Multimodal cachexia management

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“Do you have anything that you can give me Doc to stop me losing weight?”

“I dread going to the table for food”

“My wife nags me because I am not eating and am losing weight”

“Why am I losing weight?”
Cachexia
Skeletal muscle and fat mass wasting

Lipogenesis
Proteosynthesis
Energy intake

Lipolysis
Proteolysis
Energy expenditure

Inflammation
IL6, TNFα, IL1β, IL8

Catecholamines
Adrenalin, Noradrenalin

Cancer
COPD
ESRD/CKD
CHF
Do patients with weight loss have a worse outcome when undergoing chemotherapy for lung cancers?

NSCLC

- weight loss associated with delivery of fewer cycles of chemotherapy (p<0.003)
- more treatment delays (p=0.04),
- more anaemia (p=0.003),
- more symptoms at presentation (p<0.0001)
- less symptomatic benefit from chemotherapy (p=0.004).
“A well designed study to evaluate the benefit of nutritional support in patients with weight loss receiving chemotherapy is needed”  

PJ Ross et al 2004
Why has research in cachexia been slow?

- Unimodal therapy trials
- Prerequisite of oncology trials
- Late phase
- You are not eligible if you are taking part in another trial “fastidious vs pragmatic trials” – gatekeeping...

- Limited pharmaceutical funding
- Lack of a consensus definition
“When you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of science, whatever the matter may be” Lord Kelvin 1824-1907
A multifactorial syndrome characterised by an ongoing muscle loss (with or without fat loss) that cannot be fully reversed by nutritional support and leads to progressive functional impairment. The pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced nutritional intake and abnormal metabolism.
Cachexia is Not “Starving”

• Starving
  – Metabolism slows down
• Cachexia
  – Metabolism speeds up (catabolic)
Diagnosis

• Mostly a clinical Dx
• Complete history (trying to determine if secondary causes at play)
• ESAS appetite score
• Physical exam
  – Weight, wasting, edema, gait, rising from chair, gross muscle strength, mucositis, trush, neck masses, abdominal exam...etc...
• Laboratory
  – CBC, Cr, lytes, LFTs, TSH, albumin, CRP
SMI 29.7 cm$^2$/m$^2$, BMI 15.3 kg/m$^2$

SMI 29.8 cm$^2$/m$^2$, BMI 28.1 kg/m$^2$

SMI 29.8 cm$^2$/m$^2$, BMI 40.2 kg/m$^2$

SMI 33.7 cm$^2$/m$^2$, BMI 29.5 kg/m$^2$

SMI 46.3 cm$^2$/m$^2$, BMI 29.4 kg/m$^2$

SMI 58.3 cm$^2$/m$^2$, BMI 29.4 kg/m$^2$

Skeletal muscle index (cm$^2$/m$^2$)

Body mass index (kg/m$^2$)

V Baracos
Assessment of Cachexia according to:

- Anorexia or reduced food intake
- Catabolic drivers
- Functional and psychosocial effects
- Muscle mass and strength

### Stages of Cancer Cachexia

<table>
<thead>
<tr>
<th>Normal</th>
<th>Precachexia</th>
<th>Cachexia</th>
<th>Refractory cachexia</th>
</tr>
</thead>
</table>
| Weight loss ≤5%  
Anorexia and metabolic change | Weight loss >5% or BMI <20 and weight loss >2% or sarcopenia and weight loss >2%  
Often reduced food intake/systemic inflammation | Variable degree of cachexia  
Cancer disease both procatabolic and not responsive to anticancer treatment  
Low performance score  
<3 months expected survival | Death |

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Inflammation & Cancer

- Inflammation predisposes to certain tumour types
- Inflammation implicated in oncogenic mutations & experimental animal models of tumour development
- Inflammation can be a result of cancer.
- Targeting inflammation can reduce cancer risk and cancer spread.

7th hallmark of cancer

1. Mantovani Nature 2008;454
Systemic Inflammatory Response

Cachexia

Anorexia

Physical Inactivity

ANABOLIC BLOCKADE
Multimodal Therapy:
• High protein nutrition
• Anti-inflammatory agents to down regulate the APIR
• Routine mobilisation programmes to prevent deconditioning and encourage physical activity-induced stimulation of post prandial anabolism.

