CANCER CACHEXIA

A wasting syndrome characterized by loss of muscle and fat caused by an aberrant host response to a wide variety of chronic illnesses. Anorexia usually accompanies cachexia, and is caused by related mediators acting upon the hypothalamus."

> MacDonald et al JACS, July 2003



Negativity - cancer nutrition

- Lack of past success
 - alimentation trials
 - counselling
 - therapeutic failures
 - (cyproheptadine, pentoxyfylline, hydrazine)
- Qualified success
 - (corticosteroids, megestrol)

Negativity - cancer nutrition

False Dichotomy

Tumour Growth vs Symptom Control

Skewed Research

Do we think it's important?

- <u>ASCO 2005</u> <u>4119 presentations</u>
- Nutrition 15
- Gemcitabine 106

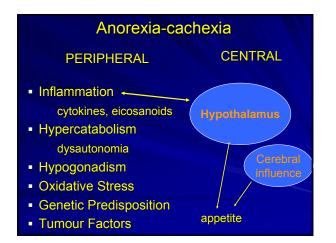
ASCO STATEMENT JCO16: MAY 1998

"ONCOLOGISTS MUST LEARN TO RECOGNIZE AND RESPOND TO THAT TRANSITION POINT IN A PATIENT'S CARE WHEN DISEASE ORIENTED ANTICANCER THERAPY MUST GIVE WAY TO SYMPTOM ORIENTED PALLIATIVE THERAPY"

Canadian Institutes of Health Research Cancer Institute

Palliative care aims to improve the life of patients and families through early identification and impeccable management of suffering associated with cancer, and emphasis on the positive aspects of life inclusive of physical, psychosocial and spiritual sources. Palliative care is an exercise in prevention prevention of suffering through prioritizing the diagnosis and skillful care of sources of distress throughout the course of cancer and for the family during the bereavement period. It is not simply an end of life concept separate from other aspects of cancer research and control.

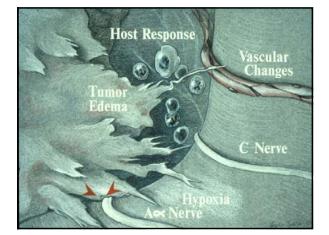




PROTEOLYSIS INDUCING FACTOR

- Glycoprotein
- Induces proteolysis, not anorexia
- Does not cause anorexia
- Present in : serum MAC 16 mice
- urine cancer patients with weight loss
- Activates Prostaglandin E₂
- Attenuated by EPA (omega-3 fatty acid)

(Tisdale)



Advancing Cancers							
Infiltrating \rightarrow	TAM	TIL					
	Growth Factors Angiogenesis Proteases – matrix	↓ Tumour Immunity Th2 ↑ Th1 ↓					
tumours are n progression and	nore likely to contr l immunosuppression	ells and cytokines found in ribute to tumour growth than they are to mount an some types of inflammation ames'.					

Metabolic Changes in Tumor Related Weight Loss

- [↑]Anaerobic Glycolysis Insulin Resistance Diminished Lipogenesis Lipolysis Protein Catabolism Decreased Muscle Protein Synthesis
- Acute Phase Protein Response CRP
- **Pro-Inflammatory Cytokines**

A Wound That Doesn't Heal' Wound Infection Organise cellular response Suppress when resolved Tumours Organise cellular response Suppression cues lost Chronic Inflammation Support tumour growth Growth factors Angiogenesis Symptoms – cachexia

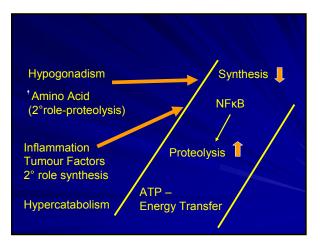
Balkwill, Lin, others

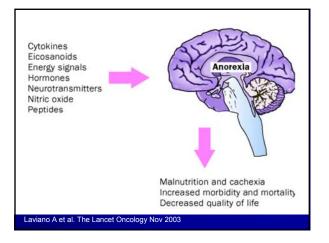
TUMOUR LIVER MUSCLE ↑AFP (note CRP) ↓drug metabolism ↓synthesis ↑proteolysis **HYPOTHALAMUS** BRAIN ↓appetite CHRONIC ↑sympathetic activity ↑REE depression NFLAMMATION , ↑cortisol ↓testosterone FAT GUT †lipolysis ↓lipoprotein lipase early satiety

