ESPEN Congress Krakow 2019

Nutrition In Palliative Care

CACHEXIA-ANOREXIA SYNDROME AND ITS PHARMACOLOGICAL TREATMENT

T. Yavuzsen (TR)
Cachexia-Anorexia Syndrome and Its Pharmacological Treatment

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No conflict of interest related to this presentation
My Presentation Outlines

• Cachexia definition/classification
• Prevalence
• Pathophysiology
• Management
Cancer Cachexia: Terminology

“Kakos” = Bad
“Hexis” = Condition

Hippocrates (Kos 460 BC - Larissa 377 BC)

It is defined as a multifactorial syndrome characterised 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.

_Fearon K. et al, 2011_
Classification of Cancer Cachexia

Fearon K. et al, 2011
Introduction

• Frequency of cancer cachexia
  ✓ End-stage cancer patients 80 %
  ✓ Major cause of death 20 %

• Frequency at diagnosis depends on the primary site:
  ✓ Gastric cancer
  ✓ Pancreatic cancer
  ✓ Head and neck cancer
  ✓ Lung cancer
  ✓ ........
Malnutrition Prevalence in Turkey

Table 2
Symptoms prognostic for survival.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. of studies (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Total no. of patients (range)</th>
<th>Mean symptom prevalence % (SD)</th>
<th>Correlation with survival in UV (%)</th>
<th>No. of studies with MV analysis</th>
<th>Correlation with survival in MV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion</td>
<td>5 (11)</td>
<td>756 (98–200)</td>
<td>13.1 (3.9)</td>
<td>5 (100)</td>
<td>5</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>37 (84)</td>
<td>11,889 (41–1164)</td>
<td>65.3 (14.3)</td>
<td>32 (86)</td>
<td>35</td>
<td>13 (37)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27 (61)</td>
<td>7658 (41–809)</td>
<td>66.5 (23.4)</td>
<td>23 (85)</td>
<td>26</td>
<td>8 (31)</td>
</tr>
<tr>
<td>Cachexia</td>
<td>8 (18)</td>
<td>2269 (77–530)</td>
<td>35.3 (20.5)</td>
<td>6 (75)</td>
<td>8</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>17 (39)</td>
<td>6901 (47–1555)</td>
<td>50.6 (19.1)</td>
<td>12 (71)</td>
<td>16</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>20 (45)</td>
<td>4474 (47–501)</td>
<td>32.3 (20.0)</td>
<td>14 (70)</td>
<td>20</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>6 (14)</td>
<td>1603 (100–500)</td>
<td>53.1 (23.5)</td>
<td>4 (67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>35 (80)</td>
<td>9155 (41–756)</td>
<td>40.2 (19.9)</td>
<td>22 (63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>13 (30)</td>
<td>4154 (47–1164)</td>
<td>28.6 (17.5)</td>
<td>8 (62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>10 (23)</td>
<td>3003 (47–1164)</td>
<td>39.0 (12.5)</td>
<td>6 (60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressed mood</td>
<td>8 (18)</td>
<td>2300 (47–500)</td>
<td>46.7 (22.1)</td>
<td>4 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>26 (59)</td>
<td>7874 (47–1164)</td>
<td>35.2 (17.0)</td>
<td>12 (46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>38 (86)</td>
<td>12,447 (41–1164)</td>
<td>62.0 (18.8)</td>
<td>17 (45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>22 (50)</td>
<td>6845 (53–1164)</td>
<td>28.1 (8.03)</td>
<td>7 (32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (27)</td>
<td>3681 (53–1164)</td>
<td>21.1 (7.2)</td>
<td>3 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>16 (36)</td>
<td>6037 (53–1164)</td>
<td>36.6 (13.4)</td>
<td>4 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep impairment</td>
<td>13 (30)</td>
<td>2798 (53–501)</td>
<td>54.7 (27.9)</td>
<td>3 (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coughing</td>
<td>9 (20)</td>
<td>2823 (41–1555)</td>
<td>73 (0)</td>
<td>2 (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>8 (18)</td>
<td>2522 (47–756)</td>
<td>49.2 (21.3)</td>
<td>1 (13)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation; UV, number of studies in which univariate analysis shows significant association with survival; MV, number of studies in which multivariate analysis shows statistical significance for a symptom.