Exercise prescription

‘FITT’ structure

• frequency
• intensity
• time
• type

Resistance vs. Aerobic training

Dependant on the central aim of training

- muscle strength & mass: resistance > aerobic
- fatigue & CV fitness: resistance < aerobic
• Research has shown that, for people with cancer (including advanced-stage cancer), exercise can decrease anxiety, stress, and depression while improving levels of pain, fatigue, shortness of breath, constipation, and insomnia.

During cancer cachexia

Exercise for cancer cachexia in adults (Review)

Grande AJ, Silva V, Riera R, Medeiros A, Vitoriano SGP, Peccin MS, Maddocks M
Grande et al. Cochrane Database of Systematic Reviews 2014

・“insufficient evidence to determine the safety and effectiveness of exercise for patients with cancer cachexia”
Nutritional interventions in patients with advanced cancer

• Oral nutritional interventions are effective at increasing nutritional intake and improving some aspects of QOL in patients with cancer who are malnourished or are at nutritional risk but do not appear to improve mortality.
  (Baldwin et al., J Natl Cancer Inst, 2012)
• − Weight and energy intake may stabilize or increase for a period
• − QoL may improve
• − No evidence for the effect of
• • Function
• • Fatigue
• • Survival
• • Several nutritional guidelines with conflicting recommendations (Champ et al., Nutr Cancer, 2013)
Nutritional interventions in patients with advanced cancer

• No studies combining nutrition and exercise therapies in patients with advanced lung cancer in a recent review (Payne et al. Curr. Oncol, 2013)

• In frail elderly studies have shown that nutrition will not usually improve function unless muscles are exercised using resistance exercise (Breen L, Br J Clin Pharmacol, 2013; Tieland M J Am Med Dis Assoc, 2012)
Nutritional interventions in patients with cachexia

• Five publications retrieved
• –3 RCT
• Two out of five studies showed less weight loss with dietary counseling
• Two presented positive effect on energy intake
• Dietary counseling can effect energy intake and body weight
• However, not enough proof of evidence that dietary counseling given to patients with cancer is beneficial for improving weight or energy balance in the different cachexia stages
• (Balstad et al., Crit Rev Oncol Hematol, 2014)
Single agents/interventions in isolation have limited benefit ~ 100 clinical trials

There is now a persuasive argument that combination therapy should be administered to maximise benefit
To date there are only a few reports on programs combining exercise, nutritional counseling and management of symptoms by palliative care professionals.

**Methodology and selection of reports goes here**

For this review Rapid Evidence Assessment methodology was employed in which 75 articles which touch on rehabilitation for advanced cancer patients were located from 2008-2013. Searches on the following databases were conducted:
- All adult patients with stage III and IV cancer; I-Intervention-Rehabilitation delivered by the following professions: Medical Oncologist / Palliative care Physicians, Dietitian, Physiotherapists, Occupational Therapists, Nurse, Psychologist and Social worker; C-Context- Hospital, hospice, cancer centre and palliative care unit.

- Only studies published in English were included. All the databases were searched with combinations of terms related to advanced cancer, cancer rehabilitation common symptoms and/or interventions of interest.
• In an Australian non-randomised study 25 of 41 enrolled participants who remained in the combined program for 2 months demonstrated improved nutritional status and functional status, endurance, and strength, with a decrease in reported symptoms and felt better supported.

• The MD Anderson program reported on 151 patients assessed at a cachexia clinic. 59 did not return for follow up. All patients received dietary counseling by a dietician and standard exercise recommendations. A combination of simple pharmacological and nonpharmacological interventions improved appetite significantly, and increased weight in one third of patients who were able to return for follow-up. No functional outcomes were reported.
• Significant improvements in:
  • physical performance ($P < 0.000$), nutrition ($P = 0.001$), symptom severity ($P = 0.005$ to $P = 0.001$), symptom interference in functioning ($P = 0.003$ to $P < 0.001$), fatigue ($P = 0.001$), and physical endurance, mobility, and balance/function ($P = 0.001$ to $P < 0.001$)
• Strong improvements in the **physical and activity dimensions of fatigue** (effect sizes = 0.8–1.1).
• moderate reductions in the severity of **weakness, depression, nervousness, shortness of breath and distress** (effect sizes: 0.5–0.7),
• moderate improvements in **six-minute walk distance, maximal gait speed, coping ability and quality of life** (effect sizes = 0.5–0.7)
• 77 % of patients either maintained or increased their body weight.
Nutritional Rehabilitation (pre-habilitation) in Oncology
(cancer associated muscle loss)

