Integration between medical oncology and supportive care: Two sides of the same coin

Development of rational therapeutic strategies for patients with pre-cachexia and cachexia through the integration of oncology and palliative care and collaborative clinical trials (EAPC-Research Network)

Florian Strasser, MD ABHPM
Oncological Palliative Medicine,
Oncology, Dept., Internal Medicine and Palliative Centre
Cantonal Hospital St.Gallen, Switzerland

MASCC Working Group Nutrition and Cachexia
ESMO Palliative Care Working Group
Eur Assoc Pall Care TF Integrated Oncol & Pall Care; EAPC-RN
Society Sarcop Cachexia Wasting Diseases
Intl Assoc Hospice Pall Care
ESPEN
## Disclosure Slide

### Unrestricted grants for clinical research
- Bachem (bulk Ghrelin)
- Celgene (Lenalidomide Cachexia trial)
- Fresenius (Survey parenteral nutrition malignant bowel obstruction)
- Grünenthal (opioid rotation trial)

### Participation in clinical cachexia trials
- Novartis (BYM338 cachexia trial)

### Punctual Advisorship
Acacia, Alder, Amgen, Baxter, Fresenius, Helsinn, Nutricia, GSK, Otsuka, Ono, Pfizer, Santhera, Solvay, Teva, Wyeth

**No:** Mono-sponsored Industry Satellite meetings  
**No:** Personal financial interest (stocks, private use of honoraria, ..)
Mr K, 72-j, Pancreas-adenocarcinoma liver-mets 
Gemcitabine weekly first-line, since 3 weeks

„How are you“: swollen legs, people do nothing about it. Am tired and weak, I want to go home, when can I go?

What is our therapeutic strategy?
Why does this happen to me? Mechanism of cancer cachexia

- No desire to eat
- Taste, Smell
- Catabolism - Tumoractivity - Inflammation
- Liver
- Fat
- Muscle-Proteolysis
- Muscle
- Muscle-Protein synthesis
- Stomach/Gut
- Dysmotility, Early satiety
- Constipation
- Anabolic Stimuli
- Brain
- Hypothalamic Extra-hypoth. Melanoc., Ghrelin
- Motivation, psychol. Function
- Neuro-muscular Function
- Motivation, psychol. Function
- Neuro-muscular Function
Key features of cancer cachexia

The domains to „always“ consider:

- Depletion of reserves: muscle mass and fat mass
- Nutritional intake and „gut-brain axis“ symptoms appetite
- Inflammation and tumor dynamics
- Neuro-muscular and emotional-cognitive function

For phenotyping patients:
prospective cohort studies and phase II/III trials needed

→ Intl. consensus project for common datasets and on outcomes for clinical trials: 11.2012-7-2013
“What” is NOT cancer cachexia?

Patients “neglected” for maintenance of adequate nutritional intake

- Diet mistakes / misconceptions: too healthy, ..
- Periods of nausea/vomiting, mucositis, diarrhea, constipation
- (partial) bowel obstruction, dysphagia
- Periods of “no eating” due to procedures

→ The “epidemy” of Malnutrition [ESPEN et al.]
The faces of cancer cachexia: a spectrum

Main Goal: Prevention  Muscles, function  Alleviation

How to identify patients with cancer cachexia in daily practice?

### Screening
- physical fatigue¹
- perceived problems with appetite/eating
- weight loss

### Diagnosing²
- pre-cachexia: no standard yet
- cachexia: 5% weight loss 6 mts (no fluid retention) or 2% and (BMI<20 or sarcopenia)
- refractory cachexia: no standard yet

→ Intl. consensus project minimal common datasets 11.2012-7-2013

---

1: Käser I et al., JPSM 2009;38:505-14
Why treat patients with cachexia?

**Impact on Survival**

1473 canadian patients (lung, gastrointestinal), obese: Weight loss (WL), low lumbar skeletal muscle index (MI)*, altered mean muscle attenuation (MA)*, and BMI.

- BMI not prognostic for survival

- If WL + MI + MA below/above defined thresholds:
  survival 8 mts, if no prognostic fct: 28 mts (p<0.001)

* Assessed from routine lumbar computed tomography (CT).


Why treat patients with cachexia?
A supportive care need – anticancer tx toxicity

Metastatic renal cell cancer, resistant to standard therapy (n=80): sorafenib 400 mg b.i.d. or placebo

Muscle mass loss:
- 6 mts (4.9%; P .01)
-12 mts (8.0%; P .01)

→ Independent of tumor response

Why treat patients with cachexia?