<sup>a</sup> Vigano et al. includes 2 cohorts, % of total of 33 cohorts.

- Prevalence is high >50%
- Worse QOL
- Negative prognostic – high mortality, high morbidity
- Hospitalization and risk of infection
- Cost
Pathophysiology

- Chronic inflammation
- Metabolic changes
- Lipolytic / proteolytic substances
- Hormonal changes
- Role of neurotransmitters
- Cytokine impact on hypothalamus

It is important that to be characterized the pathways affected in each tissue for understanding complex mechanism

- By negative protein, and negative energy balance driven
- By a variable combination of reduced food intake and abnormal metabolism
**Figure 1.** Balance Between the Anorexigenic and Prophagic Signals to the Hypothalamic Arcuate Nucleus, Which Controls Appetite and Food Intake.

AgRP = agouti-related protein; CART = cocaine- and amphetamine-regulated transcript; IL = interleukin; NPY = neuropeptide Y; POMC = pro-opiomenalocortin; TNF-α = tumor necrosis factor α.
Cancer Cachexia Multifactorial Syndrome

**Figure 1** Multimodality Rx model. NSAID, nonsteroidal anti-inflammatory drug; REE, resting energy expenditure; IL, interleukin.
Cancer Cachexia Multimodality Therapy

- Pharmacological treatment
- Nutritional treatment
- Exercise treatment
- Psychosocial treatment
Many different drugs have been suggested to be an effective against cancer cachexia. Therefore, in a general classification, these drugs perform 3 basic functions:

1. Reduction of the tumor-associated inflammation
2. Capitalization on the anabolic potential of the body to counter the wasting and hyper-catabolic state
3. Appetite stimulation
Pharmacological Treatments

1. Appetite stimulants
   - Progestins (Megestrol acetate – MA, Medroxyprogesteron acetate – MPA)
   - Corticosteroids, Cannabis sativa, Nabilone, Melatonin, Anamorelin

2. Cytokines modulators
   - Etanercept, Infliximab, Thalidomide, Pentoxifyline

3. Anabolic agents
   - Insulin, Enobosarm
4. **Combination therapies**

- MA + Thalidomide,
- MA + meloxicam + eicosapentaenoic acid (EPA)
- MA + EPA + L-carnitine + thalidomide
- MA + EPA + L-carnitine + thalidomide
- L-carnitine + celecoxib + MA
- Celecoxib + MA
Metabolic Targets for the Main Therapeutic Strategies Used for Cancer Cachexia

Stimulating appetite:
1. Megestrol acetate
2. Ghrelin agonists
3. MC4 receptor antagonists
4. Serotonin antagonists

Interfering with metabolic alterations:
5. Pro-cachectic cytokine antagonists
6. Anti-cachectic cytokines
7. COX-2 inhibitors
8. Beta-2 agonists
9. ACE inhibitors
10. Beta blockers
11. SARMs
12. Myostatin antagonists
13. Proteasome inhibitors
14. Phosphodiesterase inhibitors
15. αβ-fatty acids
Megestrol Acetate (MA)

- MA is a orexigenic (appetite stimulating) agents that have been relatively well-evaluated in cancer related anorexia cachexia syndrome.

- MA is the only drug in clinical use for the treatment of cachexia and has been approved by the FDA for treating AIDS-associated cachexia.
Megestrol Acetate (MA)

• To date, no other drug has been shown to be superior to MA in efficacy and tolerability\(^1\)

• The mechanism that the weight gain is mostly unknown

• Some researchers have asked the value of MA, representing that weight gain increased body fat and fluid retention without significant improvement in lean body mass\(^2,3\)

\(^1\) Tuca et al., 2013, \(^2\) Madeddu et al., 2009; \(^3\) Perez De Oteyza et al., 1998
Dose of MA

• Some studies have addressed the optimal dosing of MA in cancer cachexia\textsuperscript{1-4}

• In dose response trial\textsuperscript{1} there was a positive relationship between appetite stimulation and increasing MA doses ranging from 160 to 800 mg/day. A higher dose was not more effective.

