Binary Views

Oncology

Anatomy Rules All!

Symptoms? Handmaidens

Adopt concept

Biology (Symptoms) key as anatomy

Suffering

Tumour Progress
Factors driving tumor and symptoms

Chronic Inflammation

Chronic Stress

Reinforcement ... Common Endpoints
Acute Inflammation

• Innate Immune System
  – Wound healing
  – Tissue repair
  – Angiogenesis

• Adaptive Immune System
  – Specific response to antigen
  – Cytotoxic T cells
Chronic Inflammation

• Innate
  Promote tumour growth and spread

• Adaptive
  Reduced NK cell activity
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
### Immune cells regulating tumor growth

**Stimulate Cancer Growth**

<table>
<thead>
<tr>
<th>Innate immune cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>neutrophils</td>
</tr>
<tr>
<td>macrophage (M2)</td>
</tr>
<tr>
<td>myeloid-derived suppressor cells</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adaptive immune cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Th2 CD4(^+) T cell</td>
</tr>
<tr>
<td>CD4(^+) T regulatory cell</td>
</tr>
<tr>
<td>B lymphocytes</td>
</tr>
</tbody>
</table>

**Inhibit Cancer Growth**

<table>
<thead>
<tr>
<th>Innate immune cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>macrophage (M1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adaptive immune cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxic CD8(^+) T cell</td>
</tr>
<tr>
<td>Th1 CD4(^+) T cell</td>
</tr>
<tr>
<td>TH17 CD4(^+) T cell</td>
</tr>
</tbody>
</table>

Adapted – Disis – *JCO* Oct 10 2010
ACS - Cytokines

**Not helpful**
- Int. 1 – B
- IL – 8

**Helpful?**
- IL – 12
- IL - 15
- IL - 24

**Both ways:**
- IL-6
- IL – 10
- IL -17
- TNFα

“Taoist – not linear”
CHRONIC INFLAMMATION

LIVER
- ↑AFP (note CRP)
- ↓drug metabolism

MUSCLE
- ↓synthesis
- ↑proteolysis

HYPOTHALAMUS
- ↓appetite
- ↑sympathetic activity
- ↑REE
- ↑cortisol
- ↓testosterone

BRAIN
- depression

FAT
- ↑lipolysis
- ↓lipoprotein lipase

GUT
- early satiety

TUMOUR

CRP
CRP - Prognosis

- Ovarian
- Lung
- Melanoma
- Pancreas
- Stomach
- Head and Neck

Resectable Tumours – colorectal, upper GI, renal, bladder
Median survival by CRP Trajectory

<table>
<thead>
<tr>
<th>CRP Trajectory</th>
<th>Median survival (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal ⇒ Normal</td>
<td>21.6</td>
<td>11.9-31.6</td>
</tr>
<tr>
<td>Normal ⇒ Abnormal</td>
<td>12.3</td>
<td>6.5-18.1</td>
</tr>
<tr>
<td>Abnormal ⇒ Normal</td>
<td>10.7</td>
<td>7.6-13.5</td>
</tr>
<tr>
<td>Abnormal ⇒ Abnormal</td>
<td>8.3</td>
<td>7.0-9.5</td>
</tr>
</tbody>
</table>

Log Rank (Mantel-Cox)<0.001

JCO suppl. 2009 abstract 8092
Stress

HPA

Cortisol

Autonomic tone

Norepinephrine

Metastatic Risk

Tumor Growth

Inflammatory Factors

(Modeled on Lutgendorf et al, JCO - 2010; 28-4094)
Inflammation

Immuno-neuroendocrine aberrations

1. CRF – cortisol
2. Sympathetic activity
   - Cytokine activity
   - Pulse – REE
   - Psychosocial stress
3. Testosterone
   - Hypogonadism
     - Sex drive
     - Activity
Stress

**Mechanisms:**
cancer initiation
tumor growth
angiogenesis
metastases
reduce apoptosis
reduce TH$_1$ AND lymphocytes

Armaiz-Pena et al
Brain behavior and immunity 2009; 23:10-15
Stress

Animal Data

- Riley..................................................Tumor Growth
- Sloan et al.................................Metastases

Chronic stress mouse model

30 x metastases

Blocked by propranolol

Sloan et al. CancerRes2010;70:1042
Stress

Basic data

Yang et al... Cytokines
Tumor cell lines
Human melanoma

Ben Eliyahu... Survival
Mouse tumor models
Post surgery
Etodolac and Propanolol

Lee et al... Human Ovarian nude mice
Propranolol

Reiche et al... Stress hormone
Switch from Th1 to Th2 immune response
A Human Rodent

1. Elderly
2. Small Tumour Mass
3. Chronic Inflammatory State
4. REE up
5. Both Anorexia and Cachexia
6. Fatigued – low function
7. On chemotherapy/opioids
8. Gender balance
Stress – human correlation