Pre-cachexia | Cachexia | Refractory-cachexia | Death
---|---|---|---
Weight loss <5%
Anorexia & metabolic change

Weight loss >5% or BMI <20 and weight loss >2%
or sarcopenia and weight loss >2%

Variable degree of cachexia. Cancer disease both procatabolic and not responsive to anti-cancer treatment. Low PS, survival <3 months

Tora S Solheim
Cancer pain and its relationship to systemic inflammation: An exploratory study


The Systemic Inflammatory Response and Its Relationship to Pain and Other Symptoms in Advanced Cancer

Barry J. Laird, Donald C. McMillan, Peter Fayers, Kenneth Fearon, Stein Kaasa, Marie T. Fallon, Pål Klepstad

Prognostic Factors in Patients with Advanced Cancer: A Comparison of Clinicopathological Factors and the Development of an Inflammation-Based Prognostic System

Barry J. Laird, Stein Kaasa, Donald C. McMillan, Marie T. Fallon, Marianne J. Hjermstad, Peter Fayers, and Pål Klepstad
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\begin{align*}
\text{mGPS (0, 1, 2 from top to bottom). Log-rank } P < 0.001 \\
\text{PS (ECOG grouping 0-1, 2, 3, 4 from top to bottom). Log-rank } P < 0.001
\end{align*}
**CANCER**

Anti-inflammatory

Pro-inflammatory
What now......

- rather than systemic inflammation being cause for individual symptoms, inflammation may be implicated in the genesis of multiple cancer symptoms

- Animal models of cytokine induced sickness behavior have concentrated on cachexia and have confirmed the role of pro-inflammatory cytokines in cachexia development - hypothesis is now a decade old

- little in the way of work examining the modulation of symptoms by attenuating the inflammatory response.
Can we modulate the inflammatory response to treat cachexia through a multimodal approach?
Interventions should be multimodal tackling all of these issues simultaneously.
Multimodal Intervention

Critical pre-cachexic phase

In combination with anti-cancer therapy
First Clinical Trial of a Nutritional Intervention
The “Perfect” Multimodal Cachexia Trial

- Randomised - Contamination of control group
- Blinded - possible?
- Placebo controlled
- Standardisation of Best Supportive Care
- Pre-cachexia phase
- Standardised multimodal intervention
- Excellent participant compliance
- Standard oncology care
- Meaningful endpoints
- Transferable to real-life clinical setting
- FEASIBLE
HYPOTHESIS: Early intervention to treat or minimise weight loss may improve symptoms and allow anti-cancer therapy to be given more efficiently with the ultimate aim of improving survival.
Challenges.....

- Trial design (duration, endpoints...)
- Recruitment
- Exercise
- Technical aspects
- ONS palatability
- Complications of chemotherapy
- Frail population
- Conflicting trials
Pre-MENAC study: A feasibility study of Multimodal Exercise/Nutrition/Anti-inflammatory treatment for Cachexia

A multicentre, open, randomized phase II study comparing a multimodal intervention for cachexia versus standard cancer care

The multimodal intervention consisted of:

- Nutritional supplements enriched with EPA (n-3 fatty acids) and nutritional advice
- Home-based self-assisted exercise program
- Anti-inflammatory medication (celecoxib)

Results:

- As of Feb 2014, 399 patients have been screened with 43 patients recruited from three centres across two countries.

- An interim analysis has been conducted on 34 patients: Intervention 19, Control 15
  Primary endpoints: Compliance to the intervention, (>80% of that prescribed): anti-inflammatory 80%, ONS 47%, resistance training 26%, aerobic exercise 42%

ClinicalTrials.gov Identifier: NCT01419145
Forty-six patients were recruited from three regional cancer center’s (Glasgow (UK), Trondheim and Oslo (Norway). Overall compliance was > 54% in all components of the intervention. Patients’ in the treatment arm weight increased (0.91% (SD 2.46)), whilst those in the control arm lost weight (-2.12% (SD 2.50)), p < 0.001 (N = 41). Patients in the control arm lost 2.2% more muscle than the treatment arm, p = 0.69.