• Side effects are important problem such as edema, thromboemboli, impotence and infections

\textsuperscript{1} Loprinzi CL et al., 1993; \textsuperscript{2} Vadell C et al., 1998; \textsuperscript{3} Bruera E et al., 1998; \textsuperscript{4} Pardo J et al., 2003
### Systematic Review *, Cochrane Database of Systematic Reviews **

<table>
<thead>
<tr>
<th>Authors (yrs)</th>
<th>RCT</th>
<th>Treatment</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maltoni M (2001)*</td>
<td>15</td>
<td>High dose MA/MPA</td>
<td>Weight gain, appetite</td>
</tr>
<tr>
<td>Lopez P (2004)*</td>
<td>26</td>
<td>MA</td>
<td>Weight gain, appetite</td>
</tr>
<tr>
<td>Yavuzşen T (2005)*</td>
<td>55</td>
<td>All drugs</td>
<td>Progestin ,c/s evidence</td>
</tr>
<tr>
<td>Berenstein EG (2007)**</td>
<td>30</td>
<td>MA</td>
<td>MA better than placebo</td>
</tr>
<tr>
<td>Lesniak W (2008)**</td>
<td>30</td>
<td>MA</td>
<td>MA better than placebo</td>
</tr>
<tr>
<td>Garcia RV (2013)**</td>
<td>35</td>
<td>MA</td>
<td>MA better than placebo</td>
</tr>
</tbody>
</table>

**edema, thromboembolic events, and deaths were more frequent in pts treated MA**

**The level of evidence of progestins are high in cancer cachexia.**
Corticosteroids

• Its mechanism of action in cachexia has not been established.

• Euphorogenic and anti-inflammatory effects, and perhaps stimulation of orexigenic hormones within the hypothalamus, may be responsible for an increase in appetite.

• Many patients treated with corticosteroids experience an increase in appetite and sense of wellbeing but not BW, compared with placebo\textsuperscript{1-3}.

\textsuperscript{1} Mortel CG et al., 1974, \textsuperscript{2} Bruera E et al., 1985; \textsuperscript{3} Popiela T et al., 1989
Corticosteroids

• It effect only on appetite, only 1-2 wks placebo- ctrl RCTs: 4 mg dexamethasone 2 wks or 16 mg methylprednisolone bid 7 days improve anorexia, fatigue \(^1,2\)

• The duration of appetite stimulation is often short-lived. Furthermore, prolonged steroid therapy produces variety of side effects (proximal myopathy, candidiasis, anxiety, depression)

\(^1\) Yennu S et al., 2013, \(^2\) Paulsen O et al., 2014
Figure 1. Mechanisms through which cannabinoids can affect cancer- and chemotherapy-related symptoms.

1. Binding to a cannabinoid receptor.
2. THC and other lipophilic cannabinoids can diffuse freely through the cellular membrane, where they are then transported intracellularly by fatty acid binding proteins. Lipophilic cannabinoids also freely diffuse into the membranes of intracellular vesicles.
3. Cannabinoids are hydrolyzed into various metabolites that can bind to CB1 and other receptors involved in immune function, cellular signaling, etc.

2-AG, 2-arachidonoylglycerol; AEA, arachidonoyl-ethanolamide; ATP, adenosine triphosphate; CB, cannabinoid; CBD, cannabidiol; P450, cytochrome P450; PPAR-α, peroxisome proliferator-activated receptor α; ROS, reactive oxygen species; THC, Δ⁹-tetrahydrocannabinol; TRPV1, transient receptor potential cation channel subfamily V member 1; Δm, membrane potential.
Cannabis Sativa

Comparison of Orally Administered Cannabis Extract and Delta-9-Tetrahydrocannabinol in Treating Patients With Cancer-Related Anorexia-Cachexia Syndrome: A Multicenter, Phase III, Randomized, Double-Blind, Placebo-Controlled Clinical Trial From the Cannabis-In-Cachexia-Study-Group

