Pharmacological treatments

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Pharmacologic treatment: Basic concept

Interfere with undesired physiology

Drug a specific target
Major problems in cachexia

→ insufficient energy intake

→ decreased physical activity

→ deranged metabolism/inflammation
food intake

- Appetite
- GI defects

Pain
Distress
Depression
Nausea
Disturbed Taste
Disturbed Smell
Inflammation

Vomiting
Dysphagia
Infections
Ulceration
GI resections
Fistulas
Bloating, cramping
Diarrhea
Radiation defects
Pain
Fatigue
Depression
Nausea
Fever

Inactivity
Weight loss
Catabolic agents
Inflammation

Drive

Muscle

activity
Cancer

Infections

inflammation
Potential targets for anticachexia treatment

**APPETITE**
- pain treatment
- psychological support
- anti-anorectic agents

**GI TRACT**
- taste/smell
- nausea
- vomiting
- dysphagia
- ulcerations
- diarrhea

**CATABOLISM**
- endocrine agents
- anticatabolic / anabolic agents

**INFLAMMATION**
- anticancer
- anti-infective agents
- anti-inflammatory agents
Appetite stimulation

Corticosteroids
Progestins
Cannabinoids
Ghrelin
Cyproheptadine
Branched-chain amino acids
Herbal medicine, bitters
Corticosteroids

<table>
<thead>
<tr>
<th></th>
<th>Effectivity</th>
<th>Typical Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Prednisolone, methylprednisolone</td>
<td>5</td>
<td>20 mg</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>20</td>
<td>4 mg</td>
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</table>

Systematic review: 6 RCT (n=647) 4d to 8w:

- Stimulation of appetite, anti-emetic, increase well-being
- Effects disappear after 4 weeks!

Side-effects:
- Myopathy
- Osteoporosis
- Immune suppression
- Edema
- Edema
- Insulin resistance
- GI ulcers

Yavuszen T et al. J Clin Oncol 2005
Progestins

**Typical dose**

- **Megestrolacetate (MA)**: 160-1600 mg
- **Medroxyprogesterone acetate (MPA)**: 300-1200 mg

**Stimulation of appetite**
- Increase in body weight, **but no increase in LBM**
- Improve QoL

**Side-effects:**
- Thromboembolism (5%)
- Impotence in males
- Vaginal spotting or bleeding
- Hypertension, hyperglycemia
- Edema
- Adrenal insufficiency
Progestins

**Cochrane metaanalysis 2005**

31 RCT (n=4123)  MA vs PLAC:  app +, WT +

**Metaanalysis 2008**

30 RCT (n=4430)  MA vs PLAC  app +, WT +  survival ∅, QoL ∅

Not approved for cancer anorexia

Berenstein EG et al. Cochrane Database Syst Rev 2005; CD004310
Dronabinol (D) vs megestrolacetate (M) vs combination (C) in patients with cancer cachexia (4 wk)

Appetite improved

Weight increased

Quality of life improved

Cannabinoids

RCT (n=164) 6 weeks:

- cannabis extract (5 mg THC)
- vs THC (5 mg)
- vs placebo: app ∅, QoL ∅
Ghrelin and Analogues

**Ghrelin**, peptide hormone of gastric mucosa

- **2004:** RCT (n=7) 3 h: food intake +
- **2008:** RCT (n=21) 1 h: app ∅
- **2010:** RCT (n=15) 10 d: app +, food +, WT-loss -
- **2010:** RCT (n=31) 8 w: fat loss -

**Anamorelin**, oral ghrelin analogue

- **2007:** RCT 12 w: WT +, grip strength +
- **2013:** RCT 3 d: WT +

**experimental agent, Phase 3 trials ongoing**

Neary NM et al. J Clin Endocrinol Metab 2004
Holst B et al. Br J Cancer 2008
Adachi S et al. Gastroenterol 2010
Lundholm K et al Cancer 2010
Garcia J et al. Supp Care Cancer 2012
Garcia J et al. Supp Care Cancer 2013
Anamorelin

