Innovazioni terapeutiche in Oncologia Medica

Valutazione e approccio di trattamento della fatigue

Cagliari, 23-24 giugno 2005
Fatigue is a major problem for patients with advanced cancer.

Patients with cancer commonly report a lack of energy during the course of their disease and treatment which they report as “fatigue”.
Fatigue

Fatigue is present at the time of diagnosis in approximately 50% of cancer patients.

Several studies have shown a correlation between fatigue and different modalities of cancer therapy.

It is known that fatigue is one of the most common side-effects of chemotherapy and radiotherapy: 65-100% of patients undergoing radiotherapy and up to 82-96% of those receiving chemotherapy suffer from fatigue during treatment.

The National Comprehensive Cancer Network Fatigue Practice Guideline Panel defined fatigue as “an unusual, persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning”.

Cancer-related fatigue criteria have been proposed for the International Classification of Disease 10th Revision-Clinical Modification.
ICD-10 Criteria for Cancer-Related Fatigue

The following symptoms have been present every day or nearly every day during the same 2-week period in the past month:

1. Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level, plus 5 or more of the following:
   - Complaints of generalized weakness, limb heaviness.
   - Diminished concentration or attention.
   - Decreased motivation or interest to engage in usual activities.
   - Insomnia or hypersomnia.
   - Experience of sleep as unrefreshing or nonrestorative.
   - Perceived need to struggle to overcome inactivity.
   - Marked emotional reactivity (e.g., sadness, frustration, or irritability) to feeling fatigued.
   - Difficulty completing daily tasks attributed to feeling fatigued.
   - Perceived problems with short-term memory.
   - Postexertional fatigue lasting several hours.

2. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

3. There is evidence from the history, physical examination, or laboratory findings that the symptoms are a consequence of cancer or cancer therapy.

4. The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder, or delirium.
Fatigue

Fatigue is a multidimensional symptom and can be described in terms of perceived energy, mental capacity and psychological status: it can impair daily functioning and lead to negative effects on quality of life, self-care capabilities, and desire to continue treatment.
Fatigue Assessment

- **Subjective** fatigue rating is the most clinically relevant assessment tool. **Multidimensional fatigue assessment**, incorporating multiple characteristics and manifestations of fatigue and its impact on function, is more informative than the measurement of its severity alone, but more time consuming to administer.

- **Examples include:**
  1) the Functional Assessment of Cancer Therapy-Fatigue Scale, 2) the Piper Fatigue Self Report Scale, 3) the Brief Fatigue Inventory and 4) the MFSI
Fatigue

Only recently fatigue has been included among the most important symptoms in cancer patients, and indeed its evaluation is still not routinely included among the symptoms attributable to the toxicity of chemotherapy.
Fatigue

Fatigue may be caused by the disease itself, antineoplastic therapies, and/or a broad range of physical and psychological comorbidities.

Fatigue may represent a final common pathway to which many factors may contribute and therefore its pathophysiology is multifactorial.
Fatigue and CACS

Fatigue
The paucity of knowledge about the phenomenon of fatigue among the physicians and the patients themselves has lead to a lack of treatment or inappropriate treatment, based most frequently on dietary and vitamin support, in some case, pharmacologic treatment, and in others complete rest.
L-carnitine

Trimethylated amino acid roughly similar in structure to choline

\[
\begin{array}{c}
\text{CH}_3 \quad \text{HO} \quad \text{H} \quad \text{O} \\
\text{CH}_3 \quad \text{N}^+ \quad \text{CH}_2-C'-\text{CH}_2-C'-\text{O}^- \\
\text{CH}_3
\end{array}
\]
L-carnitine

- Cofactor required for transformation of the free long-chain fatty acids into acylcarnitines, and for their subsequent transport into the mitochondrial matrix, where they undergo β-oxidation for cell energy production.

- Mitochondrial fatty acid oxidation is the primary fuel source in heart and skeletal muscle, pointing to the importance of this nutrient for proper function in these tissues.
The mitochondrial carnitine system

- CPT-I
- CPT-II
- AcylCoA
- AcylCarnitine
- Carnitine
- Acetyl-CoA
- Citric Acid Cycle
- β-Ox
- Cytoplasm
- Mitochondrion

Acyl-CoA dehydrogenase

Acyl-CoA + CoA → Acetyl-CoA + CoA

Acetyl-CoA + Carnitine → Acetyl-Carnitine + CoA

Acetyl-Carnitine enters the mitochondrial matrix via the carnitine palmitoyltransferase II (CPT-II) system.

Acetyl-CoA is then produced in the mitochondrial matrix through the β-oxidation (β-Ox) pathway.

Acetyl-CoA is then further oxidized in the citric acid cycle, generating energy in the form of ATP.