Florian Strasser, Diana Luftner, Kurt Possinger, Gernot Ernst, Thomas Ruhstaller, Winfried Meissner, You-Dschun Ko, Martin Schnelle, Marcus Reif, and Thomas Cerny

Strasser F et al. J Clin Oncol 2006; 24:3394-400
• Similar to THC, derivates of Nabilone (synthetic analogue) has been approved for CINV.
• One study compared the effect of Nabilone vs placebo among patients with lung cancer.
• Total of 47 patients were randomized to either Nabilone (0.5 mg/2 weeks followed by 1.0 mg/6 weeks) or placebo.
• End of treatment evaluation reported no significant difference in weight, appetite or QOL between 2 groups.
To compared the effect of Melatonin (20 mg/d) vs plc on pts with advanced lung and GI cancers for 28 days.

The primary outcome was change in appetite using the ESAS.

The study was closed when 48 patients were recruited due to reasons of non-inferiority and interim analysis showed no difference between groups.

Del Fabbro E et al. J Clin Oncol 2013; 31:1271-6
Ghrelin

- The orexigenic mediator ghrelin is a novel endogenous ligand for the GH secretagogue receptor.

- It is secreted by the stomach and pancreas, has been reported as having a key role in increasing appetite and food intake.

- In addition, it has important metabolic effects and regulates energy metabolism through GH-dependent and -independent mechanisms.
Anamorelin for patients with cancer cachexia: an integrated analysis of two phase 2, randomised, placebo-controlled, double-blind trials

José M Garcia, Ralph V Boccia, Charles D Graham, Ying Yan, Elizabeth Manning Duus, Suzan Allen, John Friend

Summary
Background Cancer anorexia-cachexia syndrome is associated with increased morbidity and mortality. Anamorelin is an oral ghrelin-receptor agonist with appetite-enhancing and anabolic activity. We assessed the effects of anamorelin on body composition, strength, quality of life, biochemical markers, and safety in patients with cancer anorexia-cachexia.

Anamorelin (ONO-7643) in Japanese patients with non-small cell lung cancer and cachexia: results of a randomized phase 2 trial

Koichi Takayama¹ · Nobuyuki Katakami² · Takuma Yokoyama³ · Shinji Atagi⁴ · Kozo Yoshimori⁵ · Hiroshi Kagamu⁶ · Hiroshi Saito⁷ · Yuichi Takiguchi⁸ · Keisuke Aoe⁹ · Akira Koyama¹⁰ · Naoyuki Komura¹⁰ · Kenji Eguchi¹¹

Support Care Cancer (2016) 24:3495–3505
DOI 10.1007/s00520-016-3144-z
Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials

Jennifer S Temel, Amy P Abernethy, David C Currow, John Friend, Elizabeth M Duus, Ying Yan, Kenneth C Fearon

ROMANA 3: a phase 3 safety extension study of anamorelin in advanced non-small-cell lung cancer (NSCLC) patients with cachexia

D. Currow1*, J. S. Temel2, A. Abernethy3, J. Milanowski4, J. Friend5 & K. C. Fearon6†

Anamorelin (ONO-7643) for the Treatment of Patients With Non-Small Cell Lung Cancer and Cachexia: Results From a Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Japanese Patients (ONO-7643-04)

Nobuyuki Katakami, MD; Junji Uchino, MD; Takuma Yokoyama, MD; Tateaki Naito, MD; Masashi Kondo, MD; Kouzo Yamada, MD; Hiromoto Kitajima, MD; Kozo Yoshimori, MD; Kazuhiro Sato, MD; Hiroshi Saito, MD; Keisuke Aoe, MD; Tetsuya Tsuji, MD; Yuichi Takiguchi, MD; Koichi Takayama, MD; Naoyuki Komura, MS; Toru Takiguchi, MS; and Kenji Eguchi, MD
<table>
<thead>
<tr>
<th></th>
<th>ROMANA 1</th>
<th>ROMANA 2</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Anamorelin</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Primary endpoints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n)</td>
<td>323</td>
<td>161</td>
</tr>
<tr>
<td>Median lean body mass (kg)</td>
<td>0.99</td>
<td>-0.47</td>
</tr>
<tr>
<td></td>
<td>(0.61 to 1.36)</td>
<td>(-1.00 to 0.21)</td>
</tr>
<tr>
<td>Median handgrip strength (kg)</td>
<td>-1.10</td>
<td>-1.58</td>
</tr>
<tr>
<td></td>
<td>(-1.69 to -0.40)</td>
<td>(-2.99 to -1.14)</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
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<tr>
<td>(n)</td>
<td>284</td>
<td>141</td>
</tr>
<tr>
<td>Mean bodyweight (kg)</td>
<td>2.20 (0.33)</td>
<td>0.14 (0.36)</td>
</tr>
<tr>
<td>Mean anorexia-cachexia scale score</td>
<td>4.12 (0.75)</td>
<td>1.92 (0.81)</td>
</tr>
<tr>
<td>Fatigue scale</td>
<td>0.26 (0.89)</td>
<td>-1.91 (0.93)</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.