Impact on oncology anticancer drug toxicity

Preliminary data suggest significant association of muscle mass with chemotherapy toxicity

24 breast cancer receiving adjuvant intravenous 5-FU: Lean Body Mass in patients with versus without chemotherapy toxicity: 41.6 vs. 56.2 kg, P = 0.002.¹

55 women with metastatic breast cancer, capecitabine: 25% were sarcopenic: toxicity 50% vs 20%, P = 0.03.²

Why treat patients with cachexia?

Palliative cancer care needs from diagnosis to death

Abundant data on association of weight loss / cancer cachexia on deterioration of
- physical function, performance status, fatigue
- breathlessness
- psychosocial distress of patient & family members
- distressing cachexia/related symptoms (anorexia, chronic nausea, early satiety, constipation, etc.)

Global challenge with increasing cancer burden,
In resource-challenged countries more patients present with stage IV disease
The challenge of therapeutic strategies for cancer cachexia

- A multidimensional problem requires a multi-modal and multi-disciplinary approach
- For mono-dimensional interventions, the other domains need to be standardized
- Treatment and outcomes are different for the three cachexia phases
- A close interaction between palliative cancer care and (medical) oncology management is required
- A consensual phenotyping of cancer cachexia pts (also necessary for molecular profiling) pts is missing: work in progress (consensus project)
Common Cachexia interventions delivered by multiprofessional teams

- Various anti-cachexia drugs (soon?; still experimental)
- Tumor control - slowing progression / activity\(^1\)
- Nutritional intake optimize (own habits, ONS, educate)\(^2\)
- Physical activity increase & maintenance
- Coping with disease, life goals, support of and by family
- Alleviate eating-, weight loss related distress\(^3\)

Example of a «mono-dimensional» cachexia trial exploring a muscle specific agent

Main outcomes: muscle mass & muscle function (Ph II)

Standardize
- Nutritional intake (e.g. ≥ 20kcal, 0.6 Prot/ kgBW; pragmatic)
- Physical activity (e.g. maintain Borg ≥ 4)
- Tumorsituation and its treatment (e.g. estimate cancer-related prognosis, anticancer treatment tolerability proven)
- Inflammation (e.g. defined treatment, no active infection)
- Emotional & social participation (e.g., life goals, coping)
Treatment and outcomes are different for the three cachexia phases

<table>
<thead>
<tr>
<th>Pre-cachexia*</th>
<th>Stabilisation of muscle mass &amp; function „Oncology outcomes“: toxicity, RR, OAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cachexia</td>
<td>≥ 1 domain-specific effect** Patient functions*** improve - stabilize Oncology outcomes</td>
</tr>
<tr>
<td>Refract cachexia</td>
<td>Alleviation of burdensome symptoms</td>
</tr>
</tbody>
</table>

* NOT equal to a muscle mass & function stable patient without neuro-hormonal / inflammatory / metabolic alterations
** The other domains are controlled for with defined management
*** Physical function, emotional function, „Quality of life“
A close interaction between palliative cancer care and (medical) oncology management is required

- Palliative Cancer Care starts early in the trajectory\(^1\)

- Anticancer treatments can (and shall) a patient-derived clinical benefit: weight & function gain\(^2\)

- The quality of “Best Supportive Care” may impact outcomes, and can be defined\(^3\)

---


Zafar Y et al., Lancet Oncology Feb 2012

Check: E-learning www.ESMO.org
Can cancer cachexia phenotypes \textit{(and genotypes?)} be differentiated? \textit{-- prospectively, consensual work needed

Examples of planned phase „specific“ clinical trials: pre-cachexia and refractory cachexia

**MENAC**: Multimodal Exercise/Nutrition/Anti-inflammatory treatment for Cancer Cachexia
Patient Eligibility: new diagnosed stage IV solid tumor
→ Mixed pre-cachexia & cachexia study

**Family Approach to Weight and Eating (FAWE)**: a new psycho-educational intervention for people affected by refractory cachexia
→ Focus on mainly refractory patients

---

1: European Association of Palliative Care Research Network
2: Cardiff University, Jane Hopkinson et al.
emerging therapeutic approaches for cachexia

