Multimodal therapy of cancer cachexia

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Multimodal therapy for cancer cachexia

KCH Fearon
Learning objectives

• Understand why the diverse aetiology of cachexia demands a multimodal approach
• Understand the need for robust outcomes
• Understand basic assessment
• Understand elements of multimodal therapy
• Understand the issues of compliance and behaviour modification
Background to cachexia and key therapeutic outcomes
Cancer is the collective name for more than one hundred distinct diseases.....

- Global incidence: 12.6 million/yr (Lung most common)
- Global mortality: 7.5 million/yr.......11.5 in 2030
Complexity of modern colon cancer management

- Diagnosis
- Neo-adjuvant therapy
- Resection of primary and liver mets
- Adjuvant chemotherapy
- Resection of pulm. mets
- Chemotherapy
- Palliative chemotherapy
- Palliative surgery/stenting
- Phase 1 drug trials
CACHEXIA

QoL / Survival
Clinical Sequelae
Body Composition and Function
Mechanisms
Mediators
Initiators

Rx Rx Rx Rx Rx Rx Rx
Multimodal supportive care

- Multidisciplinary team work
- Early intervention
- Treat secondary factors
- Anti-inflammatory therapy (e.g. NSAID, EPA)
- Anabolic/anti-catabolic therapy
- Nutritional Support (e.g. high protein ONS)
- Optimal oncological management
- Exercise
- Awareness (diagnostic acumen)

Multimodal therapy

Fearon KCH EJC 2008
Outcomes
Oncology outcome measures hierarchy

Tier 1
Health status achieved or retained
- Survival
- Degree of health or recovery

Tier 2
Process of recovery
- Time to recovery and time to return to normal activities
- Disutility of care or treatment process (e.g., diagnostic errors, ineffective care, treatment-related discomfort, complications, adverse effects)

Tier 3
Sustainability of health
- Sustainability of health or recovery and nature of recurrences
- Long-term consequences of therapy (e.g., care-induced illnesses)
- Recurrences
- Care-induced illnesses

NEJM 2010;363:2477-81
Definition and classification of cancer cachexia: an international consensus

Clinical importance of muscle

Life (breathing!)

Reserve / recovery

Work / Economic

Self expression
The elephant in the room is...
EMEA

- Sponsor should be advised that a successful Phase II study with a muscle mass and function endpoint would not be enough to give a market authorisation to a new product. **Clinical benefit should also be demonstrated**
Physician-reported outcomes
Performance Status Definition

ECOG PERFORMANCE STATUS

0. Fully active, able to carry on all pre-disease performance without restriction

1. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work

2. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours

3. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4. Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair

Patient-centred outcomes
Physical Activity
Spontaneous PA (time spent sitting / lying, time standing, time walking and number of steps/day) of cancer patients at different stages of disease (n = 75) and healthy volunteers (n = 20).
Clinical assessment
“……in the beginning of the malady it is easy to cure but difficult to detect, but in the course of time……it becomes easy to detect but difficult to cure”

Niccolo Machiavelli “The Prince”
Early intervention: pre or early cachexia
Philosophy of assessment: one size fits all or bespoke?

- Pre-cachexia
- Cachexia
- Refractory cachexia
Clinical Heterogeneity

- e.g. Small cell lung cancer patient with severe B-type symptoms (pyrexia, sweating etc) and cachexia mainly due to hypermetabolism

- Variable proportion of metabolic change that can be reversed by treating catabolic factors

- Reduced Food Intake

- Variable proportion of reduced food intake that can be reversed by treating ‘secondary anorexia’

- e.g. Pharyngeal cancer patient with cachexia mainly due to reduced food intake secondary to dysphagia
### Four Domains of the Conceptual Framework

<table>
<thead>
<tr>
<th>Domain</th>
<th>Examples</th>
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<tbody>
<tr>
<td>I. Depletion of Reserves</td>
<td>e.g. Underweight, Weight loss, Lean tissue wasting, Sarcopenia (severe muscle wasting)</td>
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<td>II. Limitation of food intake</td>
<td>e.g. Nutrition impact symptoms: Anorexia, Dysphagia, Nausea, Social / psychological</td>
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<td>III. Catabolic Drivers</td>
<td>e.g. Inflammation, Tumor burden, Insulin resistance, Hypogonadism, Corticosteroids, Comorbidities</td>
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<td>IV. Impact and outcomes</td>
<td>e.g. Physical function, Quality of life, Distress, Survival, Treatment outcomes, Costs</td>
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Management/therapy
Rehabilitation is multisource!

