A Phase II study with antioxidants, both in the diet and supplemented, pharmaco-nutritional support, progestagen and anti-COX-2 showing efficacy and safety in patients with cancer-related anorexia/cachexia (CACS) and oxidative stress (OS)

1. Diet with high polyphenols content (400 mg).
2. Oral nutritional supplement enriched with n-3 PUFA containing 2.6 g EPA/DHA
3. Oral progestagen: MPA 500 mg/day.
4. Antioxidant treatment with alpha lipoic acid 300 mg/day + carboxycysteine lysine salt 2.7 g/day + vitamin E 400 mg/day + vitamin A 30000 IU + vitamin C 500 mg/day.
5. Celecoxib 400 mg/day orally

PATIENT ELIGIBILITY:

✓ age 18 - 80 years

✓ hystologically confirmed tumors of any site especially cancers inducing early CACS (head and neck and gastrointestinal cancer)

✓ patients with the following nutritional characteristics:
  1) patients who had lost at least 5% of ideal or pre-illness body weight in the last 3 months (clinical CACS);
  2) patients with pathological levels of proinflammatory cytokines and/or leptin and/or ROS and/or antioxidant enzymes predictive of CACS

✓ patients treated with either antineoplastic therapy with curative or palliative intent or supportive care

✓ patients with a life expectancy of at least 4 months.

EFFICACY VARIABLES:

The following variables have been evaluated and the following changes were to be considered as significant for response:

**Clinical:** - Objective clinical response: improvement or disease stability; - Performance status (ECOG PS): improvement of 1 unit; - Disease free survival at the end of treatment

**Nutritional/Functional:** - Weight: increase of at least 5%; - Lean Body Mass (LBM) by bioimpedentiometry: increase of at least 10%; - Appetite evaluated by analogue visual scale (VAS): an increase of at least 2 units; - Resting Energy Expenditure (REE) by indirect calorimetry: a decrease of at least 10%; - Grip strength by dynamometer: an increase of at least 30%.

**Laboratory:** Proinflammatory cytokines (IL-6 and TNF α): a decrease of at least 25%; leptin: an increase of at least 100%; Reactive Oxygen Species (ROS): a decrease of at least 80-100 Fort U; Activity of Glutathione Peroxidase (GPx): an increase of at least 2000 Units.

**Quality of Life:** EORTC QLQ C30; EQ-5D index and EQ-5D vas: an increase of at least 25% of the score
CONCLUSIONS

The treatment has demonstrated to be EFFECTIVE (22/39) as for:

- increase of body weight
- increase of lean body mass
- decrease of proinflammatory cytokines
- improvement of quality of life parameters
- amelioration of fatigue symptoms

The treatment has demonstrated to be SAFE with good compliance of patients.
ONGOING DEVELOPMENTS

A phase III randomised study has started as a multicenter trial aimed to test the safety and efficacy of the innovative integrated approach of CACS/OS to improve both objective clinical symptoms such as LBM and subjective symptoms such as functioning and QL.
RANDOMIZED PHASE III STUDY

Eligibility criteria will be the same of the phase II study.
Patients will be randomised to the following arms (95 patients for each arm for a total of 475 patients).

Poliphenols (300 mg/day) + antioxidants agents are the basic treatment. The following component was added to each arm:
Arm 1. Medroxyprogesterone Acetate 500 mg/day.
Arm 2. Oral nutritional supplement containing 2.6 g EPA/DHA
Arm 3. L-carnitine 4 g/day.
Arm 4. Thalidomide 200 mg/day
Arm 5. Medroxyprogesterone Acetate + Pharmaco-nutritional support + L-carnitine + Thalidomide

The planned treatment duration is 16 weeks.

Antioxidant agents include: Alpha lipoic acid 300 mg/day + carbocysteine 2.7 g/day + vitamin E 400 mg/day + vitamin A 30000 IU + Vitamin C 500 mg/day
A Critical Reappraisal of the Evaluation Criteria for drug therapy of CACS

• At the present time, it is difficult to find an absolute method of evaluation for the various drugs employed in the clinical CACS treatment... none of them is thought to be wholly satisfactory, and if some of these methods are formally validated for clinical decision making and they may be utilised daily (weight loss, visual analogue scales for appetite), others can be used preferably only in clinical trials (biomarkers).

• In a practical way, only the body weight measurement and the VAS or QOL scales are useful for clinicians.

• We suggest that a combination of body weight/appetite/quality-of-life with biomarker evaluation could be considered the method of reference only for future studies.

Sono necessarie Linee Guida !!!

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