Drugs to treat and relief patients with cancer cachexia

Tora Skeidsvoll Solheim, MD, PhD

Zurich February 2017
• Aim of pharmacological symptom relief in cachexia
• Current pharmacological management
  – Nutritional Impact Symptoms
  – Targeted to treat appetite or weight
• New cachexia based mechanisms
• Optimal outcomes in clinical trials
• Future
Treatment aim depends on stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Precachexia</th>
<th>Cachexia</th>
<th>Refractory cachexia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>≤5% or BMI &lt; 20 and weight loss &gt; 2% or sarcopenia and weight loss &gt; 2%</td>
<td>≥5% or BMI &lt; 20 and weight loss &gt; 2% or sarcopenia and weight loss &gt; 2%</td>
<td>Variable degree of cachexia</td>
</tr>
<tr>
<td>Anorexia and</td>
<td>Anorexia and metabolic change</td>
<td>Weight loss &gt; 5% or BMI &lt; 20 and weight loss &gt; 2% or sarcopenia and weight</td>
<td>Cancer disease both procatabolic and not responsive to anticancer treatment</td>
</tr>
<tr>
<td>metabolic change</td>
<td></td>
<td>loss &gt; 2%</td>
<td>Low performance score</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;3 months expected survival</td>
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</table>

ref. Fearon, Strasser, et al. 2011
Aim – in refractory cachexia

• Refractory cachexia impairs QoL, food intake, physical function and causes psychosocial distress

• The aim of the pharmacological treatment in refractory cachexia is immediate symptom relief
  – The ability to eat more or to appreciate the meal/eating situation
  – Improve QoL and reduce eating-related distress
  – The ability to maintain physical function
Aim – in precachexia and cachexia

• Stabilise/improve:
  – Weight
  – Muscle mass
  – Physical performance
  – Appetite
  – Nutritional intake
  – Quality of life
  – Eating related distress
Current pharmacological management - Nutritional Impact Symptom

- Patients with advanced cancer have a multitude of symptoms

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<tr>
<th>Symptom</th>
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<td>Pain</td>
<td>84</td>
<td>Sleep problems</td>
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<td>Constipation</td>
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<td>24</td>
<td>Memory problems</td>
<td>12</td>
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<tr>
<td>Early satiety</td>
<td>51</td>
<td>Anxiety</td>
<td>24</td>
<td>Headache</td>
<td>11</td>
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<tr>
<td>Dyspnea</td>
<td>50</td>
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<td>23</td>
<td>Sedation</td>
<td>10</td>
</tr>
<tr>
<td>10% weight loss</td>
<td>50</td>
<td>Confusion</td>
<td>21</td>
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Current pharmacological management

- Patients with advanced cancer have a multitude of symptoms
  - and a wealth of these have impact on nutritional aspects

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ref: Walsh et al 2000
Pharmacological symptom relief

• It is imperative that symptoms or conditions that can interfere with nutritional intake are addressed and treated
  
  – It is for instance not to be expected that one is to improve nutritional intake in patients undergoing pain or who are suffering from severe oral stomatitis
    • ref Del Fabbro et al 2011
Pharmacological symptom relief

• We all know our medical armamentarium, and it should be used
  – Laxantia, opioids, PPI, antiemetics etc.
Pharmacological symptom relief

• But symptom relief is not always adding a pharmacological treatment

• Always keep scrupulous attention to whether the patient really need the prescribed drug – or if the dose can be reduced
Symptom management

• A lot of side effects mimic common symptoms in advanced cancer / refractory cachexia
  – **Opioids:** nausea, constipation, sedation, dry mouth, reduced appetite
  – **Benzodiazepam:** sedation, dizziness
  – **5-HT3R antagonists:** constipation
  – **Dipyridamol:** dizziness, nausea
  – **Statins:** headache, difficulty sleeping, muscle aches, drowsiness, dizziness, myopathy
Current pharmacological management — Targeted to treat appetite or weight

- Only progestins and corticosteroids were found to have sufficient evidence to support their use in improvement of appetite

Ref: Yavuzsen 2005
Corticosteroids

- Can improve QoL, appetite, vomiting, wellbeing, fatigue
  - Weight is often not significantly affected

- Side effects: hyperglycaemia, myopathy, mood changes, pseudo rheumatism, immunosuppression etc.
**ESPEN-guidelines**

<table>
<thead>
<tr>
<th>B5 – 1</th>
<th>Corticosteroids to improve appetite</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strength of recommendation</strong></td>
<td><strong>WEAK</strong></td>
</tr>
<tr>
<td><strong>Level of evidence</strong></td>
<td><strong>High</strong></td>
</tr>
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We suggest considering corticosteroids to increase appetite of anorectic cancer patients with advanced disease for a restricted period of time (1-3 weeks) but to be aware of side effects.