- **Hospital** (Oncology Centre; Palliative and Supportive Care)
- **Community** (Cancer Support Groups or Nurses)
- **Home** (self-help, web-sites)
Why treat cachexia during chemotherapy? ......a window of opportunity?

- Commencement of chemotherapy is a portal of entry to supportive oncology
- Poor nutritional status associated with adverse oncological outcomes
- Chemotherapy can induce further loss of muscle mass and this may limit treatment
- Response to chemotherapy may decrease tumor-related catabolic drivers and enhance the efficacy of cachexia intervention
How to treat sarcopenic obesity?

> 50% adults in the UK are overweight or obese
Behavioural change!

Couch potatoe!
Philosophy of intervention: one size fits all or bespoke?
Multimodal supportive care

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Multimodal therapy

Fearon KCH EJC 2008
Nutrition

- Main goal is to promote energy balance and optimise protein intake
- Usual deficits are approx 300-400 kcal/d and 0.5gP/kg/d
- Best approach is with normal food
- Can use conventional oral supplements but recent meta-analysis did not show benefit after correction for heterogeneity*
- EPA enriched supplements used during chemotherapy result in increased energy and protein intake, increased LBM (1.6kg) and improved appetite and fatigue**

** Sanchez-Lara K et al Clin Nutr 2014;e-pub
Exercise

- Improved lower and upper limb strength (~20%)
- Increased lean body mass (~1kg)
- Improved HRQoL including physical functioning, role functioning, social functioning and fatigue

Mishra SI et al Cochrane 2012
Stene GB et al Crit Rev Oncol Haematol 2013
Exercise regimen

• Home-based
• Combined aerobic (x2/w) and functional resistance (x3/w) exercise
• Delivered by initial interview with trained HP supported by standardised booklet
• Supervision dependent on centre
Effect of progressive resistance training in the elderly

Effect

- Small .................. physical function
- Moderate ............... physical limitations (e.g. gait speed, 6 min walk)
- Large ..................... strength

Lui CJ et al, Cochraine Syst Rev 2009, CD 002759
Anti-inflammatory treatment

• NSAIDs are generally well tolerated. Recent systematic review* suggested possible improvement in weight, performance status and QoL but heterogeneity precluded meta-analysis

• EPA probably best administered during chemotherapy **

*Solheim TS et al Acta Oncol 2013;52: 6-17
**Sanchez-Lara K Clin Nut 2014
Novel agents in Phase II/III

- Ghrelin analogues
- Anti-myostatin strategies
- SARMS

No standard of care in control arms!
Compliance

- Drug treatment ............... 70-80% compliance
- Nutritional supplements .... 0-70% compliance
- Aerobic exercise ............. 0-75% compliance
- Resistance exercise .......... 0-50% compliance
Interdisciplinary rehabilitation (10-12w) in advanced cancer (n=188)

30% did not complete all sessions
Physician, nurse, dietician and OT visits and calls
Improved QoL; activity and physical fatigue (E.S. 0.8-1.1)
Six min walk increased by 41m (10%)
Gait speed increased by 0.15m/s (10%)

Gagnon B et al  Curr Oncol 2013;20:310-8
Evolution of Cachexia Therapy

- Single agents/elements
- Definition of best supportive multimodal care
- Phase III trials incorporating best supportive care
- Supportive Oncology (nutritional response, QoL, treatment tolerance, survival)
- Palliative therapy (symptoms, nutritional response)

Time (years/decades)
Summary

• No simple solution
• Cachexia therapy should be integrated in overall oncology management
• Early intervention
• Professionals and nurses need adequate knowledge on nutrition and exercise
• Assessment should be linked to treatment
• Goals should be realistic
• Multimodal care pathways are self-evident but still to be evidence-based
Any questions?