Cancer Cachexia

Current and Future Management Options
Cancer Cachexia

- Overview
- Symptoms
- Pathophysiology
- Current Treatment Options
- New Drugs
Cancer Cachexia Overview
“…the shoulders, clavicles, chest and thighs melt away. This illness is fatal…”

—Hippocrates (460–370 BC)
International Definition

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

The pathophysiology is characterised by a negative protein and energy balance, driven by a variable combination of reduced food intake and abnormal metabolism.”

International Definition

- Diagnostic criterion:
  - >5% weight loss
  or
  - >2% weight loss with a BMI < 20kg/m²
  or
  - sarcopenia and weight loss >2%
Cancer Cachexia — Overview

- Occurs in 60-80% of patients with advanced cancer
- Incidence is higher in patients with solid tumours
  - gastric or pancreatic cancer, incidence >80%
  - lung, prostate or colon cancer, incidence ≈ 50%
  - breast, incidence ≈ 50%
- Cachexia thought to contribute to the death of 10–30% of cancer patients
- Cachexia is associated with a poor prognosis, reduced treatment tolerance and a marked reduction in quality of life (QoL)
Two driving forces behind weight loss in cancer cachexia are reduced food intake and abnormal metabolism.

Cancer-associated anorexia is common in the advanced stages of many cancers:
- Drug-induced side effects (fatigue, constipation, nausea, vomiting)
- Reduced activity
- Bowel obstruction
- Psychological factors
• Cachexia is a continuum with three suggested stages of clinical relevance
• Not all patients traverse the entire spectrum
Cancer Cachexia - Continuum

Pre-cachexia
- Weight loss ≤ 5%
- Early clinical and metabolic signs: anorexia, impaired glucose tolerance

Cachexia
- Weight loss >5%, or
- BMI <20 and weight loss >2%, or
- Sarcopenia and weight loss >2%
- Often reduced food intake/systemic inflammation

Refractory cachexia
- Variable degree of cachexia
- Cancer is both catabolic and not responsive to anticancer treatment
- Low performance score
- <3 months expected survival

Normal to Death
Cancer Cachexia

Symptoms
1. Muscle wasting
2. Anorexia
3. Inflammation
4. Weight loss
5. Fatigue
6. Altered taste/smell
7. Early satiety
8. Nausea/vomiting

Symptoms of cancer cachexia
Teunissen et al. performed a systematic review to assess symptom prevalence in patients with incurable cancer.

Identified 44 studies that included a total of 25,074 patients.

Fatigue, pain, lack of energy, weakness and appetite loss were experienced by more than 50% of patients.

Cancer Cachexia Pathophysiology
Cancer Cachexia — Pathophysiology

Cancer cachexia is a complex multi-organ syndrome involving many biological processes. Caused by both primary (host response to tumour) and secondary factors (tumour-related).

- Pro-inflammatory cytokines
- Endocrine dysfunction
- Systemic inflammation
  - Acute phase response
  - Proteolysis
  - Lipolysis
  - Elevated resting energy
- Poor appetite (anorexia)
- Reduced food intake
- Malabsorption
- Muscle wasting
- ↓ LBM
- ↓ fat mass
- Weight loss

Cancer cachexia
Cancer Cachexia — Pathophysiology

- Cancer patients can lose weight as a result of their disease, or aggressive therapy.
- Cancer cachexia related weight loss involves a complex cascade of events leading to changes in protein, lipid and carbohydrate metabolism.

**Tumour, host & tumour-host interaction**

- Pro-inflammatory cytokines
- Endocrine dysfunction

**Pro-inflammatory cytokines**

- Poor appetite (anorexia)

**Poor appetite (anorexia)**

- Reduced food intake

**Reduced food intake**

- Therapy

**Therapy**

- Malabsorption
- Muscle wasting

**Malabsorption Muscle wasting**

- ↓ LBM
- ↓ fat mass
- Weight loss

**↓ LBM
↓ fat mass
Weight loss**

**Cancer cachexia**
Skeletal muscle ≈ 40% of body weight - seems to be the main tissue involved in cancer cachexia

Cachexia is a multi-organ syndrome:
- adipose tissue (both BAT and WAT)
- brain
- liver
- gut
- heart

Are directly involved in the cachectic process and may be connected to muscle wasting
Adipose tissue wasting appears to precede skeletal muscle degradation in cancer patients.

