PATHOPHYSIOLOGY AND MANAGEMENT OF CANCER CACHEXIA

An update

I. Gioulbasanis MD, PhD
Dept. of Chemotherapy
Larissa General Clinic “E. Patsidis”
INTRODUCTION

Cancer Cachexia: Terminology

“Kakos” = Bad

“Hexis” = Condition

Hippocrates (Kos 460 BC - Larissa 377 BC)

Definition

“Cancer cachexia 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.

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

INTRODUCTION


Penman AD et al., Prev Chronic Dis 2006; 3(3): A74, with permission from PCD
**INTRODUCTION**

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

- Frequency at diagnosis depends on the primary site:
  - Pancreatic cancer
  - Head-neck cancer
  - Lung cancer
  - …

PATHOPHYSIOLOGY

Major organs affected in cancer cachexia

Porporato PE, Oncogenesis (2016) 5, e200; doi: 10.1038/oncsis.2016.3 Under a Creative Commons CC-BY license 4.0
PATHOPHYSIOLOGY

Anorexia

Cytokines

Leptin

Ghrelin

Bloodstream

Adipose tissue

Stomach

Nucleus tractus solitarius

Hypothalamus

Central Ghrelin

Vagal nerve

Cytokines
Resting energy expenditure

- **Tumor**
  - $\uparrow$~5-1000 kcal/day
  - $\uparrow$ REE, especially in late stages

- **Liver metastases and hepatomegaly**
  - $\uparrow$ REE, especially

- **Muscle**
  - $\downarrow$ mass,
  - $\downarrow$ REE $\sim$12 kcal/kg/day

- **WAT**
  - $\downarrow$ mass,
  - $\downarrow$ REE $\sim$4 kcal/kg/day

- **BAT**
  - May $\uparrow$ REE ($\sim$200 kcal), but only if fully activated

Activity Energy Expenditure $\downarrow$

Thermic Effect of Food $\downarrow$

Food intake = $\downarrow$ Thermic Effect of Food

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PATHOPHYSIOLOGY

Lipid metabolism (WAT browning)

Petruzelli M, et al., Genes Dev 2016; 30:489-501; open access and e-coursepack
Reprinted from Cell Metab 2012; 16(2), Fearon KC, et al., Cell Metab 2012; 16(2, Cancer Cachexia: Mediators, Signaling, and Metabolic Pathways:153-166, Copyright (2012), with permission from Elsevier
PATHOPHYSIOLOGY

Muscle wasting $\rightarrow$ Sarcopenia

$\uparrow$ morbidity
$\uparrow$ risk of falls
$\downarrow$ tolerance to therapy
$\downarrow$ quality of life
$\downarrow$ survival

PATHOPHYSIOLOGY

Muscle wasting

PATHOPHYSIOLOGY

Cross talks (fatty acid catabolism ➔ muscle wasting)

From Arner P. Science 2011;333(6039):163-164. Reprinted with permission from AAAS
Chronic inflammation

Increased production of Acute Phase Proteins
- C-reactive protein
- Serum amyloid A (SAA)
- α1-antitrypsin
- Fibrinogen
- Complement Factors B and C3

Decrease synthesis
- Albumin
- Transferrin
### Gene polymorphisms

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism</th>
</tr>
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<tbody>
<tr>
<td>IL-1B</td>
<td>rs16944, rs1143634</td>
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<tr>
<td>IL-10</td>
<td>rs1800896, rs1800871</td>
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<tr>
<td>IL-6</td>
<td>rs1800796</td>
</tr>
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<td>IL-8</td>
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<tr>
<td>SELP</td>
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<td>TNF</td>
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<tr>
<td>ACE gene</td>
<td>rs4291</td>
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</table>


Johns N, et al., J Cachexia sarcopenia and muscle, 2016, DOI: 10.1002/jcsm.12138

Sarcopenia (other contributing factors)

INFLAMMATION
- cytokines
- oxidative stress
- hypoxemia, acidosis
- tumor-derived factors

AGING
- sex hormones, apoptosis
- mitochondrial dysfunction
- DNA mutations
- ↓ antioxidant capacity

