Cancer Anorexia Cachexia Syndrome

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Cancer Cachexia - Definitions

- **Derives from the Greek 'kakos' meaning bad & 'hexis' meaning condition**
- **A physical fading of wholeness**
- **Syndrome of decreased appetite, weight loss, metabolic alterations & inflammatory state**

Cancer Cachexia - What it is?

- **An extreme on the continuum of weight loss in cancer**
- **Seen in cancer, cardiac disease & chronic infection but not neurological disease**
- **Due to a systemic inflammatory response**
- **Mediated through cytokines & other factors such as proteolysis inducing factor (PIF) & lipid mobilising factor (LMF)**

(Regnard, 2004)

Cancer Cachexia - Features

- **Some or all of the following features are exhibited in varying degrees:**
  - **Hypophagia / anorexia**
  - **Early satiety**
  - **Anemia**
  - **Weight loss with depletion & alteration of body compartments**
  - **Edema**
  - **Asthenia (weakness)**

(Freeman & Donnelly, 2004)

Theories of Nutrition & Cachexia in Cancer

It is NOT:

- **Due to starvation**
- **Due to malnutrition**
- **Due to competition by the tumor**
- **Restricted to cancer**
- **Reversed by nutritional support**

(Regnard, 2004)

Cancer Cachexia - Prevalence

- Occurs in ~ 70% of patients during the terminal course of disease
- Weight loss > 10% pre illness weight occurs in up to 45% of hospitalised cancer patients
- Cancer of the Upper GI & lung have the highest prevalence of weight loss
- Lung cancer patients with 30% weight loss show 75% depletion of skeletal muscle
- Breast cancer, sarcomas & NHL show the least weight loss

(Payne-James *et al.*, 2001)

Cancer Cachexia - Etiology

- Understanding is limited & based upon the knowledge of abnormalities in nutrition behaviour & metabolic patterns
- Appears as a classic case of malnutrition
- 3 theories have been suggested:
- Metabolic competition
- Malnutrition
- Alterations of metabolic pathways

(Payne-James *et al*., 2001)

Cancer Cachexia - Metabolic Competition

- Neoplastic cells compete with host tissues for protein, functioning as a 'nitrogen trap'
- In experiments where tumor is a high % of animal weight this theory holds, but in human tumors – even patients with a very small tumour can have severe cachexia

(Morrison, 1976)

Cancer Cachexia – Malnutrition

- Upper aerodigestive disease is an obvious cause of malnutrition
- Regardless of tumor location, anorexia is the most common cause of hypophagia & usually consists of a loss of appetite &/or feelings of early satiety
- Hypophagia has been related to the presence of dysgeusia
- Diminished ability to perceive sweet flavors leads to anorexia

(Payne-James *et al*., 2001)

Cancer Cachexia – Malnutrition

- Reduced threshold for bitter flavors linked to an aversion to meat
- Dysosmia is also related to an aversion to food
- Malnutrition leads to secondary changes in the GI tract which may be responsible for the feeling of fullness, delayed emptying, defective digestion & the poor absorption of nutrients
- However, malnutrition alone is not thought to be the main cause of cachexia

(Payne-James *et al*., 2001)

Metabolic Alterations in Starvation v Cancer Cachexia – CHO Metabolism

Metabolic Alteration	Starvation	Cancer Cachexia
Glucose tolerance	Decreased	Decreased
Insulin sensitivity	Decreased	Decreased
Glucose turnover	Decreased	Increased
Serum glucose level	Decreased	Unchanged
Serum insulin level	Decreased	Unchanged
Hepatic gluconeogenesis	Increased	Increased
Serum lactate level	Unchanged	Increased
Cori cycle activity	Unchanged	Increased

Adapted from Rivadeneira *et al*.,1998

Metabolic Alterations in Starvation v Cancer Cachexia – Fat Metabolism

Metabolic Alteration	Starvation	Cancer Cachexia
Lipolysis	Increased	Increased
Lipoprotein lipase activity	Unchanged	Decreased
Serum triglyceride level	Unchanged	Increased

Adapted from Rivadeneira *et al.,*1998

Metabolic Alterations in Starvation v Cancer Cachexia – Protein Metabolism

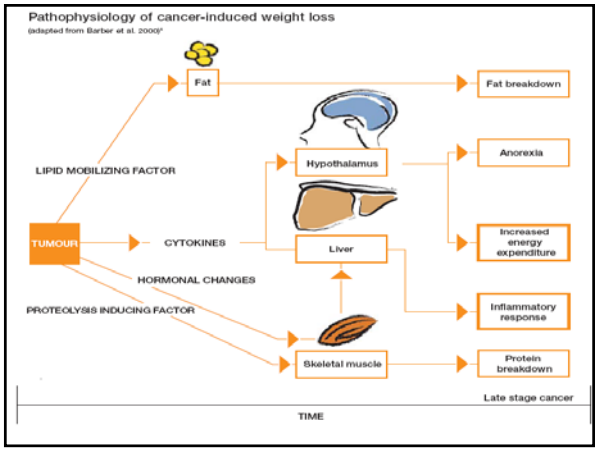
Metabolic Alteration	Starvation	Cancer Cachexia
Protein turnover	Decreased	Increased
Skeletal muscle catabolism	Decreased	Increased
Nitrogen balance	Negative	Negative
Urinary nitrogen excretion	Decreased	Unchanged