WAT actively expresses and secretes a plethora of pro-inflammatory factors including leptin.

WAT may therefore play an important role.
Lipolysis is the breakdown of triacylglycerols into glycerol and free fatty acids (FFAs).

FFAs used by the tumour cell as energy source.
Lipid-mobilising factor (LMF) identified as a pro-cachectic signalling molecule
- Secreted by the tumour
- Sensitises WAT to stimuli that induce the breakdown of triacylglycerols, leading to loss of adipose tissue
Reduced activity of lipoprotein lipase (LPL) impairs entry of fatty acids in to WAT

Contributes to loss of WAT
WAT acquires some of the molecular machinery that characterizes BAT. This represents a ‘browning’ of white cells, Uncoupling protein-1 (UCP1) levels increase, Promoted by IL-6 (host) and PTHRP (tumour), Leads to energetic inefficiency and cachexia.
In cachexia, a decrease in protein synthesis (anabolism), an increase in protein degradation (catabolism), or a combination of both leads to muscle atrophy. Synthesis seems to be relatively well preserved. May be a decreased regenerative capacity or regeneration may be abnormal in cancer cachexia. There are several pathways that can be altered in skeletal muscle.
Cancer Cachexia — Skeletal Muscle Metabolism
Many intracellular signals are activated by inflammatory mediators and tumour derived factors.

- Cytokines are “chemical messenger” proteins released by cells of the immune system.
- Systemic inflammation occurs when the innate immune system is chronically activated by pro-inflammatory cytokines.
- Pro-inflammatory cytokines may drive the cachexia process.
- Uncertain if primarily driven by cytokines produced by the tumour, or the patient’s own inflammatory response.
- Cachexia can rarely be attributed to one cytokine.
- TNFα and IL-1 thought to play key role.
- Proteolysis inducing factor (PIF) is a pro-cachectic signalling molecule secreted by the tumour.
- Is a major promotor of skeletal muscle atrophy.
- PIF and cytokines lead to proteolysis and apoptosis.
Insulin-Like Growth Factor-1 (IGF1) is a hormone that stimulates protein synthesis and decreases protein degradation.

IGF-1 regulates myostatin signalling. In normal conditions, IGF-1 signalling is dominant and blocks the myostatin pathway.

Myostatin is an extracellular cytokine.

Mostly expressed by skeletal muscle.

Also secreted by cachexia-inducing tumours.

Normal function of myostatin is to decrease muscle growth.

Inhibition of IGF-1 occurs when myostatin is over-expressed.

IGF1 is down-regulated in cancer-cachexia.

IGF-1 regulates myostatin signalling.

In normal conditions, IGF-1 signalling is dominant and blocks the myostatin pathway.
Reactive oxygen species (ROS) are involved in cell signalling and homeostasis. Formed as a natural by-product of oxygen metabolism. Under oxidative stress conditions, excessive ROS can damage cellular proteins, lipids and DNA.
Cancer Cachexia — Skeletal Muscle Metabolism

- ROS stimulate the breakdown of protein
- Leads to protein catabolism
TNFα results in the activation of PGC1α
PGC1α causes the production of uncoupling proteins (UCPs)

Cancer Cachexia – Skeletal Muscle Metabolism

Protein synthesis

Rate of ATP synthesis

Muscle wasting

Uncoupling proteins (UCPs)

Proteasome

Autophagy

Apoptosis

Caspases

Protein degradation
Uncoupling proteins (UCPs) in skeletal muscle and BAT may play a role in the increased REE observed in cachexia. Switch the use of mitochondria from ATP synthesis to thermogenesis. Results in increased energy expenditure.
During tumour growth, substantial metabolic alterations take place. Protein degradation and lipolysis lead to negative energy balance and tumour growth.
Important flow of amino acids from skeletal muscle to the liver takes place and serves for both:

- gluconeogenesis
- acute-phase protein synthesis
APR is a complex early-defence system

C-reactive protein seems to be a very important prognostic parameter

Associated with inflammation and weight loss in cachexia together with reduced quality of life and shortened survival in cachexia patients

Pro-inflammatory cytokine IL-6 implicated in mediating the APR in cancer cachexia

The exact mechanism linking APR and cachexia is not yet known

APR may increase the need for muscle mobilisation accelerating muscle wasting in cachectic cancer patients

This breakdown of muscle to amino acids may fuel the further production of APR proteins
Ghrelin and leptin are crucial in regulating appetite and may play a role in cancer-associated anorexia and cachexia.

