Cancer Anorexia
Cachexia Syndrome

John Mulder, MD
Chief Medical Consultant for Hospice and Palliative Care
Holland Home
Medical Director, Trillium Institute
Grand Rapids, MI

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)

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)

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 - 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

<table>
<thead>
<tr>
<th>Metabolic Alteration</th>
<th>Starvation</th>
<th>Cancer Cachexia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose tolerance</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Glucose turnover</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Serum glucose level</td>
<td>Decreased</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Serum insulin level</td>
<td>Decreased</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Hepatic gluconeogenesis</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Serum lactate level</td>
<td>Unchanged</td>
<td>Increased</td>
</tr>
<tr>
<td>Cori cycle activity</td>
<td>Unchanged</td>
<td>Increased</td>
</tr>
</tbody>
</table>

Adapted from Rivadeneira et al., 1998

Metabolic Alterations in Starvation v Cancer Cachexia – Fat Metabolism

<table>
<thead>
<tr>
<th>Metabolic Alteration</th>
<th>Starvation</th>
<th>Cancer Cachexia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipolysis</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Lipoprotein lipase activity</td>
<td>Unchanged</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Serum triglyceride level</td>
<td>Unchanged</td>
<td>Increased</td>
</tr>
</tbody>
</table>

Adapted from Rivadeneira et al., 1998
Adapted from Rivadeneira et al., 1998

### Metabolic Alterations in Starvation v Cancer Cachexia – Protein Metabolism

<table>
<thead>
<tr>
<th>Metabolic Alteration</th>
<th>Starvation</th>
<th>Cancer Cachexia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein turnover</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Skeletal muscle catabolism</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Nitrogen balance</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Urinary nitrogen excretion</td>
<td>Decreased</td>
<td>Unchanged</td>
</tr>
</tbody>
</table>

### 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)

**Pathophysiology of cancer-induced weight loss**

Adapted from Barta et al., 2000

**PATHOGENESIS OF CACS**

Cancer-induced cachexia is invariably associated with the presence and growth of tumor

Neutrope/necrosis

Anorexia

**Energy metabolism**

metabolic changes

proteins, lipids and carbohydrates

**Weight loss**

**NEOPLASTIC CACHEXIA SYNDROME**

In addition, the competition for nutrients between tumor and host leads to an accelerated starvation state characterized by severe metabolic disturbances and hypermetabolism resulting in an increased energetic inefficiency.

**Levels of c-reactive protein, fibrinogen, proinflammatory cytokines and leptin in advanced cancer patients**

* p<0.005 in comparison to controls


**Serum levels of leptin and proinflammatory cytokines in a population of cancer patients according to performance status**

Lowest RCD 3 P1 (2 and 3) are associated with lowest levels of leptin and highest levels of proinflammatory cytokines (especially IL-6)

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.

Mantovani G et al, Drugs 2011; 61, 49-514

Managing Cancer-related Cachexia

- Ineffective Drugs
  - Cyproheptadine (Periactin)
  - Metoclopramide (Reglan)
  - Pentoxifylline (Trental)

- Commonly Used Drugs
  - Progestagens – megestrol acetate (Megace), medroxyprogesterone (Provera)
  - Corticosteroids – prednisone, dexamethasone

Mantovani G et al, Drugs 2011; 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 (eicosapentenoic acid)
  - Cannabinoids (including Marinol)
  - Bortezomib (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 2011; 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.

Simon, J et al Cancer 1998; 82:355
Managing Cancer-related Cachexia

**Future Trends**
- Melanocortin antagonist
- β2 agonists (formoterol)
- Anti-myostatin
- Anti-IL-6
- SARMs (selective androgen receptor modulators)

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

Role of Nutritional Support

**Ghrelin Mimbic with Cachexic and Anabolic Activity**

Recently, much research interest has focused on ghrelin, a 28 amino-acid peptide produced by the IGF1 cells of the stomach. Not only does ghrelin stimulate GH secretion (via the GH secretagogue receptors GHS-R1a) and decreases sympathetic nerve activity, but it also promotes food intake (via the orexigenic NPY system) and increases unsynaptic nerve activity. Synthetic human ghrelin has been shown to improve muscle wasting and functional capacity in patients with cardio-respiratory-associated cachexia, and to improve energy intake in anorexic cancer patients.

Recent issues form ASCO 2008

E. Bisdas, S. Dore, A. Kharega, H. Badha, E. Benon, R. Hamamoto


Background: Paliperidone (E10), a typical antipsychotic with a high therapeutic index for the treatment of side effects associated with cancer. To explore if paliperidone (E10) can improve cachexia in patients with advanced cancer, we conducted a phase I/II study in patients with weight loss or cachexia.

Methods: A total of 22 patients received oral paliperidone, starting at a dose of 2.5 mg/day, dose escalation at 2.5, 7.5, 10, 25.5, and 50 mg. Results: 22 patients with advanced cancer were enrolled at 2.5, 7.5, and 25 mg/m2 dose-levels.

Conclusions: Our preliminary data suggest that lower doses of paliperidone may be well tolerated in patients with advanced cancer and may provide relief from muscle wasting.

Role of Nutritional Support

**EFFECTIVE TREATMENTS**

Corticosteroids

Among chemotherapeutic agents, corticosteroids are widely used. In randomized controlled studies, they have been shown to improve appetite and quality of life compared with placebo [Adams OS, Cancer 1976; 375: 201-255]. Megestrol acetate and corticosteroids seem equally effective, although for long-term use, corticosteroids have more side effects [Loprinzi et al, J Clin Oncol 1995]: 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.
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., 1996)

• 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)