INACTIVITY
- bed rest
- immobility

ENDOCRINE
- glucocorticoids
- vitamin D status
- GH, IGF-1
- myostatin, thyroid
- insulin resistance

ANOREXIA
- ↓ energy intake
- social and psychiatric factors
- polypharmacy, dyspepsia
- edentulism, dysphagia
- ↓ protein intake
- maldigestion, malabsorption
- ↑ energy expenditure

NEURODEGENERATION
- vascular
- motoneuron loss
- demyelination

Reprinted from Clin Nutr 2014; 33(5), Biolo G, et al., Muscle contractile and metabolic dysfunction is a common feature of sarcopenia of aging and chronic diseases: From sarcopenic obesity to cachexia; 737-748. Copyright (2014), with permission from Elsevier
Secondary causes of malnutrition

**Obstruction of the GI track**
- Dysphagia…

**Uncontrolled symptoms**
- Pain
- Dyspnea
- Depression…

**Side-effects of anticancer therapies**
- Anorexia
- Mucositis
- Nausea - vomiting
- Diarrhea, constipation

**Medications for symptom management**
- Nausea
- Constipation…
PATHOPHYSIOLOGY

Direct effects of anticancer therapies on muscle mass:

Corticosteroids
Cytotoxic chemotherapy
Anti-androgen therapy
Targeted therapy

Stages of cachexia:

- **Precachexia**
  - Weight loss $\leq 5\%$
  - Anorexia and metabolic change

- **Cachexia**
  - Weight loss $>5\%$
  - 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 disease both procatabolic and not responsive to anticancer treatment
  - Low performance score
  - $<3$ months expected survival

**Usual approach**

- (%) weight loss

**Nutritional Screening**

- Clinical Questionnaires
  - PG-SGA
  - MNA
  - MUST
  - ...
- Lab tests
  - Albumin
  - CRP
  - (GPS)
  - (..?)

**In-depth nutritional assessment**

- Determination of daily nutritional requirements
  - (Food frequency Questionnaires, 1- / 3- day recall)
- Body composition analysis
  - (BIA, CT-scan, DEXA scan, ...)
- Assessment of energy expenditure
  - Equations, indirect calorimetry
Development of grading systems

**Figure A:** Estimated Hazard Ratio for Reduced Overall Survival and Median Survival across BMI deciles.

**Figure B:** Estimated Hazard Ratio for Reduced Overall Survival and Median Survival across Weight Loss deciles.

Obesity Paradox (?)

<table>
<thead>
<tr>
<th>Weight Loss (%)</th>
<th>28</th>
<th>25</th>
<th>22</th>
<th>20</th>
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<td>15</td>
<td>13.1</td>
<td>10.2</td>
<td>8.1</td>
<td>6.1</td>
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<tr>
<td>11</td>
<td>7.1</td>
<td>4.8</td>
<td>4.7</td>
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<tr>
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<td>10.7</td>
<td>9.2</td>
<td>6.8</td>
<td>6.2</td>
</tr>
<tr>
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<td>8.1</td>
<td>8.1</td>
<td>6.2</td>
<td>5.4</td>
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<td>4</td>
<td>14.2</td>
<td>11.9</td>
<td>10.5</td>
<td>10.6</td>
</tr>
<tr>
<td>3</td>
<td>21.5</td>
<td>19.9</td>
<td>15.7</td>
<td>13.5</td>
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</table>

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>28</th>
<th>25</th>
<th>22</th>
<th>20</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
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<td>3</td>
</tr>
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<td>2</td>
<td>3</td>
<td>3</td>
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<td>4</td>
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<tr>
<td>3</td>
<td>3</td>
<td>3</td>
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<td>4</td>
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<tr>
<td>4</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

DIAGNOSIS

Sarcopenic obesity

Effective antineoplastic therapy


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TREATMENT

Targets for potential treatment interventions

TREATMENT

Nutritional Care Plan

(Regular) nutritional screening

(Nutrition assessment)

Artificial nutrition

Timely identification of nutritional defects and initiation of nutritional support

Brief and casual nutritional “advice”