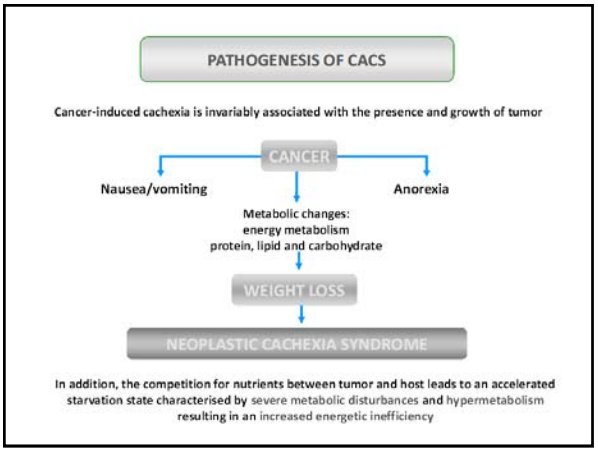
Adapted from Rivadeneira *et al.*, 1998

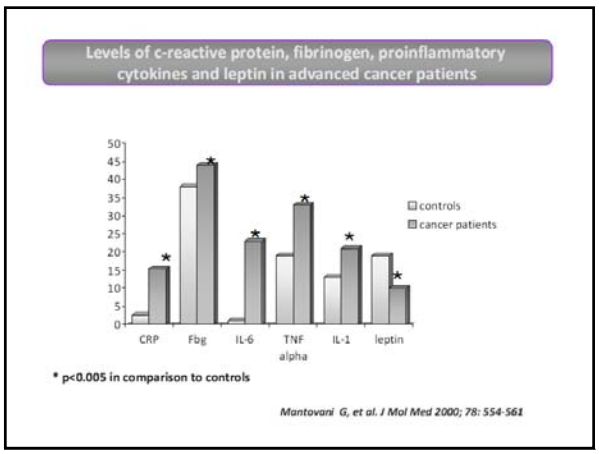
Cancer Cachexia - Cytokines

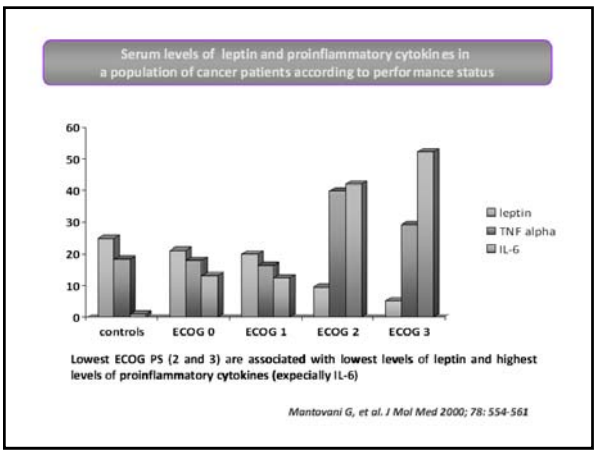
- Produced by host in response to tumor
- Cytokines regulate many of the nutritional & metabolic disturbances in the cancer patient leading to:
  - Decreased appetite
  - Increase in BMR
  - Increased glucose uptake
  - Increased mobilization of fat & protein stores
  - Increased muscle protein release

(Tisdale, 2004)









MANAGEMENT OF CANCER CACHEXIA

The best management of cancer cachexia is to cure the cancer, as this will completely reverse the cachexia syndrome. Unfortunately, this remains an infrequent achievement in adults with advanced solid tumours.

The second option would be to increase nutritional intake, but a large number of randomized controlled trials of nutritional intervention did not show a significant benefit with regard to weight change or quality of life.

These results have led to attempts to manipulate the process of cachexia with a variety of pharmacological agents, with the main purpose of providing symptomatic improvement.