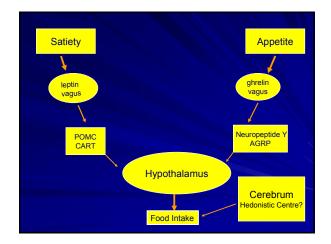
Lung Cancer – 1ST Presentation <u>C-reactive Protein – 80</u> Survival -- < 10 mgm/L -- 11 months (median) -- >100mgm/L -- 3 months <u>Correlations</u> -- weight loss fatigue poor performance status j albumin and hemoglobin Scott et al BCJ/2002 87-284

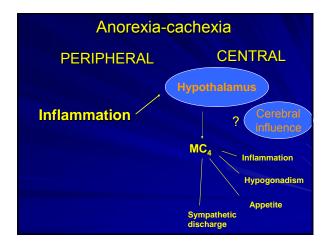
Cancer Inflammation -Chemotherapy Pharmacokinetics > ↓ cytochrome P450 docetaxel, vinorelbine Pharmacodynamics > Acute phase proteins ↑ binding? > Cytokines receptor interference? 2nd messenger interference? (platinum, interleukin 2)

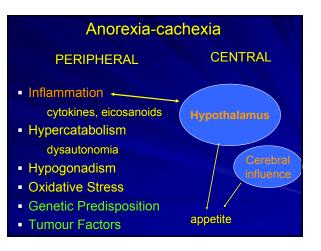
Slaviero et al Lancet Oncology April 2003 22











Upon this gifted age, in its dark hour, Rains from the sky a meteoric shower Of facts...they lie unquestioned, uncombined. Wisdom enough to leech us of our ill Is daily spun, but there exists no loom To weave it into fabric.

Edna St Vincent Millay

WHO Definition Palliative Care — 2002

Palliative care is an approach which improves the quality of life of patients and their families facing the problems associated with lifethreatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.

Cachexia – Early Rx

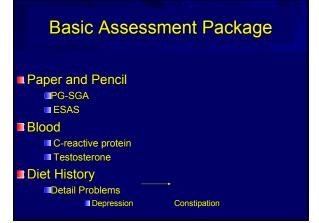
Informed Opinion Clinical Trials Time from diagnosis Appetite loss Correlation Inflammation Cachexia Cachexia Early – Atrophy – fibres intact Late - Apoptosis – fibres disappear

CANCER NUTRITION – REHABILITATION PROGRAMME

Objectives

- To provide an assessment and therapeutic clinical programme for patients with cancer and early identified anorexia-cachexia, fatigue and functional loss.
- To create a centre of excellence for the conduct of research on cancer induced anorexiacachexia and fatigue.





Screen – Referral - CNR

Albumin	<	35gm/L
CRP	>	50
Weight Loss	>	5% in 6 months
Fatigue	>	6 ESAS
Anorexia	>	judgment
Function	>	judgment

Mechanisms of secondary cachexia

Impaired oral intake

- cognitive impairment, delirium
- depression, fatigue
- pain, dyspnoea, other uncontrolled symptoms
 stomatitis, taste alteration
- dry mouth
- dysphagia, odynophagia
- gastric stasis
- bowel obstruction
- nausea & Vomiting
- severe constipation



Anorexia-cachexia general approach

- 1. Correct other symptoms mouth care, anxiety, pain , constipation
- 2. Gastric Atony prokenetics
- 3. Review patient family goals
- 4. Nutritional counselling
- dietitian, print dietary guide, internet

Muscles Need

Blood Supply

oxygenAnemianutrientsAmino acid deliveryEnergy SupplyATP HypercatabolismProtein SynthesisAnabolic factorsBalanced ProteolysisUbiquitin ligasesExerciseInanition SpiralNeuromuscular Junction.... ???