After 3 Days Treatment

- Anamorelin 50 mg/d (n = 15)
- Placebo (n = 16)

Mean (SEM) Change in Body Weight (kg)

p = .016

0.77

-0.33

Garcia JM et al. Support Care Cancer 2013
Anticatabolic agents

Insulin and insulin sensitivity modulators
Growth hormone, secretagogues, IGF-1

Anabolic androgenic steroids and SARMs
Proteasome inhibitors
ß-receptor modulators
ß-hydroxy ß-methylbutyrate and amino acids
Hydrazine sulfate
Adenosine triphosphate (ATP)
Anabolic androgenic steroids/SARMs

Nandrolone  
RCT (n=37) 4 w  WT (+)

Fluoxymesterone  
RCT (n=475) 4 w  app +, WT (+)

Oxandrolone  
RCT (n=155) 12 w  LBM +

⇒ less effective than corticosteroids and progestins
⇒ depression, thromboembolism, hypertension etc.

Selective androgen response modifiers (SARMs)

Enobosarm  
Phase 2b trial  N=100, 113 days: LBM +

Phase 3 trial NSCLC  NCT 01355484

Chlebowski RT et al. Cancer 1986  
Loprinzi CL et al. J Clin Oncol 1999  
Dobs AS et al. Lancet Oncology 2013
Anti-inflammatory agents

Corticosteroids
Progestagens
Cannabinoids
Non-steroidal anti-inflammatory drugs (NSAID)
N-3 fatty acids
Anti-cytokines
Melatonin
Antioxidants
NSAID in 135 cancer patients with weight loss (RCT)

Fig. 2. Survival curves in curve analysis on pooled patients treated with anti-inflammatory drugs (either indomethacin or prednisolone) compared to patients treated with placebo. The survival was significantly prolonged in patients on anti-inflammatory treatment ($P < 0.03$).
**NSAID in cancer cachexia**

Systematic review: 13 studies total, 6 controlled studies

- Small studies
- Suboptimal design
- Many without comparator

11/13 → stabilization or improvement of WT or LBM

→ „NSAIDs may improve weight in cancer patients.“
→ „Evidence is too frail to recommend.“

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*Solheim T et al. Acta Oncol 2012*
N-3 Fatty acids

Arachidonic acid

N-6 PUFA

Prostanoids
2 and 4 series

pro-inflammatory

COX

N-3 PUFA

Eicosapentaenoic acid

Prostanoids
3 and 5 series

anti-inflammatory

Side effects: dyspepsia, nausea, prolonged bleeding time?
ONS with fish oil during chemotherapy

**Open label study / free choice**
- n=46 NSCLC: N=31 „Standard-of-care“
  - N=15 fish oil: 2.5 g (EPA+DHA) per day as capsule or oil
- Chemother: different regimens
- Duration: 1 year

**Results**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Fish oil</th>
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<tbody>
<tr>
<td>Response rate = CR + PR</td>
<td>26%</td>
<td>60%</td>
</tr>
<tr>
<td>CR + PR + stable disease</td>
<td>42%</td>
<td>80%</td>
</tr>
<tr>
<td>Dose limiting toxicity</td>
<td>no difference</td>
<td>no difference</td>
</tr>
<tr>
<td>1-Year survival</td>
<td>39%</td>
<td>60%</td>
</tr>
</tbody>
</table>

**References**
- Murphy RA et al., Cancer 2011
Conclusion

- To improve appetite relieve psychological distress and chronic pain
- Optimize gastrointestinal function and relieve nausea

- To stimulate appetite, corticosteroids and progestins are best established; both have unwanted side-effects that need to be considered
- Anticancer treatment may improve metabolism and decrease inflammation
- Anti-inflammatory agents, like NSAIDs and N-3 fatty acids may be used to counteract chronic inflammatory states in cancer patients

- Hunger-inducing peptides like ghrelin and MC4R antagonists as well as anabolic-androgenic agents as well as anti-myostatin and anti-IL6 antibodies are being investigated as potential anticachectic agents
- All anticachectic agents should be accompanied by exercise training