Childhood stress - chronic disease risk
Social deprivation – ovarian cancer (lutgendorf)
  colorectal cancer (McMillan)

Correlation with immune neuroendocrine change

“Collective evidence points to a prominent role for chronic stress in cancer growth and metastasis”

Future Oncology Dec2010
Stress – human correlation

Breast cancer..............................Spiegel
                        Anderson
GI cancer......................................Kuchler
Melanoma.................................Fawzy

Programs
   Cognitive/Behavioural
   Mindfulness
   Supportive
   Exercise – Yoga

Correlations with immuno endocrine change

Biobehavioral influences on cancer progression
• Effects on $\beta$ adrenergic blockade

Breast cancer


Correlation Between CRP and Severity of Symptoms Reported by Patients

Mean score on ESAS

- Strength
- Appetite
- SOB
- Daytime Sleepiness
- Nervousness
- Constipation
- Depression
- Others
- Nausea
- Vomiting

C- Reactive Protein

0-9 g/L

>10 g/L
Sleep - Inflammation

• Acute –
  • Deprivation - CRP Il-6 Il- 1β
  • Inflammation –
    Poor sleep quality
    Insomnia
    Fatigue

• Bidirectional – vicious circle

• Simpson et al *Nutrition Reviews* Dec 2007
Pain - Inflammation

Animal Studies

- Il-6: pain models
- Il-6 KO: pain response
- Interference: opioid response

Human Studies

- Il-6, TNFα, Il-1β: Regional CSF (neuropathic pain)

Cancer

Laird et al:

Trial 1 CRP  
275 patients  0.036  0.126 (Pearson)

Trial 2  
174 patients  0.032  0.163

Pain 2011;152:460-463
Activation of microglial cytokines

CNS

Hypothalamus

MC4

Sympathetic tone
REE
Norepinephrine

Circulating cytokines

Balance Vagal Input

anorexia
Metabolic changes in tumor related weight loss

• insulin resistance
• diminished lipogenesis
• increased lipolysis
• increased protein synthesis – liver
• muscle synthesis \[\uparrow\] proteolysis
• acute phase protein response – CRP
• inflammatory cytokines
  • Il-1\(\beta\), Il-6, other Th\(_2\) cytokines)
• REE
Anorexia-cachexia

PERIPHERAL

- Inflammation
cytokines, eicosanoids
- Muscle loss
- Hypercatabolism
dysautonomia
- Hypogonadism
- Oxidative Stress
- Activin?
- Genetic Predisposition
- Tumor Factors

CENTRAL

- Hypothalamus
- Cerebral influence
- STN

appetite
Chronic Inflammation - Cancer

- Immune response often facilitates tumor progress
- Tumor cells produce inflammatory chemical mediators assisting growth
- Inflammatory mediators enhance many cancer symptoms
- Early evidence – anti-inflammatory agents may modify the course of cancer
- Will anti-inflammatory (palliative) therapies improve life quality and quantity?
- Relief of cachexia - survival?
Palliative Care-improve outcomes?

- **Quality of life** --- Seven studies
  - Yes – 5/7

- **Symptoms** --- Fifteen studies
  - “overall the results of these 15 studies provide little evidence to support the efficacy of palliative care interventions in alleviating physical symptoms” –

WHO Definition Palliative Care - 2002

“Palliative care is an approach which improves the quality of life of patients facing the problems associated with life-threatening illness, through prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.”
The McGill Cancer Nutrition-Rehabilitation Program

www.mcgill.ca/cnr
PHYSICIAN
ONCOLOGISTS
Medical Intervention

PHYSIOTHERAPIST
Functional Evaluation
and Rehabilitation

DIETITIAN
Nutritional Evaluation
and Recommendations

NURSING, PSYCHOLOGIST,
OCUPATIONAL THERAPIST,
SOCIAL WORKER

PATIENT
AND
FAMILY

Slide courtesy Nelda Swinton
Conceptual model of cancer trajectory
Workup

- Questionnaires
  - ESAS
  - Distress
  - PG-SGA
  - CHAMPS
- CRP
- WBC
- Testosterone - bioavailable
- Thyroid
Rehab Tests

- Tests (endurance, strength, ROM, balance)
  - 6MW, Gait, Balance
  - CHAMPS (general activities – all types)- fatigue
- Sit to stand
- Gait speed
- Review safety
Program

• 8 – 10 weeks with clear initial and end evaluation
• Nutritional counselling
• Basic intervention= physio 1-2 times /week
• 1 visit / 2 weeks other team members
• Caregiver information
• Weekly psycho-education groups – meet once /week x 9 rotating sessions
Changes in ESAS Scores after 8-week CNR program for Patients with Advanced Cancer presenting with CRP < 12 at Initial CNR Evaluation (N = 95)

Note: Higher scores indicate worse symptoms

* p < 0.05 vs. Initial
Initial and Final Total ESAS Scores for Patients with Advanced Cancer presenting with CRP < 12 or CRP ≥ 12 at Initial CNR Evaluation (N = 103)