Carnitine is transported out of the mitochondria in exchange for CoA, ready to repeat the cycle.
L-carnitine

Patients with cancer are especially at risk for carnitine deficiency and its prevalence in cancer patients with self-reported symptoms of fatigue is extremely high (>80%). They frequently present with decreased caloric intake and increased metabolic requirements. In addition, numerous drugs can interfere with the absorption, synthesis and excretion of carnitine. In particular, chemotherapy with ifosfamide and cisplatin-based agents may result in increased urinary excretion and serum carnitine deficiency because they compete with carnitine reabsorption at the proximal convoluted tubule.
L-carnitine

- Dodson et al observed a significant decrement in LC level in 23 cancer patients compared to 13 healthy aged-matched controls.
- Cruciani et al observed that 67% of adult-hospice-cancer patients with fatigue had carnitine deficiency.
- Graziano et al treated with LC 4 mg/day for 7 days 50 cancer patients undergoing cisplatin- or ifosfamide-based chemotherapy: after 1 week, fatigue (assessed by Functional Assessment of Cancer Therapy-Fatigue questionnaire) significantly ameliorated in 45 patients.
- Cruciani et al found a total carnitine increase and an improvement of fatigue symptom (measured by Brief Fatigue Inventory, BFI) as well as mood and quality of sleep after 1 week of LC supplementation (from 250 mg/day to 1750 mg/day) in 13 untreated cancer patients with self-reported moderate to severe fatigue for at least 1 week prior to accrual.
Efficacy of L-carnitine administration on fatigue, nutritional status, oxidative stress and related quality of life in 12 advanced cancer patients undergoing anticancer therapy

Accepted for publication in Nutrition June 2005
Aim of the study

The aim of the present study was to test the efficacy and safety of LC supplementation in 12 advanced cancer patients who experienced fatigue or had high levels of ROS or both.
Patients

Patients with advanced solid tumors who experienced fatigue every day or nearly every day in the week prior to study entry and/or had high levels of ROS were considered eligible for study.

Inclusion Criteria

- histological evidence of advanced solid tumor
- experienced fatigue or had high levels of ROS or both
- concurrent anticancer treatment
Treatment plan

A high daily oral dose (6 g) fractionated in three single doses (2 g each) of LC for 4 weeks was selected for the present study.

The total dosage was spaced throughout the day, during or following the three mains meals.
Study Design

Enrolled patients were evaluated at baseline ($t_0$), after 2 ($t_1$) and 4 ($t_2$) weeks of LC supplementation for fatigue, QoL, nutritional/functional and laboratory variables.

After baseline evaluation patients started treatment with oral LC 2 g solution (Carnitene, Sigma Tau, Rome, Italy) T.I.D. for 4 weeks.
Outcome measures

- **Fatigue**: Multidimensional Fatigue Symptom Inventory-Short Form, MFSI-SF

- **Quality of life**:  
  - oxidative stress-related QoL (QoL-OS)  
  - global health status (EQ-5D visual analogue scale)

- **Nutritional/functional status**:  
  - lean body mass and body impedance by bioelectric impedance analyzer,  
  - appetite by a visual analogue scale  
  - grip strength by dinamometer

- **Laboratory variables**:  
  - ROS levels  
  - Glutathione Peroxidase (GPx)  
  - Proinflammatory cytokines  
  - C-Reactive Protein and Hemoglobin
Results
## Patient characteristics

### Patients

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### Age, years

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Fatigue assessment

Multidimensional Fatigue Symptom Inventory
Short Form

MFSI-SF

p < 0.05

p < 0.001
Fatigue assessment

Multidimensional Fatigue Symptom Inventory

Short Form

*M = p < 0.05

MFSI-SF Subscale

- General
- Physical
- Emotional
- Mental
- Vigor

Graph showing changes in fatigue assessment scores over different time points (t0, t1, t2) for general, physical, emotional, mental, and vigor subscales. The graph indicates significant changes (p < 0.05) for physical and emotional subscales at certain time points, and no significant changes (NS) for other subscales.
QoL assessment

QoL-OS Subscale Part A

* = p < 0.05

- Functional
- Physical
- Social/Family
- Emotional
- Fatigue

** = p < 0.01
QoL assessment

EQ 5D-VAS

- t0: p < 0.05
- t1: p < 0.05
- T2: p < 0.001
Nutritional/Functional assessment

Lean Body Mass

Kg

t0  t1  t2

p < 0.001  p < 0.05

36.5  37.5  38.5

37  38  39  39.5  40  40.5
Laboratory variables

REACTIVE OXYGEN SPECIES (ROS)

FORT

NS

NS

200 250 300 350 400 450 500

t0  t1  t2
Conclusion

The results demonstrated a significant improvement of

- **Fatigue** (General and Physical scales)
- **QoL**

  - oxidative stress-related QoL (all subscales of QoL-OS questionnaire)

  Regarding the results of QoL-OS Part B, the mean score at baseline corresponds to a slightly unbalanced diet as for antioxidant vs prooxidant content in favor of prooxidant

  - **EQ 5D-VAS** (which expresses a global subjectively perceived health status).

- **LBM and appetite.** It may be considered the most important nutritional/functional parameter in assessing the cachectic state of patients: indeed, the decrease of LBM is the most important nutritional symptom present in CACS.
Conclusion

- ROS levels decreased, although not significantly, during the study. The concomitant chemotherapy may have contributed to maintain a high rate of ROS production, or, alternatively, the too short duration of LC treatment.

- The haemoglobin levels at baseline were 10.9 g/dl and the values remained unchanged during treatment. Anaemia, commonly considered the main cause of fatigue in cancer patients, has been demonstrated not to be always involved (Graziano et al).

- Serum levels of proinflammatory cytokines did not change significantly during the study, although baseline levels were not significantly different from controls.
Further studies could investigate in more depth the effect of LC supplementation on more detailed metabolic indexes, laboratory parameters and significant clinical outcomes.
Corso di Aggiornamento

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