Cancer Cachexia: an update on the aetiology and management

BDA Oncology Specialist Group Study day, October 2016

Rhys White
Principal Oncology Dietitian
Guys and St Thomas’ NHS Foundation Trust
Rhys.white@gstt.nhs.uk
Overview

• Definition
• Aetiology/mechanism
• Classification and assessment
• Medical management
• Nutritional management

What’s new?

• Fat metabolism and it’s impact on muscle
• Exercise
Cachexia definition

“Cancer cachexia is a complex syndrome characterized by a chronic, progressive, involuntary weight loss which is poorly or only partially responsive to standard nutritional support and it is often associated with anorexia, early satiety and asthenia. It is usually attributable to two main components: a decreased nutrient intake (which may be due to critical involvement of the gastrointestinal tract by the tumour, or to cytokines and similar anorexia-inducing mediators); and metabolic alterations due to the activation of systemic proinflammatory processes”

“An multifactorial syndrome characterised by an on-going 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

Clinical Features

• Cancer related weight loss cannot be simply defined as malnutrition

• Comprises:
  – Skeletal and adipose tissue loss
  – Anorexia
  – Hyper-metabolic state where the metabolic responses occur as a combination of the host-tumour interaction
  – resistant to standard nutritional support
Prevalence

• Occurs in approximately 50-80% of cancer patients

• Most common in solid tumour cancers and in particular in those of the upper gastrointestinal (UGI) tract and lung.

• Up to 20% of all cancer related deaths are thought to be directly related to cachexia

Are we always talking about cachexia?

Universal definitions?

- Cachexia
- Sarcopenia
- Malnutrition
- Myopenia/Dynapenia
Definition and classification of cancer cachexia: an international consensus

- **Precachexia**: Weight loss ≤5%
  - Anorexia and metabolic change

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

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

Death
European consensus on definition and diagnosis of sarcopenia

Diagnosis is based on documentation of criterion 1 plus (criterion 2 or criterion 3)

1. Low muscle mass
2. Low muscle strength
3. Low physical performance

<table>
<thead>
<tr>
<th>Conceptual stages of sarcopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
</tr>
<tr>
<td>Presarcopenia</td>
</tr>
<tr>
<td>Sarcopenia</td>
</tr>
<tr>
<td>Severe sarcopenia</td>
</tr>
</tbody>
</table>
Why do we care about cachexia and sarcopenia?

Negative impact on outcomes including

- Survival and prognosis
- Function
- Performance status and fitness for treatment
- Treatment toxicity/complications
- QOL
- LOS
Pathogenesis

Anorexia in advanced cancer

- Delayed gastric emptying
- Resistance to peripheral signals e.g. leptin and ghrelin
- Disordered taste and smell
- Cytokines and lactate

Increased hypothalamic serotonin levels that induce satiety and therefore reduce appetite

Inhibit stimulation of orexigenic peptides Neuropeptide-Y(NPY) that stimulate an increased appetite and reduce resting energy expenditure (REE).

Increase activity of anorexigenic peptides (melanocortins) that reduce appetite and increase REE.

Protein metabolism

• Unchanged or decreased muscle protein synthesis
• Increased synthesis of acute phase proteins
• Increased protein breakdown via activation of proteolytic pathways
  – Pro-inflammatory cytokines (TNF, IL-1, IL-6)
  – Tumour produced pro-cachectic factors e.g. PIF (proteolysis tumour inducing factor)
• Anabolic resistance
Increased energy expenditure

1. Host metabolism is energetically inefficient due to increased futile cycling activity e.g. lactate
2. Increased brown adipose tissue where energy coupling from oxidative phosphorylation is released as heat energy instead of ATP
3. Increased synthesis of acute phase proteins and cytokines increase energy expenditure

Increased energy expenditure likely to be at least partially offset by reduced activity levels
Nutritional implications and nutritional management of cancer cachexia
1. Anabolic resistance and the impact of nutritional support
   – Protein intake

2. Omega-3 fish oil supplements (EPA/DHA)
Anabolic resistance and the impact of nutritional support

• Although cancer cachexia is associated with marked alterations in skeletal muscle metabolism most data comes from animal models