There were no statistical significant differences in physical activity in the patients that had repeated measurements of physical activity with ActivPal (n = 22). **Conclusions:** A multimodal cachexia intervention is feasible and improves weight in patients with incurable lung or pancreatic cancer. Based on these exciting findings, a definitive phase III study is now underway.
MENAC: The Multimodal Exercise/Nutrition/Anti-inflammatory treatment for Cachexia trial

MENAC is a large-scale open randomised phase III, multimodal intervention trial.

**Primary objective**
- To establish whether a multimodal intervention is effective in treating cachexia. This will be assessed after 2 cycles of chemotherapy (study endpoint -between 6 -9 weeks) by measuring weight.

**Secondary objectives**
- To examine the effect of a multimodal intervention for cancer cachexia on *muscle mass*, *physical performance*, performance *status*, *health status*, *nutritional status*, *quality of life*, *toxicity*, and *hospitalisations*.

**Patients**
- Diagnosis of lung cancer, pancreatic cancer or
- Due to commence anti-cancer therapy

**Plans/estimation**
- A total of 260 patients will be recruited from out-patient oncology clinics at multiple sites in Europe, Canada and Australia. The inclusion started in 2014
Palliative Rehabilitation Program: *Ongoing Research*

CIHR Open Operating Grant:
**Multimodal Exercise, Nutrition and Anti-inflammatory Treatment For Palliation of Cancer Cachexia: the MENAC study**

A randomized, open-label trial of a Multimodal Intervention (Exercise, Nutrition and Anti-inflammatory Medication) plus standard care versus standard care alone to prevent/attenuate cachexia in advanced cancer patients undergoing chemotherapy.

**EAPC Research Network**

**PRC European Palliative Care Research Centre**

[www.ntnu.edu/prc](http://www.ntnu.edu/prc)
Nutritional intervention:
- Dietary counselling - to promote energy and protein balance, in combination with nutritional supplements.
- Study participants - advised to increase meal frequency and their intake of high calorie food and beverages.
- Patients will be prescribed 2 cans of Eicosapentaenoic acid (EPA) enriched nutritional supplements consisting of a total of 542 Kcal – ProSure (Abbott©).
- If patients are unable to take these supplements, they will be prescribed oral capsules containing 2g Eicosapentaenoic acid.

Exercise intervention:
- Home-based exercise programme
- Prescription will consist of three times weekly functional resistance exercises and aerobic training two times weekly.

Pharmacological intervention:
- Ibuprofen a dose of 1200 mg/day (400 mg x3/d).

MENAC: The Multimodal Exercise/Nutrition/Anti-inflammatory treatment for Cachexia trial

Canadian Institutes of Health Research, Open Operating Grant, 2014
Eligibility Criteria

• Diagnosis of non operable non-small cell lung cancer (NSCLC) (stage III-IV) or pancreatic cancer
• Due to commence chemotherapy or chemoradiotherapy
• NOT receiving parenteral nutrition or enteral nutrition via feeding tube
• NO Weight loss >20% over the previous 6 months
• NO BMI >30 kg/m²
• NO Severe anorexia (less than 50% pre-illness food intake and unable to take oral supplements)
Identification Consent

Week 0

Treatment Arm
(Multimodal intervention + Standard cancer care)

Control Arm
(Standard cancer care)

Week 6

Participants are offered same treatment as treatment arm (Multimodal intervention)

Week 12
Endpoints

Primary
Feasibility, recruitment, retention

Secondary
LBM, weight, activity, nutritional, toxicity, anti-cancer therapy
Immunomodulation!
Postulated that inflammation was not a single process but a combination of various inflammatory processes
And introduced “functio laesa”

Was the first to hypothesize a link between inflammation and cancer.

200 years later still we are still discovering how targeting inflammation can prevent, treat and palliate cancer.
Advancing Cancers

Infiltrating → TAM → TIL

Growth Factors
Angiogenesis
Proteases – matrix

↓ Tumour Immunity
Th2 ↑  Th1 ↓

We suggest that the inflammatory cells and cytokines found in tumours are more likely to contribute to tumour growth, progression and immunosuppression than they are to mount an effective host anti-tumour response... some types of inflammation may provide ‘the fuel that feeds the flames’.

Balkwill, Mantovani. Lancet. February 17, 2001
Acknowledgements  BARRY LAIRD
Ken Fearon, Stein Kaasa, Tora S.Sol heim, Guro Stene, Trude Balstad, Neil Johns, Marie Fallon, Donald McMillan, Peter Fayers