*Ref: Arends et al 2016*
Different corticosteroids

- Little evidence which compound to be recommended for improved appetite
- Rarely compared head to head
- Dexamethasone most investigated

<table>
<thead>
<tr>
<th>Drug</th>
<th>Equivalent pharmacologic dose (mg)</th>
<th>Anti-inflammatory potency</th>
<th>Mineralocorticoid potency</th>
<th>Biological half-life (hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>20</td>
<td>1</td>
<td>2+</td>
<td>8–12</td>
</tr>
<tr>
<td>Cortisone</td>
<td>25</td>
<td>0.7</td>
<td>2+</td>
<td>8–12</td>
</tr>
<tr>
<td>Prednisone</td>
<td>5</td>
<td>4</td>
<td>1+</td>
<td>24–36</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4</td>
<td>5</td>
<td>0–0.5</td>
<td>24–36</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75</td>
<td>25</td>
<td>0</td>
<td>36–54</td>
</tr>
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Progestins

- RR appetite improvement: 2.57 (1.48-4.49)
- RR weight improvement: 1.55 (1.08-2.26)
- RR QoL: 1.91 (1.02-3.59)

- Increased risk; impotence, dyspnoea, oedema, thromboembolism and death

Ref: Ruiz Garcia V et al 2013
Progestines to improve appetite

We suggest considering progestines to increase the appetite of anorectic cancer patients with advanced disease but to be aware of potential serious side effects.

Ref: Arends et al 2016
Progestines

• Optimal dose is 160-800 mg/d (?)

• For short-intermediate term appetite stimulation and increase of weight but not muscle mass
Prokinetic drugs

- Metoclopramide and domperidone
- Fewer patients included in studies
- Can help in patients with early satiety and nausea
- But does it improve intake?
Newer, more targeted cachexia treatment
Cytokines
Cachectic factors
TUMOUR
Brain
↑ anorexia
↑ chemosensory changes
↑ adrenergic activation
↑ hypogonadism
Muscle tissue
↑ atrophy
↓ hypertrophy
Adipose tissue
↑ lipolysis
↑ mitochondrial uncoupling proteins
Liver
↑ acute-phase proteins
Glucose metabolism
↑ insulin resistance
↑ cori circle

Ghrelin
Brain
TUMOUR
Cytokines
Cachectic factors
Liver
Ghrelin
Brain
TUMOUR
Cytokines
Cachectic factors
Liver
Glucose metabolism
↑ insulin resistance
↑ cori circle

MC4
Selective androgen receptor
β-blockade, 5-HT1a antagonist
β-2 receptor agonism
Muscle tissue
Adipose tissue
Liver
TUMOUR
Cytokines
Cachectic factors
Liver
Glucose metabolism
↑ insulin resistance
↑ cori circle

β-blockade, 5-HT1a antagonist
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↑ insulin resistance
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Targeted cachexia interventions the last few years

• There have been studies that showed few, inconsistent or no improvements

• Several agents might have shown inferior results
  – lack of multimodal interventions
  – lack of compliance
  – administrated to late in the disease trajectory
New cachexia based mechanisms

• Most ongoing studies are now designed to include patients at an early stage
  – There is more anabolic potential, most likely to succeed in improving muscle/function
  – Better compliance and less attrition

• Few studies are multimodal
New cachexia based mechanisms

• Drugs are mainly used to:
  – Decrease systemic inflammation
  – Increase muscle mass
  – Appetite stimulation
New cachexia based mechanisms

• Drugs are mainly used to:
  – Decrease systemic inflammation
  – Increase muscle mass
  – Appetite stimulation
Decrease systemic inflammation

- **IL-6**
  - ALD518 (Phase II studies) - improved fatigue and LBM
- **TNF-α**
  - Eternacept, Infliximab, Melatonin, Thalidomid
- **Anti-IL-1α**
  - Xilonix - lesser decline in function and improved OS
- **NSAID**
  - May improve weight in cancer patients with cachexia, and some evidence of an effect on physical performance, self-reported quality of life and inflammatory parameters
preMENAC-study

• Chemotherapy vs CT and Multimodal treatment (celecoxib, EPA, exercise, ONS/nutritional advice)

• 46 patients to assess feasibility
  – Intervention group vs control group
    • Weight
    • Muscle mass
    • Physical function

(Solheim et al. in press Journal of Cachexia, Sarcopenia and Muscle)
New cachexia based mechanisms