• In the past 5 years increasing number of studies showing that cancer patients have an anabolic potential
• Stage III/IV NSCLC >5% weight loss in 12 months
• Normal anabolic response to hyper-amino acid infusion
• Blunted response to low levels of amino acids
• Suggests a substantial protein intake is required to induce protein anabolism in these patients
• No evidence of anabolic resistance to either high EAA formula or a balanced amino acid mixture
• High anabolic potential was independent of weight, muscle mass, weight loss or disease trajectory
• Anabolic potential was no different in patients in last 6 months of life
Commercially available oral sip feeds

Cachectic patients showed a comparable protein anabolic response as healthy controls
Anabolic potential – critical appraisal

- Very small studies <20 patients
- Variable definitions of cachexia
- Low evidence of systemic inflammation CRP <15mg/L
- Different formulations – EAA, standard formula, iv infusions
Anabolic potential – the possible impact

• High protein diets/supplements rich in EAA may be of benefit for cachectic cancer patients even where prognosis is poor
• With anorexia and overall symptom burden dietary protein without additional supplementation will be difficult to meet needs
• Higher protein intakes in line with other guidance
  – PROT-AGE – 1.2-1.5g/kg (acute and chronic disease)
  – ESPEN 2016 Clinical Nutrition and cancer -1-1.5g/kg
• More research required on amino acid formulations, timing and dosage
Omega 3 Fish oils (EPA/DHA)
Mechanism

**n-6 series**
Linoleic acid 18:2
- Arachidonic Acid
- Prostaglandins E₂ PGE₂
- Leukotriene LTB₄
- Thromboxane A₂ TxA₂

**Pro-inflammatory**

**n-3 series**
Linolenic acid 18:3
- Docohexaenoic acid (DHA) 20:5
- Eicosapentaenoic acid (EPA) 20:5
- Prostaglandins E₃ PGE₃
- Leukotriene LTB₅
- Thromboxane A₃ TxA₃

**Anti-inflammatory**
↓ IL-6, ↓ CRP
Effect on nutritional status

• Several small clinical trials including RCT’s since 2007 have reported improvement in appetite, energy intake, body weight and LBM

• Largest RCT (Sanchez-Lara et al (2014) Clin Nutr, 33) - 92 patients with advanced lung Ca Prosure bd (2.2g EPA/day)

| Table 2 |

| Anthropometrical, biochemical and inflammatory parameters differences between ONS-EPA and C groups (t-student) and within groups between baseline and after 2 cycles of chemotherapy (Friedman test). |

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Δ</th>
<th>ONS-EPA</th>
<th>Δ</th>
<th>p**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>T0 64.7 ± 13</td>
<td>-2.2 ± 3</td>
<td>60.4 ± 11</td>
<td>-0.33 ± 3</td>
<td>**0.01</td>
</tr>
<tr>
<td></td>
<td>T2 62.6 ± 14</td>
<td></td>
<td>60.1 ± 11</td>
<td></td>
<td>0.523</td>
</tr>
<tr>
<td>% Usual weight loss</td>
<td>T0 7.1 ± 9</td>
<td>2.8 ± 5</td>
<td>8.9 ± 8</td>
<td>0.54 ± 4</td>
<td>0.733</td>
</tr>
<tr>
<td></td>
<td>T2 9.9 ± 11</td>
<td></td>
<td>9.4 ± 8</td>
<td></td>
<td>0.325</td>
</tr>
<tr>
<td>Kg lean body mass</td>
<td>T0 43.9 ± 14</td>
<td>-2.0 ± 6</td>
<td>36.2 ± 10</td>
<td>1.6 ± 5</td>
<td>**0.01</td>
</tr>
<tr>
<td></td>
<td>T2 42.0 ± 13</td>
<td></td>
<td>37.8 ± 9</td>
<td></td>
<td>0.124</td>
</tr>
</tbody>
</table>
Effect on chemotherapy

• DHA/EPA have been shown promote cytotoxic effects of several anti-cancer drugs improving cancer treatment outcome
• Mechanism - ↑lipid peroxidation, ↑tumour cell susceptibility to apoptosis, enhanced drug activation
• Non-randomised controlled studies have shown improved responses to chemotherapy in patients supplemented with fish oils


BUT...
• Pre-clinical models indicate N-3 FA’s may enhance tumour cell proliferation and induce chemo resistance

ESPEN guidelines on nutrition in cancer patients (2016)