- Melanocortin Receptor 4-antagonists
- Ghrelin & its analogues
- Androgen (SARMs, ...), β2-mimetics,...
- Muscle pathways (anti-myostatin, ActRIIB,..)
- Anti-inflammatory agents (IL-1, Il-6, TNF, Lenalidom, ...)
- many other promises ¹

C-steroids, progestins, prokinetics
Olanzapine, Mirtazapine
Cannabinoids

¹: Cancer cachexia conference Boston September 2012
Conclusions

A rational therapeutic strategy for cancer cachexia is based on the defined phase of cancer cachexia and its target domains, treatments and outcomes are different. To optimize personalized cancer care for this multidimensional problem, a close interplay of medical oncology and palliative cancer care interventions is required.

A close collaboration between oncology, palliative, supportive, nutritional, cachexia and other societies is mandated for necessary consensus projects, prospective cohort studies and intervention trials.
Backup Slides
Physical function interventions in palliative care?

- Exercise in **elderly**: long-term benefits on muscle function, less falls, more independence, QoL\(^1\)

- Physical exercise: reduce fatigue, improve QoL and physical functioning in **cancer patients**\(^2\)
  - mostly survivors, breast cancer: large effects
  - with chemotherapy moderate effects: QOL, physical activity levels, aerobic fitness, muscular strength
  - palliative patients: phase II studien positive trends\(^3\)
    
    RCT (n=231), superv. PA 60 min 2x/w x 8 w; 70% complete
    Fatigue nicht (Fatigue Quest.), physical fct (SWT/HGS) besser\(^4\)

---

The evolution of clinical trial design in cancer cachexia: a systematic review based on the novel classification and definition criteria

Lisa Martin¹,², Aurelius Omlin¹, Vickie Baracos², Kenneth C. H. Fearon³, Florian Strasser¹

Systematic literature review: all papers and ongoing clinical trials ≥ 2000

<table>
<thead>
<tr>
<th>RESULTS</th>
<th>Studies</th>
<th>Domain III. Catabolic Drive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domain I. Depletion of Reserves</td>
<td></td>
<td>Inflammation</td>
</tr>
<tr>
<td>Body Weight</td>
<td>86</td>
<td>32 32%</td>
</tr>
<tr>
<td>Body Composition</td>
<td>72</td>
<td>CRP 21 21%</td>
</tr>
<tr>
<td>CT</td>
<td>60</td>
<td>Altered Metabolism (REE, indirect calorimetry) 13 13%</td>
</tr>
<tr>
<td>DEXA</td>
<td>2</td>
<td>Response to chemotherapy 5 5%</td>
</tr>
<tr>
<td>Anthropometrics</td>
<td>9</td>
<td>Domain IV. Functional/Psychosocial Effects 73 74%</td>
</tr>
<tr>
<td>BIA</td>
<td>14</td>
<td>Physical Function</td>
</tr>
<tr>
<td>Muscle Strength</td>
<td>33</td>
<td>Physician reported (ECOG, KPS, WHO, etc.) 27 27%</td>
</tr>
<tr>
<td>upper limb hand-grip dynamometry</td>
<td></td>
<td>Objective measures (PA, exercise capacity) 12 12%</td>
</tr>
<tr>
<td>lower limb extension</td>
<td>21</td>
<td>Patient-reported</td>
</tr>
<tr>
<td>Domain II. Limitations to Nutritional Intake</td>
<td>72</td>
<td>Quality of Life 53 54%</td>
</tr>
<tr>
<td>Food Intake</td>
<td>33</td>
<td>Fatigue 18 18%</td>
</tr>
<tr>
<td>Patient-reported food records (calculated)</td>
<td>26</td>
<td>Distress (depress., anxiety, mood, well being) 9 9%</td>
</tr>
<tr>
<td>Subjective categorical classification</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Nutrition Impact Symptoms</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Appetite</td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>

Large heterogeneity
- domains „missing“
- cachexia phases & severity

Preliminary results presented @ Cachexia conference Milano 2011
Melanocortin Receptor 4-antagonists

Inflammation $\rightarrow$ MC4R activity $\uparrow$ $\rightarrow$ cachexia

Ghrelin $\rightarrow$ GHS-1 Rec $\rightarrow$ AgRP $\uparrow$ $\rightarrow$ MC4R $\downarrow$
(Extra)-hypothalamic Ghrelin actions

