The Impact of Nutrition Intervention in Cancer Cachexia

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LEARNING OBJECTIVES

- Define cancer cachexia & its prognostic outcomes
- Discuss recent developments in nutritional assessment in cancer cachexia
- Discuss the role of stand-alone nutrition interventions as well as multimodal therapy in treating cancer cachexia
Nutritional problems are largely not permanent and reversible.

Most frequent and most severe malnutrition and wasting occur.

Cancer Outcome

CURE

DEATH

Weight Loss During the Cancer Trajectory

~80% of cancer patients undergo weight loss at some point in the disease trajectory.

Most of these cases result in cancer-associated cachexia.
Involuntary Weight Loss and Cancer Survival

All patients were beyond the scope of curative surgery or radiation therapy.

Adapted from Am J Med 69(4): 491
Cancer-Associated Cachexia

Dynamic Process of Involuntary Weight Loss

Syndrome

**Contributing factors:** anorexia, chemosensory distortion, early satiety & hyper-metabolism

**Outcomes:** wasting, asthenia, anemia, psychosocial distress & dependency on others

Cancer-Associated Cachexia

- Associated with several complications:
  - increased prognosis of death
  - decreased response to treatment
  - increased risk of therapy toxicity and treatment complications
  - decreased functional status, quality of life
MECHANISM

- Cancer Cachexia pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism.

Lancet Oncol 2011;12:489
NEURAL FACTORS (grehlin, leptin, PYY, CCK)

NUTRITIONAL FACTORS
Nutrient Availability (Quantity)
Quality of Nutrients (eg AA)

Tumor
Effects on somatic & autonomic nerves

PRO-INFLAMMATORY FACTORS (cytokines, eicosanoids)

Immune Cells

Acute Phase Proteins

APPETITE
Early Satiety

ANABOLISM
AA
Protein

CATABOLISM

AUTOCRINE & ENDOCRINE FACTORS

Insulin GH IGF-1 Testosterone

Myostatin Ang II TNF, IL-6
Catabolic Factors

Ubiquitin-proteasome system Lysosomal proteases Ca\(^{2+}\)-activated proteases

Muscle

Anabolism

Disruption of Normal Anabolic Process

Deficit causes wasting: failure of anabolic competency, with anorexia being an important feature, followed by endocrine changes and physical inactivity


Normal anabolic process: maximized overall metabolism and muscle metabolism

- Anabolic environment
- Dietary supply of energy fuels and substrates
- Trophic effects of PA
MUSCLE LOSS PROGNOSIS IN CANCER

- Decreased physical function
- Longer length of hospital stay
- Higher incidence of chemotherapy toxicity
- Shorter time to tumor progression
- Shorter survival
Cancer Cachexia – International Consensus Definition

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

Lancet Oncol 2011;12:489
Cachexia Diagnostic Criteria

- Weight loss > 5% over past 6 months (in absence of simple starvation) OR

- BMI < 20 and any degree of weight loss > 2% OR

- Sarcopenia (low muscle mass)* and any degree of weight loss > 2%

*Defined sex-specific reference values. Standardized body composition measurements are essential to undertake assessment of skeletal muscle depletion. Mid-upper arm circumference, ASM, FFM, CT L3)

Lancet Oncol 2011;12:489
Computerized tomography: an opportunistic method

- Subcutaneous adipose tissue
- Visceral adipose tissue
- Intermuscular adipose tissue
- Skeletal muscle
Same BMI = 30.3 kg/m²

MUSCLE IS COLORED IN RED

A normal or high body weight and BMI does not preclude the presence of cachexia.
MANAGEMENT OF CANCER CACHEXIA
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- There are currently no standard treatment for cancer-related cachexia

- Several therapies under investigation (drug, diet and lifestyle modification therapies)
**List of Agents Under Consideration for Cachexia Therapy**

<table>
<thead>
<tr>
<th>Action Site</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Appetite Stimulants</strong></td>
<td>Progestational Agents, Cannabinoids, Olanzepine, Corticosteroids, Ghrelin</td>
</tr>
<tr>
<td><strong>Nutritional Agents</strong></td>
<td>Amino Acids, Polyunsaturated fatty acids: eicosapentaenoic acid (n-3) (fish oil)</td>
</tr>
<tr>
<td><strong>Anabolic</strong></td>
<td>Steroids, Insulin, Insulin-like growth factor, GH, B-adrenergic agonists</td>
</tr>
<tr>
<td><strong>Exercise Combination Therapy</strong></td>
<td>Exercise + oral nutritional supplementation, Anabolic Steroids + oral nutritional supplementation</td>
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<tr>
<td><strong>Anti-inflammatory</strong></td>
<td>Polyunsaturated fatty acids: eicosapentaenoic acid (n-3) (fish oil), Nonsteroidal anti-inflammatory agents, Macrolide antibiotics, Cytokine inhibitors, Statins, Thalidomide, Pentoxyphylline</td>
</tr>
</tbody>
</table>

Efficacy, cost, additional benefits, side effect and contra-indications?
Nutrient metabolism and requirements of cancer patients?