- Ghrelin is an endogenous ligand for the growth hormone secretagogue receptor.
- Secreted by the stomach and pancreas.
Ghrelin signals hunger
Stimulates the production of orexigenic (appetite stimulating) mediators such as neuropeptide Y
Inhibits anorexigenic (appetite-suppressing) mediators such as pro-opiomelanocortin
Ghrelin may exert other effects in cancer cachexia

- Reduces the production of pro-inflammatory cytokines
- Has a direct effect on muscle cells by inhibiting protein degradation
- Inhibits apoptosis
- ↓ REE by ↓ activity of BAT
Leptin is a hormone released by adipocytes. It stimulates the anorexigenic pathway and inhibits the orexigenic pathway in the hypothalamus.
Mediators are involved in the control of food intake:

- appetite
- satiation
- taste and smell of food

Consequently, are partially responsible for anorexia of the cancer patient

The brain an important organ involved in the altered energy balance in cancer patients
Orexigenic and anorexigenic brain pathways are profoundly altered

Inflammatory response:
• activates anorexigenic pathways
• inhibits of the orexigenic pathways

Leads to a decrease in neuropeptide Y (NPY) production and consequential decrease in food intake
Cytokines also act in the hypothalamus to inhibit orexigenic and stimulate anorexigenic regulatory pathways.
Melanocortin-4 (MC4) receptor subtype plays a pivotal role in body weight regulation.

The MC4 receptor is involved in the anorexigenic cascade leading to a decrease in neuropeptide Y and a decrease in food intake.

- Increased hypothalamic serotonin levels that induce satiety and therefore reduce appetite.
- Resistance to peripheral signals e.g. leptin and ghrelin.
- Delayed gastric emptying.
- Disordered taste and smell.

Cytokines and lactate can inhibit stimulation of orexigenic peptides Neuropeptide-Y (NPY) that stimulate an increased appetite and reduce resting energy expenditure (REE).
Cancer Cachexia
Drug Treatment
Treatment strategies need to reflect the multidimensional nature of cancer cachexia.

Multimodal approaches are needed - a personalised treatment plan.

No current pharmacotherapeutic approach can completely reverse the condition.

No licensed drug treatment and no standard of care for cancer cachexia.

The ultimate aim is to be able to identify and treat patients at the earliest stages of cachexia, preferably in the pre-cachexia stage.

Treatments are less effective in the refractory stage.
Cancer Cachexia — Megestrol\(^{(1,2)}\)

- A synthetic, orally active derivative of the naturally occurring hormone progesterone
- Improves appetite, caloric intake and nutritional status
- Is associated with slight weight gain in cancer
- Higher doses are more related to weight improvement than lower doses (and AEs)
- Improved QOL is evident compared with placebo but not when compared to other drugs
- Currently the most widely prescribed agent to improve appetite and counteract cachexia

Doses ranged from 100mg-1600mg / day

Insufficient information to define optimal dose of MA

Weight improvement with higher doses v lower doses

No differences in appetite improvement between doses

Lack of benefit when compared to other drugs except for weight gain

Cancer Cachexia — Megestrol

1 in 4 will have an increase in appetite
1 in 12 will have an increase in weight
Weight gain may be predominantly based on fat or fluid, rather than skeletal muscle
Is associated with significant adverse effects: impotence, thromboembolic complications and oedema
1 in 23 will die
• Patient should be involved in decision to start megestrol

“Megestrol could be prescribed to improve appetite in the context of palliative medicine, but it should be emphasised that this drug will probably not lead to full weight loss recovery or improve QOL, and it is related to adverse events, including an increased risk of death”

Cancer Cachexia — Megestrol

- Is approved for anorexia & cachexia associated with AIDS

- Mechanism by which megestrol increases appetite is unknown, however it may be related to inhibition of:
  - pro-inflammatory cytokines such as IL-1, IL-6, TNF-α
  - neuropeptide Y stimulation in the hypothalamus

- Medroxyprogesterone is believed to work by reducing the production of:
  - serotonin (hypothalamus)
  - pro-inflammatory cytokines such as IL-1, IL-6, TNF-α
Two recent randomized, placebo-controlled trials have confirmed their efficacy in anorexia and fatigue\(^{(1,2)}\)