Serotonergic inputs to the hippocampus → neurogenesis, learning, memory

Mesolimbic dopaminergic system → hedonic & incentive value of food

Neuroprotection

Modulation of anxiety and regulation of mood

Sleep-wake regulation

Andrews ZB. Trends Neurosc. 2011;34:1

Steiger A et al., Moll Cell Endoc 2011;340:88-96
Cancer Cachexia Framework: key features

*From „anorexia/cachexia syndrome“ to cancer cachexia*

- „Muscle loss relevant for physical function, not reversible by nutrition, caused by decreased intake and alt. metabolism“

- Diagnostic criteria: based on weight loss and BMI

- Domains:
  - Muscle/(Fat)
  - Nutritional Intake & „Appetite“-Symptoms
  - Catabolic tumor, inflammation, and hormones
  - Neuro-muscular and emotional function

- Phases: from early to cachexia to refractory cachexia

- Severity described by weight loss and BMI
How could an Assessment – Approach look like

SCREEN → DIAGNOSIS → TREATMENT

**SCREEN**
- Any weight loss ≥0% and BMI ≤27
  - If BMI > 28, WL ≥ 6%
- Intake decreased, no simple starvation
- Stage-IV cancer
- KPS ≤ 70

**DIAGNOSIS**
- Specialized Cancer-Cachexia Assessment
- CachexiaSeverity
  - Phase: Early
  - Syndrome
  - Refractory
  - Phenotype
    - Inflammatory
    - Other

**TREATMENT**
- Interventions & Goals
  - Nutritional intake
  - Physical activity
  - Symptom relieve
  - Anticancer treatment
  - Anticachexia drugs
  - Psychosocial
  - Place of care / Support
The Cancer Cachexia Assessment: proposal to be further refined by consensus integrates information from the Patients’ Past, Present and Future

<table>
<thead>
<tr>
<th>SCREEN</th>
<th>DIAGNOSIS</th>
<th>RESEARCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Practice</td>
<td>Specialized Practice</td>
<td>Clinical Trials and Studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STORAGE</th>
<th>Weight loss % last 2-6 mts</th>
<th>Detailed weight loss history</th>
<th>MRI thigh / DEXA / CT L3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Mass Index</td>
<td>if fluid retention: CT L3/4 or DEXA</td>
<td>(mass of muscle, fat)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INTAKE</th>
<th>Perceived eating problems</th>
<th>2 day diet diary, % kcal/protein / needs</th>
<th>Food weight, components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple Starvation ruled out</td>
<td>Secondary nutrition impact symptoms</td>
<td>Response to treatment of S-NIS</td>
<td>Comprehensive item pools</td>
</tr>
<tr>
<td></td>
<td>Symptoms: appetite, early satiety, etc.</td>
<td>(instruments: FAACT, et al.)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>POTENTIAL</th>
<th>Stage IV cancer</th>
<th>Tumor dynamics</th>
<th>History of anticancer treatment:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>. responsive to anticancer treatment</td>
<td>. Past and expected responses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>. symptomatic progression &lt; 3 months</td>
<td>. Short term muscle loss response</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CRP &gt; 10mg/I, without clinical infection</td>
<td>Cytokines, hormones</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PERFORMANCE</th>
<th>Cancer related KPS ≤ 70</th>
<th>Physical function measurement</th>
<th>Muscle power, 6-MWT, et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cachexia, a care priority</td>
<td>(muscle strength, physical functioning)</td>
<td>Body worn sensor tests</td>
</tr>
<tr>
<td></td>
<td>Psychosocial distress: weight, eating</td>
<td>Decisions towards care goals</td>
<td>Comprehensive item pools</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prognosis tools</td>
<td></td>
</tr>
</tbody>
</table>
Refractory (late) cancer cachexia

Advanced muscle wasting (with or without loss of fat) due to progressive cancer, not anymore responding to anticancer treatment. Patients have a low performance status and short life expectancy (<3months). It is evident that the burden of artificial nutritional support would outweigh any potential benefit.

Therapeutic interventions focus typically on alleviating the consequences/complications of cachexia, e.g. symptom control (appetite stimulation, nausea), eating-related distress of patients and families.
When should palliative care interventions start?

European Association of Palliative Care (EAPC): year(s) before death

Main area of care provision for palliative care, supportive care and end-of-life care (using a narrow definition of end-of-life care)

Radbruch L et al. EUROPEAN JOURNAL OF PALLIATIVE CARE, 2009; 16(6)