Identify all reversible causes of weight loss

Treatment of symptoms impairing food intake

(Professional) Nutritional counseling

Oral nutritional supplements

Via enteral tubes (enteral nutrition)

Parenteral infusions (parenteral nutrition)

TREATMENT

Nutritional deficits and goals

Weight-losing advance cancer patients

- Caloric deficiency 200 kcal/day
- Protein deficiency 0.3-0.5 g/kg/day

Goals of nutritional intervention

- ↑ energy intake 300-400 kcal/day
- ↑ protein intake +50%

Average nutritional requirements

- Energy intake: 25 - 30 kcal/kg/day
- Protein intake: >1 g/kg/day (if possible up to 1.5 g/kg/day)

TREATMENT

Nutritional support (evidence from clinical trials)

- Nutritional therapy in cancer patients improves body weight and energy intake but not survival
- Neither nutritional counseling nor oral nutritional supplements had a clear positive effect on patient’s quality of life
- Combination of both dietary advice and oral nutritional supplements may be more effective

- Heterogeneity:
  - ≠ cancer sites and stages
  - ≠ antineoplastic therapies
  - ≠ length and type of dietary interventions

Nutritional support (evidence from clinical trials)

- Studies examine effect of nutritional support in cachexia (N=5)
- Energy intake may be increased by various combinations of high energy foods, fortifications and oral nutritional supplements
- No clear effect in quality of life
- Dietary counseling may increase leisure activities and psychological functions

- It was not possible to give information on whether there were differences in the effectiveness of dietary treatment between patients having pre-cachexia, cachexia or refractory cachexia
Artificial nutritional support

### Prognosis-Based Decision Making Regarding Artificial Nutrition

<table>
<thead>
<tr>
<th>Nutritional State</th>
<th>Life expectancy: months or longer (active cancer treatments considered; pre-cachexia/cachexia state)</th>
<th>Life expectancy: days to weeks (progressive cancer with no standard treatment options; refractory cachexia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced oral intake and normal absorption</td>
<td>Continue with oral intake, consider nutritional supplements</td>
<td>Continue with oral intake, consider nutritional supplements</td>
</tr>
<tr>
<td>Significantly compromised oral intake (e.g. dysphagia, severe mucositis) and normal absorption</td>
<td>Consider enteral nutrition</td>
<td>Conservative measures Consider parenteral hydration Artificial nutrition not recommended</td>
</tr>
<tr>
<td>Significantly compromised absorption (e.g. bowel obstruction) or failure of enteral nutrition</td>
<td>Consider parenteral nutrition</td>
<td>Conservative measures Consider parenteral hydration Artificial nutrition not recommended</td>
</tr>
</tbody>
</table>

Hui D, et al., Curr Opin Support Palliat Care 2015
Nutritional support (specific considerations)

- For short-term nutritional support there is no need for any specifically formulated amino acids mixture.
- An increased ratio of energy from fat to energy from carbohydrates may be used to reduce the glycemic load.
- No evidence that glutamine or branched-chain amino acids improve clinical outcomes in cachectic patients.
- Vitamins and minerals to be supplied in amounts close to the RDA.
- Dietary provisions that restrict energy intake in patients with or at risk of malnutrition should not be used.
- No evidence supports that nutrients "feed the tumour".

Pharmaconutrients: Omega-3 fatty acids

- EPA can reduce inflammation and has the potential to modulate nutritional status/body composition
- Omega-3 fatty acids are present in relatively high amounts in oily fish or are available as nutrition supplements
- Patients with advanced tumours consume very low amounts EPA (and DHA) ≠ of energy intake, tumour site, BMI category, or PS
- At least 2 g EPA/day are required for clinical benefit on nutrition-related endpoints (dose-response relationship)

Pharmaconutrients: Omega-3 Fatty Acids

- Several small positive clinical trials
- Some larger negative randomised trials
- 3 systematic reviews conducted in 2007, 2009 and 2012 concluded that there was insufficient evidence to support any recommendation

Strength of recommendation: 

<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 stabilise or improve appetite, food intake, lean body mass and body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of evidence</td>
<td>Low</td>
</tr>
</tbody>
</table>
Pharmacconutrients and other drugs used in common practice