Extent to which utilization of essential nutrients is altered by cancer progression and therapies is largely unknown.
Nutritional Agents

- Nutrient mixtures

- Several amino acids appear to show increased utilization in the tumor-bearing state

→ There is not yet an understanding of amino acid utilization that is sufficiently extensive to support the formulation of cancer-specific formula for nutrition support.
**OMEGA-3 FATTY ACIDS**

- Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) are found in fish oil and are known for their ability to reduce inflammation in the human body.

- Area of intense interest:
  - Limiting and dietary needs are elevated
  - Reduce associated side effects, particularly muscle wasting

*Curr Probl Cancer, 2011;35:58-90*
**OMEGA-3 FATTY ACIDS**

- Fish oil feeding (> 2g/d of EPA):
  - stabilize weight and/or muscle loss
  - reverse anorexia
  - suppress muscle protein catabolism

*Curr Probl Cancer, 2011;35:58-90*
OMEGA-3 FATTY ACIDS

- Conversely, 3 large phase II trials have failed to demonstrate a clear benefit of omega-3 fatty acids on body weight or lean tissue in cancer patients.

- Clinical evidence on omega-3 fatty acids supplementation remains inconclusive.
There is not enough evidence to support a net benefit of omega-3 fatty acids in cachexia in advanced cancer. On the other hand, adverse effects were infrequent, with no severe adverse effects.”
Omega-3 fatty acids supplementation may help stabilize weight in cancer patients on oral diets experiencing progressive, unintentional weight loss.
**GLUTAMINE**

- Intensively used by rapidly dividing cells as source of nitrogen or alternative energy fuel

- Increase in glutamine demand → glutamine deprivation with detrimental effects on organ functions

- Adequate nutrition support including glutamine can:
  - Cover glutamine needs
  - Spare energy reserves
  - Retard severe complications such as organ failure

GLUTAMINE

Systematic Review

- Numerous experimental studies show that oral/enteral or intravenous glutamine *cover glutamine needs sparing reserves of the host, promoting mucosal integrity and retarding severe complication as multi-organ failure.*

- In various clinical situations, appropriate exogenous glutamine supply is safe and does not promote tumor growth.

ARGININE

- Key component of immunonutrition
- Strong stimulator of immune function (particularly macrophage phagocytic activity, natural killer cells activity, and lymphocyte activated killer cells activity)
- Plasma arginine concentration is lower in cancer so arginine metabolism may be disrupted

Am J Clin Nutr 2010;92:1151-1156
ARGININE

- A recent randomized study performed on malnourished patients with cancer of the head and neck, undergoing enteral supplementation with a mixture enriched with arginine, has shown a significant increase in long-term survival compared to the control group.
Kaplan-Meier curve of the overall survival of severely malnourished patients with head and neck cancer after major surgery.

Arginine group

Control group

\[ p = 0.019 \]
Kaplan-Meier curve of locoregional recurrence-free survival in severely malnourished patients with head and neck cancer after major surgery.

![Graph showing Kaplan-Meier curve with two groups: Control group and Arginine group. The control group shows a higher recurrence rate compared to the arginine group. The p-value is 0.027.](Am J Clin Nutr 2010;92:1151-1156)
ARGININE

- Has been shown to have both inhibiting and *stimulating* effects on tumor growth.
“The data on the use of arginine- or glutamine-supplemented formulas are too limited at this time to make recommendations on the use of these formulations”.
BRANCHED CHAIN AMINO ACIDS

- Regulators of protein synthesis and degradation
- Source of energy for the muscles and other tissues
- Precursors of glutamine and alanine

Use supported by short-term studies.

Oral Supplementation:
  - reduced LOS
  - allows rapid recovery of liver function

…but with no difference in mortality

MULTIMODAL THERAPIES: THE WAY OF THE FUTURE
MULTIMODAL THERAPIES: THE WAY OF THE FUTURE

Nutritional agents have prognostic importance in cancer cachexia but…

- Stand-alone nutritional supplementation: limited success with inconsistent results
- Nutrition support alone does not address the underlying catabolic metabolism

Support Care Cancer (2008), 16:447
MULTIMODAL THERAPIES

Therapies that address the nutritional deficit combined with strategies that counteract the inflammatory response and its metabolic consequences may slow down the catabolic process:

- Reducing anorexia
- Attenuating systemic inflammation
- Attenuating skeletal muscle catabolism
- Stimulating muscle protein anabolism
Nutritional support as part of a multimodal treatment may help improve metabolism, body composition and physical function ultimately affecting survival.
Cancer cachexia: developing multimodal therapy for a multidimensional problem

- Optimal oncological management
- Nutritional support
- Exercise
- Early intervention
- Multidisciplinary team work
- Anti-inflammatory therapy (e.g., NSAID, EPA)
- Anemia therapy (e.g., erythropoietin)

Adapted from: Eur J Cancer 2008; 4:1124

Mantovani, ESMO 2009
There is currently no single or combined treatment strategy which is successful in all patients.

Strategies to counteract both reduced dietary intake and hypercatabolism:
- Improve survival, function and QofL of cancer patients and should be further explored in clinical trials.
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