Temel JS, et al., Lancet Oncol 2016; 17(4):519-531
Anamorelin

(A) Change from baseline (kg)

Placebo (N) 90 83 68 65 62
Anamorelin (N) 82 73 69 58 53

(B) Change from baseline (kg)

0 1 3 6 9 12 Week

Placebo (N) 90 89 87 76 69 64
Anamorelin (N) 82 80 75 70 61 55

(C)

<table>
<thead>
<tr>
<th>Primary endpoint a</th>
<th>Placebo (n = 90)</th>
<th>Anamorelin (n = 82)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean body mass (kg)</td>
<td>-0.17 ± 0.17</td>
<td>1.38 ± 0.18</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Secondary endpoints a

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Placebo (n = 90)</th>
<th>Anamorelin (n = 82)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite b</td>
<td>0.3 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td>.0005</td>
</tr>
<tr>
<td>Cancer Fatigue Scale</td>
<td>1.4 ± 0.7</td>
<td>1.7 ± 0.7</td>
<td>.7170</td>
</tr>
<tr>
<td>Handgrip strength (kg)</td>
<td>-0.60 ± 0.28</td>
<td>0.05 ± 0.30</td>
<td>.0854</td>
</tr>
<tr>
<td>6-min walk distance (m)</td>
<td>11.7 ± 7.2</td>
<td>11.7 ± 7.8</td>
<td>.9987</td>
</tr>
</tbody>
</table>

*Least squares mean ± standard error for change from baseline over 12 weeks.

*Appetite was evaluated with QOL-ACD item 8 “Did you have a good appetite?”
• 6 RCTs included 1641 pts with NSCLC.
• Both BW ($p = 0.004$) and LBM ($p < 0.00001$) were significantly increased in the anamorelin compared to the placebo.
• The groups showed no difference in OS or HGS.
• Anamorelin significantly improved the QOL ($p = 0.0006$).
• This analysis demonstrated that anamorelin represents a promising treatment option for CACS in patients with advanced NSCLC.

*Nishie K et al. Lung Cancer 2017; 112:25-34*
These include

- Thalidomide
- Etanercept
- Infliximab
- Pentoxifylline
Cytokines Modulators

- TNF-α, IL-1,6 and IFN are the main cytokines implicated in cachexia.

- Thalidomide suppress in TNF-α synthesis in monocytes in vitro and is able to normalize elevated TNF-α invivo.

- RCT (placebo controlled) in pts with cancer cachexia showed that it was well tolerated and effective pancreatic cancer\(^1\)

- More recent data published in 2012 don’t show any beneficial effect in cachexia\(^2\)