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>(Strength of) Recommendation</th>
<th>LoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dronabinol</td>
<td>↑ Appetite</td>
<td>( - :) Insufficient consistent clinical data</td>
<td>Low</td>
</tr>
<tr>
<td>Amino acids (Leucine, HMB)</td>
<td>Anti-catabolic</td>
<td>( - :) Insufficient consistent clinical data</td>
<td>Low</td>
</tr>
<tr>
<td>Progestins</td>
<td>↑ Appetite</td>
<td>(Weak:) In anorectic patients ...be aware of serious side effects</td>
<td>High</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>↑ Appetite</td>
<td>(Weak:) For a restricted period (1-3 weeks) ...be aware of side effects</td>
<td>High</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>↓ Cytokines</td>
<td>( - :) Insufficient consistent clinical data</td>
<td>Low</td>
</tr>
<tr>
<td>Prokinetics</td>
<td>↑ Gastric emptying</td>
<td>(Weak:) Insufficient consistent clinical data</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

## Novel drugs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Physiological effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anamorelin</td>
<td>Ghrelin receptor agonist</td>
<td>Appetite-enhancing and anabolic activity</td>
<td>Garcia et al. 2015</td>
</tr>
<tr>
<td>Bimagrumab</td>
<td>Anti-ActRII monoclonal antibody</td>
<td>Prevent skeletal muscle atrophy</td>
<td>Lach-Trifilieff et al. 2014</td>
</tr>
<tr>
<td>Clazakizumab</td>
<td>Anti-IL-6 monoclonal antibody</td>
<td>Anti-inflammatory activity</td>
<td>Bayliss et al. 2011</td>
</tr>
<tr>
<td>Enobosarm</td>
<td>Selective androgen receptor modulator</td>
<td>Anabolic activity</td>
<td>Dobs et al. 2013</td>
</tr>
<tr>
<td>IP-1510</td>
<td>IL-1 receptor antagonist</td>
<td>Anti-inflammatory activity</td>
<td>Paspaliaris et al. 2011</td>
</tr>
<tr>
<td>MABpl</td>
<td>Anti-IL-1α monoclonal antibody</td>
<td>Anti-inflammatory and anti-neoplastic activity</td>
<td>Hong et al. 2014</td>
</tr>
<tr>
<td>REGN1033</td>
<td>Myostatin antagonising antibody</td>
<td>Prevents skeletal muscle atrophy</td>
<td>Ebner et al. 2014</td>
</tr>
</tbody>
</table>
TREATMENT

Ghrelin and analogues

TREATMENT

Anamorelin

Eligibility criteria
- Patients with stage III/IV NSCLC
- Cachexia [WL >5% (6 m) or BMI <20 kg/m²]
- PS = 0-2
- Patients could begin new line / receive maintenance / have completed therapy

Intervention:
- Oral 100 mg anamorelin hydrochloride or placebo once daily for the 12-week study period

(Co-primary) End-points
- Lean-body mass
- Hand grip strength

Secondary end points
- Change in bodyweight, symptoms of anorexia–cachexia and fatigue

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

Anamorelin

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

<table>
<thead>
<tr>
<th>Primary endpoints* (n)</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>Median lean body mass (kg)</td>
<td>0.99 (0.61 to 1.36)</td>
<td>-0.47 (-1.00 to 0.21)</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>
</tr>
</tbody>
</table>

Secondary endpoints† (n)

<table>
<thead>
<tr>
<th></th>
<th>ROMANA 1</th>
<th>ROMANA 2</th>
</tr>
</thead>
<tbody>
<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
TREATMENT

Androgens

Testosterone

Myostatin

Akt

Notch activation

Satellite cell activation & proliferation

Myoblasts

Muscle growth

Caspase 2

JNK

p21

Apoptosis

Proliferation

Redrawn from Kovacheva EL, et al., Endocrinology 2010;151(2):628-638
## Enobosarm (SARM)

