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?

- ASCO 2005 - 4119 presentations
- 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”
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.

Anorexia-cachexia
- Peripheral
  - Inflammation
    - cytokines, eicosanoids
  - Hypercatabolism
    - dysautonomia
  - Hypogonadism
  - Oxidative Stress
  - Genetic Predisposition
  - Tumour Factors
- Central
  - Hypothalamus
  - Cerebral influence
- Appetite

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)

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
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

Lung Cancer – 1ST Presentation

- **C-reactive Protein – 80**
  - Survival -- < 10 mgm/L -- 11 months (median) -- >100mgm/L -- 3 months
- **Correlations -- weight loss**
  - Fatigue
  - Poor performance status
  - ↓ 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)

Slatters et al Lancet Oncology April 2003 224

Hypogonadism

Amino Acid
(2°role-proteolysis)

Synthesis

NFκB

Proteolysis

Inflammation
Tumour Factors
2° role synthesis

Hypercatabolism

ATP – Energy Transfer

Bennett et al Lancet Oncology April 2003 224
Anorexia-cachexia

**PERIPHERAL**
- Inflammation
  - MC4
  - Sympathetic discharge
  - Hypothalamus

**CENTRAL**
- Cerebral influence
- Inflammation
- Hypogonadism
- Appetite

**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 life-threatening 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.

Edna St Vincent Millay

"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."
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 anorexia-cachexia and fatigue.

Basic Assessment Package

Paper and Pencil
- PG-SGA
- ESAS
Blood
- C-reactive protein
- Testosterone
Diet History
- Detail Problems
  - Depression
  - Constipation

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
   prokinetics
3. Review patient – family goals
4. Nutritional counselling
   dietitian, print dietary guide, internet

Muscles Need

- **Blood Supply**
  - oxygen
  - nutrients
- **Energy Supply**
- **Protein Synthesis**
- **Balanced Proteolysis**
- **Exercise**
- **Neuromuscular Junction**

- **Anemia**
- **Amino acid delivery**
- **Aromatic acid metabolism**
- **Anabolic factors**
- **Ubiquitin ligases**
- **Inanition Spiral**

Eicosapentaenoic acid (EPA)

EPA, an omega-3 polyunsaturated fatty acid found in deep sea oily fish (e.g. salmon, sardines, tuna, mackerel), has been shown to:
- ↓ pro-inflammatory cytokine production
- ↓ level/activity of proteolysis-inducing factor
- possess anti-cachectic properties
- slow tumour growth
- 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.

General Pharmacotherapy

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

NCI – SC18
megestrol vs EPA

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<th>End Points</th>
<th>meq</th>
<th>comb</th>
<th>EPA</th>
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<tr>
<td>10% weight gain</td>
<td>18%</td>
<td>11%</td>
<td>6%</td>
</tr>
<tr>
<td>Appetite</td>
<td>NS</td>
<td>11%</td>
<td>6%</td>
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<tr>
<td>Survival</td>
<td>NS</td>
<td>11%</td>
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<td>NS</td>
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Jatoi et al. JCO;22(12):2469-76
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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

Weight stabilization in patients who reported loss at baseline

Change in the QoL from the baseline in those who reported poor (≥5) QoL at the baseline

- Baseline
- Visit 1
- Visit 2
- Visit 3

P<0.05 (Wilcoxon Signed-Rank test) when compared to baseline
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.

Functional Improvement in pts with High Level of Training

- Within first three months of exercise

Research on CAA: McGill Studies

- Completed – Ongoing - In Planning

- Identification of some causative factors
  - Translation 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

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

Logical pragmatic trial

- Amino Acid
  - Anabolic Agent vs Anti-inflammatory
- Anti-inflammatory
  - COX 2
  - EPA

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

CANCER Rx
- Site – Size Spread
- Life Quality Symptoms
- Life – Quality Family Life Spirituality Hopes
- Priorities?
  Life Quality – Life Prolongation