- **4 mg dexamethasone BD for 14 days (n=84)\(^{(1)}\)**
  - significantly improved fatigue, anorexia and QoL compared to placebo
  - similar adverse events

- **16mg methylprednisolone 16mg BD PO for 7 days (n=47)\(^{(2)}\)**
  - improved fatigue, appetite loss, and patient satisfaction
  - similar adverse events

Cancer Cachexia – Corticosteroids

- Mechanism of action is not well understood, but may involve the
  - inhibition of prostaglandin activity
  - suppression of IL-1 and TNF-α

- Long-term use of corticosteroids is associated with a wide range of well-known AEs

- Should be limited to short-term use only
Cancer Cachexia — Other Drugs

Thalidomide has immunomodulatory and anti-inflammatory properties

Benefits in cancer cachexia remain inconclusive\(^{(1)}\)

Olanzapine has been investigated based on AE profile (weight gain)

Believed to be due to an effect on serotonin in the hypothalamus

Better results obtained when combined with megestrol — further work necessary\(^{(2,3)}\)

Cancer Cachexia
Future Options
Cancer Cachexia — Anamorelin

- Anamorelin - ghrelin receptor agonist in Phase III trials
- Promising results from Phase II trials\(^{(1)}\)
- Improvement in lean body mass, total body mass and hand grip strength

Two randomized Phase III trials, ROMANA 1 and ROMANA 2, have demonstrated the superiority of anamorelin compared with placebo in increasing lean body mass, total body mass, fat mass and appendicular lean body mass over a 12-week period.

Anamorelin also significantly improved patients’ anorexia-cachexia symptoms and concerns over 12 weeks, compared with placebo.

The safety extension ROMANA 3 study established that anamorelin was safe and well tolerated over a 24-week period, with long-term clinical signals observed.

On 18 May 2017, the Committee for Medicinal Products for Human Use (CHMP) refused a marketing authorisation for anamorelin. Intended for the treatment of anorexia, cachexia or unintended weight loss in patients with non-small cell lung cancer. The CHMP concluded that the studies show a marginal effect on lean body mass and no proven effect on hand grip strength or patients’ quality of life. In addition, CHMP considered that the safety data on the medicine had not been recorded adequately. Company currently appealing.
The s-isomer of pindolol

- Effects three potential pharmacological targets relevant for cancer cachexia
  - reduced catabolism, through non-selective β receptor blockade
  - reduced fatigue and thermogenesis, through central 5-HT1a receptor antagonism
  - increased anabolism, through partial β2 receptor agonism

- Has anticatabolic and pro-anabolic pharmacological effects
Cancer Cachexia — Espindolol

- Phase II trial promising results\(^{(1)}\)
- Multicentre, randomised, double-blind, parallel-group, placebo-controlled (N=87)
- 10mg BD espindolol over 16 weeks:
  - produced a statistically and clinically significant weight gain
  - produced a statistically significant increase in lean body mass
  - improvement in hand-grip strength
- Phase III trial awaited

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## Cancer Cachexia — Future Drugs

<table>
<thead>
<tr>
<th>Drug</th>
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<th>Type</th>
<th>Pathological condition</th>
<th>Clinical trial</th>
<th>Target</th>
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</thead>
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<td>Acceleron Pharma</td>
<td>Soluble activin receptor type IIb</td>
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<td>Acacia Pharma</td>
<td>Formoterol (β-2 agonist) + megestrol acetate</td>
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<td>Bimagrumab</td>
<td>Novartis and MorphoSys (BYM3389)</td>
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<td>Cyproheptadine (Periactin)</td>
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# Cancer Cachexia — Future Drugs

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<td>MC4 antagonist</td>
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<td>Pre-clinical</td>
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Cancer Cachexia — Summary

- Increased resting energy expenditure and alterations in metabolism of protein, fat, and carbohydrate are the reason for metabolic changes in cancer patients.
- Over expression of proinflammatory cytokines also involved.
- Inflammatory processes have been shown to maintain the wasting process in cachexia.
- Understanding the complex interplay of tumour and host factors will uncover new therapeutic targets.
- Treatment requires a multimodal approach including a combination orexigenic, anabolic, anti-catabolic and anti-inflammatory drugs with nutritional agents and exercise.