\(^1\) Gordon JN et al. 2005, \(^2\) Yennurajalingam S et al. 2012
While many studies have no effect, 2 studies showed the beneficial effects of thalidomide combined use with MA and others drugs.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Agent/phase</th>
<th>Population</th>
<th>Size</th>
<th>CRC criteria</th>
<th>Study arms</th>
<th>Outcome measures</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gordon et al. 2005</td>
<td>Thalidomide; phase II</td>
<td>Inoperable pancreatic cancer</td>
<td>50 pts; 33 evaluable</td>
<td>Weight loss &gt;10% in last 6 months</td>
<td>(a) Thalidomide 200 mg/day; (b) placebo; duration: 24 weeks</td>
<td>(I) Weight change at week 4; (II) bone free muscle mass, grip strength, QoL, and survival</td>
<td>Improved weight, and bone free arm muscle mass</td>
</tr>
<tr>
<td>Mantovani et al. 2010</td>
<td>Thalidomide; phase III</td>
<td>Different advanced cancer types</td>
<td>332 pts; all evaluable</td>
<td>&gt;5% loss of ideal or pre-illness weight in last 3 months, with or without abnormal inflammatory cytokines</td>
<td>(a) Medroxyprogesterone acetate 500 mg/day or megestrol acetate 320 mg/day; (b) EPA supplement (2.2 g/day); (c) L-carnitine 4 g/day; (d) Thalidomide 200 mg/day; (e) combination of a, b, c, and d</td>
<td>(I) LBM, REE, and fatigue; (II) appetite; grip strength; QoL; serum IL-6, TNF-alpha; ROS, and GPX blood levels; prognosis by GPS; AEE and TEE; ECOG-PS</td>
<td>LBM, REE, and fatigue improved in combination arm as compared to arms (c), (d), and (e)</td>
</tr>
<tr>
<td>Yennurajalingam 2012</td>
<td>Thalidomide; phase II</td>
<td>Different advanced cancer types</td>
<td>31 pts; 21 evaluable</td>
<td>&gt;5% weight loss within last 6 months, reporting anorexia, fatigue, and one more symptom (≥3/10 anxiety, depression, or sleep disorders) in last 24 h</td>
<td>(a) Thalidomide 100 mg/day; (b) placebo; duration: 2 weeks</td>
<td>(I) Anorexia-cachexia symptom cluster; (II) body composition, REE, and serum cytokines</td>
<td>No between-groups statistically significant differences were found</td>
</tr>
<tr>
<td>Wen et al. 2012</td>
<td>Thalidomide; phase II</td>
<td>Different advanced cancer types</td>
<td>108 pts; 93 evaluable</td>
<td>&gt;5% loss of ideal or pre-illness weight in last 3 months</td>
<td>(a) Megestrol 320 mg/day and thalidomide 100 mg/day; (b) Megestrol 320 mg/day; duration: 8 weeks</td>
<td>(I) Weight, fatigue, and QoL; (II) appetite, grip strength, prognosis by GPS, ECOG-PS, IL-6, and TNF-alpha</td>
<td>Improved weight, fatigue, QoL, grip strength, GPS, and ECOG as well as decreased IL-6, and TNF-alpha in combination arm</td>
</tr>
</tbody>
</table>
These studies failed to demonstrate any beneficial effect of anti-TNF agents to advanced cancer patients with cachexia.
Clazakizumab is an anti-IL-6, currently under development. MABp1 is a natural human monoclonal antibody targeting IL-1α.

✓ An open label Phase 1b and dose escalation trial demonstrated to be safe and tolerable.

✓ Later phase 3 study was done. Both primary and secondary end points resulted positive. More research is needed as a promising drug for the future.

Table 1 (continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Agent/phase</th>
<th>Population</th>
<th>Size</th>
<th>CRC criteria</th>
<th>Study arms</th>
<th>Outcome measures †</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rigas et al. 2010</td>
<td>Clazakizumab (ALD518); phase II</td>
<td>Advanced NSCLC</td>
<td>124 pts §</td>
<td>&gt;5% weight loss within last 3 months; CRP &gt;10 mg/dL.</td>
<td>(a) ALD518 80, 160, or 320 mg every 8 weeks; (b) placebo; duration: 24 weeks</td>
<td>(I) Safety; (II) LBM, lung cancer symptoms, fatigue, anemia</td>
<td>ALD518 group had less loss of LBM at week 12, and improved lung symptom, and fatigue scores at week 2</td>
</tr>
<tr>
<td>Hichish et al. 2017</td>
<td>MABp1; phase III</td>
<td>Metastatic colorectal cancer</td>
<td>333; 309 evaluable</td>
<td>Any weight loss ≤20% in last 6 months or serum IL-6 ≥10 pg/mL plus anorexia, fatigue or pain (EORTC QLQ-C30 &gt;10), and decreased role, emotional, and social function (score &lt;90)</td>
<td>(a) MABp1 7.5 mg/kg every 2 weeks; (b) placebo; duration: 8 weeks</td>
<td>(I) Stable or increased LBM and stability or improvement in 2 of 3 symptoms (fatigue, pain, and anorexia); (2) inflammatory response, functional performance, QoL, tumor response, safety, and survival</td>
<td>More patients in MABp1 group achieved the composite primary outcome; MABp1 group had lower IL-6, less thrombocytosis, and longer survival</td>
</tr>
</tbody>
</table>
There are a lot of drugs that targeting metabolic alterations related with cancer cachexia that ongoing phases stages.
Anabolic Agents