To date, however, despite several years of co-ordinated efforts in basic and clinical research, practice guidelines for the prevention and treatment of cancer-related muscle wasting are lacking, mainly because of the multifactorial pathogenesis of the syndrome

Boddaert MA et al Curr Opin Oncol 2006;18:335-340

Managing Cancer-related Cachexia

- Ineffective Drugs
  - Cyproheptidine (Periactin)
  - Metaclopramide (Reglan)
  - Pentoxifyline (Trental)
- Commonly Used Drugs
  - Progesagins – megestrol acetate (Megace), medroxyprogesterone (Provera)
  - Corticosteroids – prednisone, dexamethasone

Mantovani G et al, Drugs 201; 61, 49-514

Managing Cancer-related Cachexia

- Drugs with strong rationale that failed or did not show unequivocal results in trials
  - Omega-3-fatty acids (eicosapentoic acid)
  - Cannabinoids (including Marinol)
  - Bortezomid (Velcade)
- Emerging drugs with some effective results still under trials
  - Thalidomide
  - Ghrelin
  - COX-2 inhibitors (Celebrex)
  - Insulin
  - BCAA (branched chain amino acids)
  - Oxandrolone (Oxandrin)

Managing Cancer-related Cachexia

- Future Trends
  - Melanocortin antagonist
  - b2 agonists (formoterol)
  - Anti-myostatin
  - Anti IL-6
  - SARMs (selective androgen receptor modulators)

Mantovani G et al, Drugs 201; 61, 49-514

EFFECTIVE TREATMENTS
Progestagens

Progestagens, medroxyprogesterone acetate and megestrol acetate, are currently considered the best available treatment option for CACS and they are approved in Europe for treatment of cancer- and AIDS- related cachexia

However, progestational agents are nonetheless limited in their ability to treat cancer cachexia. Fewer than 30% of patients treated with megestrol acetate experience short-term appetite stimulation, and although weight and appetite improve, there is no demonstrated improvement in quality of life or survival.

Simons JP et al. Cancer 1998; 82:553
Jatoi A, et al. J Clin Oncol 2002; 20:567
Jatoi A, et al. J Clin Oncol 2004;22:2469

Cytokine involvement in cancer anorexia/cachexia: role of megestrol acetate and medroxyprogesterone acetate on cytokine downregulation and improvement of clinical symptoms

This paper describes a series of experimental and clinical studies showing that:

1) high serum levels of some cytokines, including IL-1, IL-6, and TNF, are present in advanced-stage cancer patients, particularly those with CACS;
2) megestrol acetate (MA) has a beneficial therapeutic effect on CACS symptoms, such as appetite, body weight, and quality-of-life;
3) MA downregulates the synthesis and release of cytokines and relieves the symptoms of CACS;
4) cytokines play a key role in the onset of CACS;
5) medroxyprogesterone acetate (MPA) reduces the in vitro production of cytokines and serotonin (5-hydroxytryptamine, 5-HT) by peripheral blood mononuclear cells (PBMC) of cancer patients;
6) MA and MPA reduce the cisplatin-induced 5-HT release in vitro from PBMC of cancer patients.

16 / 92 *Oncog. 1998;9(2):99-106*

EFFECTIVE TREATMENTS
Corticosteroids

Among orexigenic agents, corticosteroids are widely used.
In randomized controlled studies, they have been shown to improve appetite and quality of life compared with placebo [*Mortel CG, Cancer 1974; Willox JC BMJ 1984*].
Megestrol acetate and corticosteroids seem equally effective, although for long-term use, corticosteroids have more side effects [*Loprinzi J Clin Oncol 1999*]: protein breakdown, insulin resistance, water retention and adrenal suppression.

Therefore steroids are not suitable for long-term use, and tend to be used during the pre-terminal phase of a patient illness.

Drugs with a strong rationale that have failed or have not shown univocal results in clinical trials so far

Drugs capable of inhibiting:

- the synthesis and/or release of cytokines
  (EPA, melatonin, cyclo-oxygenase-2 inhibitors and thalidomide)
- the cytokine action
  [anti-cytokine antibodies, anti-inflammatory cytokines (interleukin-12, interleukin-15)]
- the proteasome activity
  (bortezomib)

These drugs have been tested in experimental models of cachexia, with some positive results.

Unfortunately, most clinical trials in humans have provided limited and disappointing results.

Boddaert MA et al Curr Opin Oncol 2006;18:335-340

Comparison of Orally Administered Cannabis Extract and Delta 9 Tetrahydrocannabinol in Treating Patients With Cancer-Related Anorexia-Cachexia Syndrome: A Multicenter, Phase III, Randomized, Double-Blind, Placebo-Controlled Clinical Trial From the Cannabis-In-Cachexia-Study-Group

Florian Strasser, Diane Luftner, Kurt Possinger, Gernot Ernst, Thomas Ruhstaller, Winfried Meissner, Tze-Duhan Ko, Martin Schnelle, Marcus Reif, and Thomas Cerny

J Clin Oncol 2006; 24:3394-3400

Adult patients with advanced cancer, CACS, weight loss (5% over 6 months), and ECOG performance status 2 were randomly assigned (2:2:1) to receive CANNABIS EXTRACT (CE, i.e. 2.5 mg THC and 1 mg cannabidiol) or delta-9-tetrahydrocannabinol (THC 2.5 mg) or placebo orally, twice daily for 6 weeks.