• Drugs are mainly used for:
  – Decrease systemic inflammation
  – Increase muscle mass
  – Appetite stimulation
Increase muscle mass

- **Growth Hormone**
  - Controversial/ contraindicated in cancer

- **Testosterone**
  - Not compelling evidence so far, risk of side effects

- **Formoterol fumarate (anabolic β2-agonist)**
  - Promising, but only assessed in very small studies
Increase muscle mass

• Inhibition of myostatin/myostatin receptor
  – Awaiting results: bimagrumab, Ly2495655

• Selective androgen receptor modulator
  – SARM

• Non-selective β blocker + central 5-HT1a and partial β2 receptor agonist effects
  – espindolol
Enobosarm

• Orally active selective androgen receptor modulators (SARMs) with the potential to increase LBM
  – without side effects seen with traditional anabolic agents

• Phase II trial
  – 159 patients randomized to two different doses or placebo for 113 days
  – Significant increases in LBM
  – Improvement stair climb power test
  – No improvement grip strength, 6 min walk nor ECOG
  – Loss of fat mass  
    \[\text{ref Dobs et al, Lancet Oncology 2013}\]
Enobosarm

- 2 Phase III trials: unpublished

- Endpoint: maintain or increase LBM and have a 10% or greater improvement in stair climb power

- 504 study: LBM was improved, not stair climb power
- 505 study: neither LBM nor stair climb improved significantly
Espindolol

Non-selective β blocker + central 5-HT1a and partial β2 receptor agonist effects

• Eighty-seven patients were randomized placebo vs high and low dose espindolol in 4 weeks
• High-dose espindolol produced a weight gain and increase in LBM compared to placebo
• Improved hand grip strength, but not stair climbing power, and 6-min walk test

ref. Coats et al 2016
New cachexia based mechanisms

• Drugs are mainly used for:
  – Decrease systemic inflammation
  – Increase muscle mass
  – Appetite stimulation
Appetite stimulation

- Cannabinoids
- Zinc (taste disorder)
- Ghrelin
Anamorelin

- Ghrelin is an endogenous peptide primarily secreted by the stomach
- Upon binding to its receptor, ghrelin stimulates multiple pathways
  - metabolism, appetite, GH axis, inflammation
- Anamorelin is a selective, stable, orally active ghrelin receptor agonist
Anamorelin

- ROMANA 1 and ROMANA 2 were two international, double-blind, randomized, placebo-controlled Phase III trials
- Stage III/IV NSCLC and cachexia (≥5% weight loss within six months or BMI <20 kg/m2)
- Patients were randomized anamorelin vs placebo, given daily orally for 12 weeks
- ROMANA 1 enrolled 484 patients and ROMANA 2 enrolled 495 patients.
Anamorelin

• Median lean body mass versus placebo:
  – ROMANA 1: 0.99 vs -0.47 kg; p<0.001
  – ROMANA 2: 0.65 vs -0.98 kg; p<0.0001

• Body weight:
  – ROMANA 1: 2.20 vs 0.14 kg; p<0.0001
  – ROMANA 2: 0.95 vs -0.57 kg; p<0.0001.

• In both studies changes in handgrip strength were not different between patients receiving anamorelin or placebo.
What is a good outcome in cachexia trials?

• The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are regulatory agencies responsible for scientific evaluation of medicines and licensing of drugs
  – Lean body mass (LBM) gain and improved muscle strength/power as co-primary endpoints

• But for rehabilitation programmes in COPD they focus on more patient centered outcomes such as physical activity level
What is a good outcome in cachexia trials?

- Must be clinically meaningful!
  - Must be associated with mortality or morbidity
- Related to the disease
- Biologically plausible
- Stopping decline, not necessarily improving
What is a good outcome in cachexia trials?

- Functional tests?
- PROMs
- Muscle mass/weight
  - DEXA? CT-scan? Weight alone?
- Nutritional intake?
  - 24h recall? 3-5 days food dairy? PG-SGA?
- Performance status?
- Improved cancer therapy tolerance/survival?
Pathophysiology

- Inflammation,
- Anabolism/catabolism
- Appetite
- Reduced food intake
- Reduced physical activity
- Cancer

Intervention

- Targeted pharmacological intervention
- Sufficient nutrition
- Physical exercise
- Cancer treatment
Drugs to treat and relief patients with cancer cachexia

• Take home message
  – Pharmacological treatment of nutritional impact symptoms is both adding the right medication – but also to discontinue the ones that are not needed
  – Corticosteroids, progestins (and prokinetics) for short time relief of appetite loss or early satiety
  – Newer drugs; still preferably include in clinical trials, what is good enough?
  – Drugs alone will perhaps not be enough
Thank you for the attention