• Insulin, anti-lipolytic effects was studied patients with advanced GI cancer. There was no improvement appetite, BW, and the QOL. However it was associated with improvement OS.

• Enobosarm is oral nonsteroidal selective androgen receptor modulators (SARM). It has been shown to have tissue-selective anabolic and androgenic activity, and can increase muscle mass and function.

Enobosarm

• In studies with using SARM in several diseases demonstrated muscle wasting showed positive findings.

• Enobosarm - Phase 2b double blind placebo controlled study – positive results\(^1\)

• After the positive findings phase 2 study, the phase 3 studies were planned (POWER1 and 2)\(^2\) the effect in cachexia was studied on both prevention and treatment of muscle wasting.

\(^1\) Dobs AS et al. 2013, \(^2\) Crawford J et al. 2016
The POWER studies have planned. The subjects received placebo or enobosarm 3 mg orally once daily for 147 days. Physical function is assessed as stair climb power (SCP), and LBM by dual-energy X-ray absorptiometry.

These are co-primary efficacy endpoints in both trials assessed at day 84. Preliminary data report an increase in LBM and improvement in SCP (POWER1). POWER2 also shows an increase in LBM, whereas no clinical improvement in SCP test and handgrip strength is seen.
With several drugs the combination treatments of cachexia has been studied. These are MA plus thalidomide, MA plus meloxicam, MA plus EPA supplement and MA plus celecoxib. Finally combination multidrug therapy with MA was associated improvement in weight, and other symptoms as compared to individual arms. These studies showed us, it needs to target multiple pathways in cancer cachexia.
Nutritional Treatment

- Nutritional intervention include dietary counselling, nutritional supplementation, and artificial nutrition.

- It must be done, preferably by a professional dietician, it is important ONS especially in EPA, Zinc, Vit C, D for cancer cachexia

- Recommendations include **dietary changes**, such as intake of an energy and protein rich diet, and **lifestyle changes**, such as increasing meal frequency and decreasing meal size.

- If these changes could not satisfy the patient’s energy requirement, ONS may be offered.
We looked at the association between nutritional and serum inflammatory biomarkers and the effectiveness of ONS in cancer patients with malnutrition undergoing CT and also to determine the effect of these biomarkers on clinical outcomes in patients with aNSCLC.
Newly diagnosed stage 3B/4 NSCLC 25 patients underwent assessment for nutritional status by SGA before CT.

We also has reported the relation of Glasgow Prognostic Score to serum levels of zinc and vit D as an anti-inflammatory and antioxidative agent in patients with cancer.

Following the evaluation of the patients with a BMI ≤ 20, the ONS* was started also provided by addition of MA, and nutritional counseling.

*composed of liquid-based nutrient solution supplemented with appropriate omega-3 fatty acids (1.5g/d) and high protein
In 7 pts that completed the treatment period, because most of patients died due to refractory stage of cachexia and cancer.

We showed that elevated levels of cytokines and decreased levels of albumin, prealbumin, Zn, vit D, BMI, and high GPS play a role in predicting CT outcomes including morbidity and mortality.