General Pharmacotherapy

MUSCLE Amino Acids Omega 3's Vitamins (C, E, B, zinc)

APPETITE STIMULATION

Megestrol – corticosteroids short-term

Eicosapentaenoic acid (EPA)

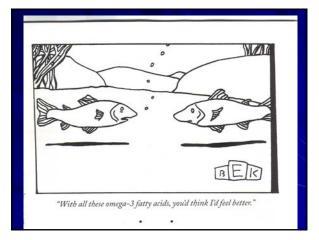
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EPA, an omega-3 polyunsaturated fatty acid found in deep sea oily fish (e.g. salmon, sardines, tuna, mackerel), has been shown to:

- \downarrow pro-inflammatory cytokine production¹ \downarrow level/activity of proteolysis-inducing factor²
- possess anti-cachectic properties³
- slow tumour growth³
- increase survival

EPA in combination with protein and calories may counteract the causes of cancer cachexia resulting in weight gain and (partial) restoration of body mass

NCI – SC18 megestrol vs EPA End Points **EPA** meg <u>comb</u> 10% weight gain 18% 11% 6% NS (range 40% - 69%) Appetite Survival NS Life Quality NS Jatoi et al .JCO;22(12):2469-76



General Pharmacotherapy

- MUSCLE
 Amino Acids
 Omega 3's
 Vitamins (C, E, B, zinc)
- APPETITE STIMULATION
 Megestrol corticosteroids short-term

Rehabilitation - Exercise

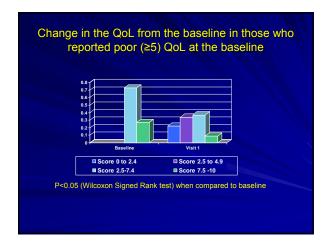
- Reduce cancer incidence
- Increase NK activity
- > Increase QOL and fitness, decrease fatigue
- Geriatric literature
 - Clear consensus increased function
- Fatigue therapy

Exercise - patient motivation

- 1. Personal Control -- Empowerment
- 2. Do 'something normal'
- 3. Belief exercise helps response toxicity

ASCO – Roubenoff & Tattersall 2002





Levels of Training (112 patients)

- 43% trained at a high level
 2-3 X per wk, progressive cardiovascular & resistance exercises
- 10% trained at a moderate level 1-2 X per wk, low level cardiovascular & resistance exercises
- 47% trained at a low level
 - 1-2 times per month, home care, theraband.

<section-header>

Progressive Training Limitations

- Cardiovascular: 93% High resting HR Low HR reserves Autonomic insufficiency
- Neurological symptoms:3%
- Dyspnea: 2%
- Bone metastases: 2%

Research on CAA: McGill Studies Completed – Ongoing - In Planning

- Identification of some causative factors
 Translational Research at McGill Cancer Centre
- Potential benefit of muscle sustaining therapies
- Omega-3 fatty acids Study completed
- ACE Inhibitors Study inaugurated June 2003
- Amino Acids Ongoing
- Creatine NCI(C) Mayo NCCTG fall
- Role of Exercise-Rehabilitation
- NET Grant PI V Baracos Univ of Alberta

Potential Clinical Trials

- Cardioctive agents ACE inhibitors
- Beta 2 agonists
- Cytokine inhibitors
- Ghrelin
- Hypothalamic mediators MC4 antagonists
- Myostatin inhibitors

Logical pragmatic trial

Amino Acid Anabolic Agent va Anti-inflammatory

? COX 2 EPA vs Anti-imflammatory Anabolic Agent

Amino Acid

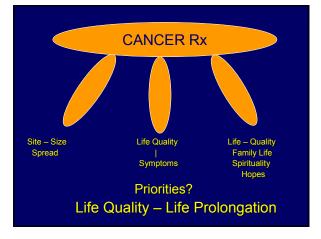
Role of Exercise

New Platform Considerations

- Address Hypogonadism
- Creatine Study
- NSAIDS
- Control Anemia

Cachexia – Developing Countries

- Specific Counselling (print)
- Vitamins
- Amino Acids
- Omega 3's
- Exercise



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