Of 289 patients screened, 243 were randomly assigned and 164 completed treatment.

Intent-to treat analysis showed no significant differences between the three arms for appetite, QOL, or cannabinoid-related toxicity.
An independent data review board recommended termination of recruitment because of insufficient differences between study arms.

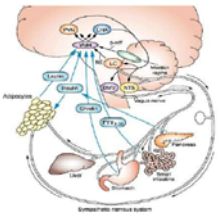
Conclusion: CE at the oral dose administered was well tolerated by these patients with CACS. No differences in patients' appetite or QOL were found either between CE, THC, and placebo or between CE and THC at the dosages investigated

GHRELIN MIMETIC WITH OREXIGENIC AND ANABOLIC ACTIVITY

Recently, much research interest has focused on ghrelin, a 28 amino-acid peptide produced by the P/D1 cells of the stomach.

Not only does ghrelin stimulate GH secretion (via the GH secretagogue-1a (GHS-1a) receptor), but it also promotes food intake (via the orexigenic NPY system) and decreases sympathetic nerve activity.

Synthetic human ghrelin has been shown to improve muscle wasting and functional capacity in patients with cardiopulmonary-associated cachexia, and to improve energy intake in anorexic cancer patients.



Recent issues form ASCO 2008

F. Braiteh, S. Dalal, A. Khuwaja, H. David, E. Bruera, R. Kurzrock
Phase I pilot study of the safety and tolerability of olanzapine (OZA) for the treatment of cachexia in patients with advanced cancer
J Clin Oncol 26: 2008 (May 20 suppl; abstr 20529)

Background: Olanzapine (OAZ), an atypical neuroleptic with safe therapeutic window for several psychotic diseases, induces significant weight gain positive metabolic gains.
To explore if OAZ can improve cachexia in pts with advanced cancer, we are investigating its safety and tolerability, its effects on weight and nutrition, and the outcome of serum metabolic and inflammatory factors.

Methods: Enrolled eligible pts received daily oral OAZ, starting at a dose of 2.5 mg (6-pts/cohort, dose-escalation at of 5, 7.5, 10, 12.5, and 15 mg).
Results: To date, 14 pts with advanced cancer tumor referred to the Phase I Clinic have been enrolled at 2.5, 5 and 7.5 mg/m2 dose-levels.

Conclusions: Our preliminary data suggest that lower doses of OAZ are very well tolerated with promising clinical activity on **weight, nutrition and function** in pts with cachexia. ELISA assays of the inflammatory and metabolic factors are in progress. The trial is currently accruing at a dose-level of daily 7.5 mg.

Role of Nutritional Support

Role of Nutritional Support

'An improvement in survival due to nutritional interventions has not yet been shown'

(Arends *et al*., 2006)

Role of Nutritional Support

'Unintentional weight loss of ≥ 10% within the previous 6 months signifies substantial nutritional deficit & is a good prognostic indicator of outcome'

(DeWys *et al*., 1980)

Cancer - Aims of Nutritional Support

- Improve the subjective quality of life (QoL)
- Enhance anti-tumor treatment effects
- Reduce the adverse effects of anti-tumor therapies
- Prevent & treat undernutrition

(Arends *et al*., 2006)

Cancer - Aims of Nutritional Support

'…the principle aim of nutritional intervention with cancer patients will be to maintain physical strength & optimize nutritional status within the confines of the disease…'

(van Bokhorst de van der Schueren *et al*., 1999)

'…nutritional intervention should be tailored to meet the needs of the patient & realistic for the patient to achieve…'

(Mick *et al*., 1991)

Aims of Nutritional Support

- Optimum nutrition improves therapeutic modalities & the clinical course & outcome in cancer patients

  (Rivadeneira *et al*., 1998)
- Numerous studies strongly suggest substantial weight loss >10% leads to adverse consequences:
  - Reduced response to chemotherapy & radiotherapy
  - Increased morbidity
  - Poor quality of life (QoL)
  - Increased mortality rate

  (Van Bokhorst de van der Scheren *et al*., 1997)

Can Nutritional Support improve Nutritional Status in Cancer?

- Yes, in patients whose weight loss is due to insufficient nutritional intake secondary to obstruction e.g. upper GI, head & neck
- In cachexic patients it is virtually impossible to achieve whole body protein anabolism
- Goals of NS are therefore different

(Arends *et al*., 2006)

Does Nutrition Support Feed the Tumor?

- There is no reliable data to support the effect of nutrition on tumor growth
- 'Feeding the tumor' should have no influence on the decision to feed a cancer patient

(Arends *et al*., 2006)

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