We need a large-scale prospective studies are required in order to establish these biomarkers as a guide for selection of pts for treatment.
In addition, exercise has an important role for cachexia treatment/prevention by affecting on the molecular mechanisms. It has also potential to improve muscle mass and strength, physical function, fatigue and QOL patients with cancer cachexia.
Of the 2424 search results, 67 abstracts were reviewed and 24 full texts examined. Eight studies (n = 685) were included comprising two randomised control trials, three prospective, one exploratory and two secondary analyses. All examined multi-modal outpatient programmes.

There are limited data for multi-modal rehabilitation programmes combining exercise and nutritional interventions in patients with incurable cancer. However, studies to date report improvements in multiple domains, most notably physical endurance and depression scores. Further, high-quality studies are needed to define the optimal approach and outcome measures.
Following this, phase III trial was planned. We look forward to the findings.
The impact of cachexia extends beyond the physical problems into the psychological, social, and emotional domains for both patients and their family.

The psychosocial aspect of cachexia is important and should be evaluated regularly. In these interventions, caregivers should also be included.
Cancer cachexia is a multifactorial syndrome.

Cytokine production and hormonal alterations play a key pathophysiologic role.

Anorexia, increased REE, presence of systemic inflammation, and metabolic alterations, are all important features of the syndrome resulting in increased lipolysis and muscle wasting.
Muscle wasting is the most dramatic event.

Muscular depletion under a certain cut off is called sarcopenia and is related with significant increase of morbidity and mortality.

Normal aging and other chronic diseases and medications may additionally contribute to sarcopenia.

Antineoplastic drugs (including targeted therapies) may also block survival and proteo-synthetic pathways of muscle cells.
Timely diagnosis of cachexia is important and all patients with cancer should be regularly screened for food intake, weight loss and BMI.

*CACHEXIA* treatment must be a multidisciplinary approach:
- Correct all reversible causes of reduced food intake,
- Nutritional intervention, exercise programmes
- Unfortunately to date, there is lack of effective pharmacological interventions to treat cancer cachexia
Promising drugs for cachexia

- Anamorelin
- Enobosarm (POWER trials)
- A multidrug approach using combination of MA plus EPA plus thalidomide and L-carnitine was associated positive results (BW, symptoms)

Old agents and being enough level of evidence

- Progestins and corticosteroids
With early diagnosis and effective multimodal approach for patients with cachexia will be able to achieve success.
References


• Alacacioglu A, **Yavuzsen T**, Dirioz M, Yilmaz U. Quality of life, anxiety and depression in Turkish breast cancer patients and in their husbands Med Oncol (2009) 26:415–419
Thank you
Phase 2 study demonstrated feasibility and safety in patients receiving CT for incurable lung or pancreatic cancer.

Tora S. Solheim¹,²⁺, Barry J.A. Laird¹,³⁺⁺, Trude Rakel Balstad¹,², Guro B. Stene², Asta Bye⁴,⁵, Neil Johns⁸, Caroline H. Pettersen¹,⁶, Marie Fallon³, Peter Fayers¹,⁷, Kenneth Fearon⁸,⁹⁺ and Stein Kaasa¹,²⁺

Results Three hundred and ninety-nine were screened resulting in 46 patients recruited (11.5%). Twenty-five patients were randomized to the treatment and 21 as controls. Forty-one completed the study (attrition rate 11%). Compliance to the individual components of the intervention was 76% for celecoxib, 60% for exercise, and 48% for nutritional supplements. As expected from the sample size, there was no statistically significant effect on physical activity or muscle mass. There were no intervention-related Serious Adverse Events and survival was similar between the groups.

Conclusions A multimodal cachexia intervention is feasible and safe in patients with incurable lung or pancreatic cancer; however, compliance to nutritional supplements was suboptimal. A phase III study is now underway to assess fully the effect of the intervention.
MC4 Receptor Antagonists

- The melanocortin receptor (MC4) participates in the anorexigenic cascade by decreasing NPY, thus decreasing food intake.

- Using MC4 receptor antagonist seems an effective way to prevent anorexia, loss of LBM, and basal energy expenditure in preclinical studies involving cancer cachexia\(^1,2\)

Several orally MC4 RA have been developed but no data on cancer patients are available yet and therefore future clinical studies are warranted.

\(^1\) Weyermann P et al. 2009, \(^2\) Dallmann R et al. 2011