<table>
<thead>
<tr>
<th>B5 – 7</th>
<th>N-3 fatty acids to improve appetite and body weight</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Strength of recommendation</th>
<th>In patients with advanced cancer undergoing chemotherapy and at risk of weight loss or malnourished, we suggest to use supplementation with long-chain N-3 fatty acids or fish oil to stabilize or improve appetite, food intake, lean body mass and body weight. Low</th>
</tr>
</thead>
</table>

No convincingly serious safety issues
Medical management

• Megesterol Acetate (Megace)

• Ghrelin (Anamorelin)
Megesterol Acetate (Megace)
Megesterol Acetate (MEGACE)

- Megestrol acetate (MA) and medroxyprogesterone are synthetic, orally active derivatives of the naturally occurring hormone progesterone.
- MA originally synthesised in 1963 as a contraceptive drug.
- 1993 approved for treatment of anorexia/cachexia.
Mechanism of action

Precise mechanisms unknown

- ↓ pro-inflammatory cytokines
- ↑ Neuropeptide-Y (orexigenic peptide)
- ↓ Serotonin (promotes satiety)
- Inhibition of whole cell calcium channels resulting in reduced firing neurons involved in satiety
• Included 35 RCTs
• Included cancer, AIDS or other underlying pathology
• Quality of evidence graded as very low or low
Key findings

• Showed a benefit of MA compared with placebo with regard to ↑ appetite and weight in cancer patients.

• Weight gain mean difference (MD) = 1.96kg (95% CI 1.11-2.81kg)

• 1 in 4 will have an increase in appetite

• 1 in 12 will have an increase in weight
Key finding - QOL

- QOL improvement was seen in cancer patients taking MA when compared with placebo but not when compared to other drugs
Key findings – dose and duration

• 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
• Duration ranged from 2-24 weeks, median 8 weeks
• Lack of benefit when compared to other drugs except for weight gain.
Key findings - safety

- 15 trials reported AE and show an increase risk of suffering them independent of dose (RR 1.20, 95%CI 1.07-1.36).
- Dyspnoea and oedema were related to MA (RR 2.23 95%CI 1.01-4.93 and RR 1.37, 95% CI 1.07-1.72 respectively).
- Death was related to MA (RR 1.42 95% CI 1.04-1.94), higher doses seemed to produce more deaths, however, this is a group of patients with high mortality.
- Thromboembolic events were increased with MA (RR 1.84 95%CI 1.07-3.18) however, this is a group that experience a high rate of thromboembolic events particularly if on chemotherapy.
Cochrane summary

“MA 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.”
Clinical practice guidelines on cancer cachexia in advanced cancer patients with a focus on refractory cachexia

EUROPEAN CLINICAL GUIDELINES

Recommendation

Megestrol or progestins seem to stimulate appetite and increase body weight, though not muscle mass (level of recommendation: weak positive; mean consensus 7.73). Progestins should be considered for patients with refractory cachexia and with anorexia as a major distressing symptom.
Ghrelin

(Anamorelin - orally active novel ghrelin receptor agonist)
How does it work?

+ causes a release of growth hormone from the pituitary
+ Inhibits production of pro-inflammatory cytokines

Esposito et al (2015) 
Cancer Treatment Reviews; 41 p.793
2 international double-blind placebo controlled trials evaluating the efficacy and safety of Anamorelin

Stage III/IV NSCLC patients with ECOG performance status 0-2 and cachexia (≥5% weight loss in 6 months or BMI < 20kg/m²)

Randomised [2:1] to 100mg Anamorelin or placebo given daily for 12 weeks
Primary end-points:
• Change from baseline over 12 weeks in
  – LBM (DEXA)
  – Hand grip strength

Secondary end-points:
• Change in body weight
• Change in FAACT/FACIT anorexia-cachexia and fatigue score
• QOL
## Results