Note: Higher scores indicate worse symptoms  * p < 0.05 vs. Initial
Percentage of Patients with Advanced Cancer who Lost, Maintained or Gained Weight during the CNR program by Inflammatory Status (N = 114)

- CRP < 12
  - Lost > 1 kg
  - Maintained ± 1 kg
  - Gained > 1 kg

- CRP ≥ 12
  - Lost > 1 kg
  - Maintained ± 1 kg
  - Gained > 1 kg

$p = 0.01$
Initial and Final ESAS Anorexia Scores for Patients with Advanced Cancer presenting with CRP < 12 or CRP ≥ 12 at Initial CNR Evaluations (N = 117)

Note: Higher scores indicate worse symptoms

* p < 0.05 vs. Initial
Percentage of Patients with Advanced Cancer with Taste &/or Smell Alterations at Initial and Final CNR Evaluations (N = 103)

* $p < 0.05$ vs. Initial; † $p < 0.05$ vs. CRP < 12
Evaluation

• High patient satisfaction
• Advanced cancer patients can exercise
• CRP status determines completion of an exercise program
• Measured improvements in appetite, weight and function
Multimodal program

Is our program anti-inflammatory?
1. Dietary advice – yes
2. Exercise – yes
3. Psychosocial component – yes
4. Drugs – not really

Note – no overall change in CRP status
Activin RIIB
Colon 26 Ca model

Activin RIIB → FOX03a

- Atrogin 1
- MURF 1

proteolysis

\textbf{NO reduction cytokines}

\textbf{Reduction tumor growth}

\textbf{BUT muscle mass \ upward}

\textbf{BUT survival}

Zhou et al. \textit{Cell} 2010;142:531
Drugs - Cachexia

• Re-examine Omega 3’s/NSAIDs
• Selective androgen receptor modifiers (SARMS)
• β agonists – formoterol
• B agonists – propanolol
• Cytokine inhibitors – anti Il-6
• Activin – myostatin
  reversal
Figure 3. Kaplan-Meier Estimates of Survival According to Study Group.

Palliative Care – what we do

1. Identify – manage psychosocial issues
2. Emphasis on caregiver support
3. Relief of physical causes of suffering
4. Focus on Nutrition
5. Focus on muscle function and rehabilitation
Hypothesis –
Palliative Care interventions may impact on patient survival as well as Q/L

Animal data is sufficient to support this hypothesis. Human data is very modest but compelling.
Palliative Care – what we do

1. Identify – manage psychosocial issues
2. Emphasis on caregiver support
3. Relief of physical causes of suffering
4. Focus on Nutrition
5. Focus on muscle function and rehabilitation
If true the importance to cancer patients is major and must lead to prioritizing integrated palliative care/chemo-bio trials.

A substantive change in both oncology thinking and trial structure is required. We must study whole care packages not simply drugs.
Ethical Issues – Trial Research

• **Priorities**
  - Set for patient interest?
    - Drug costs
    - Low probability trials
    - ‘me too’ trials

• **Patient’s best interest**
  - Business interests
    - Price per patient
    - Locale
    - Investigator CI
You are not eligible if you are taking part in another trial

Fastidious vs Pragmatic trials
Fastidious vs Pragmatic Trials

- Fastidious Trials – ‘using homogeneous groups, reducing or eliminating ambiguity’

- Pragmatic Trials – ‘would incorporate heterogeneity, ambiguity, and other messy aspects of clinical practice’

Feinstein – *Ann Int Med* 1983
Ideal Trial - I

- Pragmatic – reflecting practice
- Reflect multifactorial nature
- Wide application
- Newly diagnosed patients
Ideal Trial - II

• Patients – 1st Line
  – True ‘Best Supportive Care’
  – Symptom Control
  – Nutrition and Exercise
  – Palliative care involvement

• Chemobiotherapy vs chemobiotherapy
  • SARMS
    • anti-inflammatory agent
    • anti-myostatins

• Stratify by CRP
MENAC Trial - EAPC Research Network

Stratify advanced lung, pancreas, colorectal

Standard Palliative Care

Nutrition – counseling – HMB& EPA
Exercise
Drug - Celecoxib

Stratify – Weight Loss – CRP - Chemotherapy

Courtesy Stein Kaasa
1. Change in mind set. Symptoms reflect tumour activity and are probably as important as partial anatomic change in tumour mass.

2. Change trial priority.
   - Curative trials
   - Pragmatic trials – care package
   - Fastidious trials – limited studies on drugs with limited inclusion/exclusion clauses
   - ‘Me too’ trials
Proposals

1. Engage Binary Vision
2. Collaborative Group
   • international
3. Funding
   • public
   • probonum? – industry, philanthropic
4. End Points
   • quality of life
   • Function
   • survival
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