**Effects of enobosarm on muscle wasting and physical function in patients with cancer: a double-blind, randomised controlled phase 2 trial**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=52)</th>
<th>Enobosarm 1 mg (n=53)</th>
<th>Enobosarm 3 mg (n=54)</th>
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<tbody>
<tr>
<td></td>
<td>Grade 1–2</td>
<td>Grade 3–4</td>
<td>Grade 1–2</td>
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<tr>
<td>Abdominal pain</td>
<td>3 (6%)</td>
<td>0</td>
<td>2 (4%)</td>
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<tr>
<td>Anaemia</td>
<td>6 (12%)</td>
<td>2 (4%)</td>
<td>9 (17%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2 (4%)</td>
<td>0</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4 (8%)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>3 (6%)</td>
<td>0</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (4%)</td>
<td>0</td>
<td>9 (17%)</td>
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<tr>
<td>Cough</td>
<td>6 (12%)</td>
<td>0</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>3 (6%)</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>4 (8%)</td>
<td>0</td>
<td>8 (15%)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>5 (10%)</td>
<td>0</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (21%)</td>
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<td>8 (15%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>3 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (2%)</td>
<td>0</td>
<td>3 (6%)</td>
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<tr>
<td>Malignant neoplasm progression</td>
<td>0</td>
<td>8 (15%)</td>
<td>0</td>
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<tr>
<td>Nausea</td>
<td>7 (13%)</td>
<td>0</td>
<td>12 (23%)</td>
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<tr>
<td>Neutropenia</td>
<td>2 (4%)</td>
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<td>1 (2%)</td>
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<tr>
<td>Pneumonia</td>
<td>1 (2%)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2 (4%)</td>
<td>0</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>3 (6%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (12%)</td>
<td>0</td>
<td>8 (15%)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>5 (10%)</td>
<td>0</td>
<td>3 (6%)</td>
</tr>
</tbody>
</table>

- **Lean body mass**
- **Power and speed on a stair-climbing test**

Enobosarm (SARM) - The POWER trials

Eligibility criteria
- Patients with NSCLC referred for 1st line CMT
- Variable degree of weight loss
- PS 0-1

Intervention:
- Enobosarm 3 mg or placebo once daily for a study period of 147 days

(Co-primary) End-points
- Lean-body mass
- Physical Function (stair climb power)

Secondary end points
- QoL (FAACT-12®, FACIT Fatigue Scale®, PROMIS® Physical Functioning Short Form, PROMIS® Emotional Distress-Depression Short Form, EQ-5D-5 L™)

Crawford J, et al., Curr Oncol Rep 2016;18:37
# TREATMENT

## Clinical trials (interpretation)

<table>
<thead>
<tr>
<th></th>
<th>The Romana trials (Anamorelin)</th>
<th>The Power Trials (Enobosarm)</th>
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<tbody>
<tr>
<td>Randomised phase III</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PS</td>
<td>0-2</td>
<td>0-1</td>
</tr>
<tr>
<td>1st line therapy</td>
<td>Not necessarily</td>
<td>✔</td>
</tr>
<tr>
<td>Published</td>
<td>Full paper</td>
<td>Abstract form</td>
</tr>
<tr>
<td>Body weight</td>
<td>✔</td>
<td>-</td>
</tr>
<tr>
<td>Lean body mass</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Hand grip strength</td>
<td>✗</td>
<td>-</td>
</tr>
<tr>
<td>Stair climbing test</td>
<td>-</td>
<td>✔ (Power 1) / ✗ (Power 2)</td>
</tr>
<tr>
<td>Quality of life</td>
<td>✔</td>
<td>...</td>
</tr>
<tr>
<td>Dietary intake</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Physical activity / exercise</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Effect of antineoplastic therapy</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
Exercise

Aerobic Training
- Increased cardiovascular fitness
- Higher IL-10 and IL-1ra levels
- Decreased TNF-α levels
- Increased oxidation of lipids in skeletal muscle and liver

Anti-inflammatory

Strength Training
- Limited influence on IL-10 and IL-1ra levels
- Decreased TNF-α levels
- Increased oxidation of carbohydrate in skeletal muscle
- Increased muscle anabolism
- Decreased muscle catabolism