<table>
<thead>
<tr>
<th></th>
<th>ROMANA 1</th>
<th>Placebo</th>
<th>p value</th>
<th></th>
<th>ROMANA 2</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n)</td>
<td>323</td>
<td>161</td>
<td></td>
<td></td>
<td>330</td>
<td>165</td>
<td></td>
</tr>
<tr>
<td>Median lean body mass (kg)</td>
<td>0.99 (0.61 to 1.36)</td>
<td>-0.47 (-1.00 to 0.21)</td>
<td>&lt;0.0001</td>
<td></td>
<td>0.65 (0.38 to 0.91)</td>
<td>-0.98 (-1.49 to -0.41)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median handgrip strength (kg)</td>
<td>-1.10 (-1.69 to -0.40)</td>
<td>-1.58 (-2.99 to -1.14)</td>
<td>0.15</td>
<td></td>
<td>-1.49 (-2.06 to -0.58)</td>
<td>-0.95 (-1.56 to 0.04)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n)</td>
<td>284</td>
<td>141</td>
<td></td>
<td></td>
<td>268</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td>Mean bodyweight (kg)</td>
<td>2.20 (0.33)</td>
<td>0.14 (0.36)</td>
<td>&lt;0.0001</td>
<td></td>
<td>0.95 (0.39)</td>
<td>0.57 (0.44)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean anorexia-cachexia scale score</td>
<td>4.12 (0.75)</td>
<td>1.92 (0.81)</td>
<td>0.0004</td>
<td></td>
<td>3.48 (0.94)</td>
<td>1.34 (1.03)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Fatigue scale</td>
<td>0.26 (0.89)</td>
<td>-1.91 (0.93)</td>
<td>0.054</td>
<td></td>
<td>1.37 (1.17)</td>
<td>1.23 (1.29)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Data for primary endpoints are median (95% CI) or for secondary endpoints are mean (SE). *For primary efficacy analysis, change from baseline over 12 weeks per patient was defined as the average of the change from baseline at week 6 and the change from baseline at week 12. p values were obtained from Wilcoxon rank sum test, taking into account missing post-baseline values (ie, imputation), whereby lower ranks represent worse outcomes. †For secondary efficacy analysis, least-squares means, SEs, CIs, and p values were from a mixed-effects pattern mixture repeated measures model.

**Table 2:** Changes in primary and secondary efficacy measures from baseline over 12 weeks
Conclusions

• Ananmorelin increases LBM but not function/strength as measured by hand grip in advanced NSCLC
• Anamorelin resulted in an improvement of anorexia and cachexia symptoms
• Are results clinically significant?
• No improvement in function or fatigue—what is most important muscle size or function?
• No improvement in survival
• No measure of dietary intake—did oral intake improve as appetite improved?
• Some baseline characteristics not considered extensively:
  – CRP (similar proportions in treatment vs placebo of < and > 10mg/L)
  – Chemotherapy regimen
  – Percentage weight loss (similar proportions in treatment vs placebo of <and > 10%)

Approvals for NSCLC

• NICE Single technology appraisal
• Pre-registration with European Medicines Agency
Multimodal interventions - what research is happening currently?
Primary objective
To establish whether a multimodal intervention is effective in treating cachexia. This will be assessed after 2 cycles of chemotherapy (study endpoint -between 6 -9 weeks) by measuring weight.

Secondary objectives
To examine the effect of a multimodal intervention for cancer cachexia on muscle mass (CT at L3) and physical activity (ActivPAL).

Patients
Diagnosis of lung cancer, pancreatic cancer or cholangiocarcinoma
Due to commence anti-cancer therapy

Patients and recruitment
A total of 240 patients will be recruited from out-patient oncology clinics at multiple sites in Europe, Canada and Australia.
A randomised feasibility study of EPA and Cox-2 inhibitor (Celebrex) versus EPA, Cox-2 inhibitor (Celebrex), Resistance Training followed by ingestion of essential amino acids high in leucine in NSCLC cachectic patients - ACCeRT Study

Elaine S Rogers¹², Roderick D MacLeod¹³, Joanna Stewart⁴, Stephen P Bird⁵ and Justin WL Keogh⁶⁷

Exercise and nutrition for head and neck cancer patients: a patient oriented, clinic-supported randomized controlled trial

Lauren C Capozzi¹, Harold Lau³⁴, Raylene A Reimer¹⁴, Margaret McNeely⁵, Janine Giese-Davis²³, and S Nicole Culos-Reed¹²⁴*
Key thoughts and findings

• Consensus models of diagnosis and classification of cachexia must be incorporated into all cachexia research and further validated

• Anorexia, inflammation and increased energy expenditure have a negative impact on weight and muscle mass which contributes to worsening of clinical outcomes

• Growing evidence of an anabolic response to high protein intakes in advanced cancer/cachectic patients – aim for protein intakes close to 1.5g/kg

• Weak evidence base for routine use of n-3 fatty acids

• Anamorelin may be a safe effective new treatment for managing cancer cachexia

• Given the complex multifactorial nature of cachexia effective management is likely to involve multi-modal interventions including exercise, nutrition and drug therapy
Thanks for listening

Any questions?