cancer cachexia: Developing multimodal therapy for a multidimensional problem

K.C.H. Fearon*

Eur J Cancer 2008; 44: 1124–1132



We are aware that multimodal therapies for cancer cachexia should ideally be introduced within a context of the “best supportive care”, which includes optimal symptom management and careful psychosocial counseling.

BODY, MIND AND SPIRIT: TOWARDS THE
INTEGRATION OF RELIGIOSITY AND
SPIRITUALITY IN CANCER QUALITY OF LIFE
RESEARCH