Anti-catabolic
## Exercise

<table>
<thead>
<tr>
<th>Drawbacks</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>Delay until anaemia improved</td>
</tr>
<tr>
<td>Compromised immune function</td>
<td>Avoid public gyms and public pools</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10’ of light exercises daily</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Avoid chlorine exposure to irradiated skin (swimming pools)</td>
</tr>
<tr>
<td>Indwelling catheters and feeding tubes</td>
<td>Avoid pool, lake, ocean and other microbial exposures</td>
</tr>
<tr>
<td>Peripheral neuropathy or ataxia</td>
<td>Prefer stationary reclining bicycle</td>
</tr>
<tr>
<td>Multiple - uncontrolled co-morbidities</td>
<td>Individualised exercise programme</td>
</tr>
</tbody>
</table>

Rock CL, et al., C A Journal 2012
Exercise

Conclusion: Despite a strong rationale for the use of exercise, there is insufficient evidence to determine safety and effectiveness in patients with cancer cachexia. Findings from ongoing studies are awaited. Assessment of cachexia domains, ideally against international criteria, is required for future trials of exercise and supportive care interventions.

<table>
<thead>
<tr>
<th>Strength of recommendation:</th>
<th>We recommend maintenance or an increased level of physical activity in cancer patients to support muscle mass, physical function and metabolic pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of evidence</td>
<td>High</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strength of recommendation:</th>
<th>We suggest individualised resistance exercise in addition to aerobic exercise to maintain muscle strength and muscle mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of evidence</td>
<td>Low</td>
</tr>
</tbody>
</table>
TREATMENT

Multimodal approach

“The MENAC Study”

Patients with advanced lung, pancreatic and bile duct primaries

- Standard care
- Standard care
  - + nutritional counseling
  - + oral nutritional supplements
  - + 2 grams of EPA
  - + home-based physical exercise programme (strength and aerobic activity)
  - + 1200 mg of ibuprofen

ClinicalTrials.gov. NCT02330926
Cancer - cachexia clinical trials: Special considerations

Timely intervention (concurrent with chemotherapy)
Symptom management
Multimodal approach
Refined endpoints
## TREATMENT

### End of life care: When to stop nutritional support (?)

<table>
<thead>
<tr>
<th>Strength of recommendation:</th>
<th>We recommend offering and implementing nutritional interventions in patients with advanced cancer only after considering together with the patient the prognosis of the malignant disease and both the expected benefit on quality of life and potentially survival as well as the burden associated with nutritional care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of evidence</td>
<td>Low</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strength of recommendation:</th>
<th>In dying patients, we recommend that treatment be based on comfort. Artificial hydration and nutrition are unlikely to provide any benefit for most patients. However, in acute confusional states, we suggest to use a short and limited hydration to rule out dehydration as precipitating cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of evidence</td>
<td>Low</td>
</tr>
</tbody>
</table>
Cancer cachexia is a multifactorial syndrome characterised by weight loss and body composition alterations that cannot be restored by conventional nutritional support.

- Cytokine production and hormonal alterations play a key pathophysiologic role.

- Anorexia, increased resting energy expenditure, presence of systemic inflammation, activation of unprofitable biochemical circles, insulin resistance, are all important features of the syndrome resulting in increased lipolysis and muscle wasting.
Muscle wasting is the most striking event of the cachexia syndrome.

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 conditions, diseases and medications may additionally contribute to sarcopenia.

Obese patients may also be sarcopenic (sarcopenic obesity).

Older and newer (targeted) antineoplastic drugs may also block survival and proteosynthetic pathways of muscle cells.
Timely diagnosis of malnutrition / cachexia is important

All patients with advanced cancer should be regularly screened for inadequate nutritional intake, weight loss and low body mass index

Patients at risk should be further assessed for body composition alterations, treatable nutrition impact symptoms and metabolic derangements (i.e. systemic inflammation)
Treatment of cancer cachexia
- Correct all reversible causes of reduced food intake
- Nutritional consultation / intervention
- Exercise training programmes
- No standard drug therapy – entry into clinical trials

Multidisciplinary approach
THANK YOU!