Development of sickness symptoms related to inflammatory response during aggressive cancer therapy

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Symposium: Genes, Cells and Symptom Clusters – What’s the Story?

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Health-related quality of life (HRQOL) is an inclusive concept that includes many domains outside of those that are most likely to be affected by disease and treatment.

Symptoms are patients’ perceptions of what is closest to the disease and treatment process.

Biology of symptom burden provides rationale of effective management strategy development.
M. D. Anderson Symptom Inventory (MDASI) Core Items

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

<table>
<thead>
<tr>
<th></th>
<th>Not Present</th>
<th></th>
<th>As Bad As You Can Imagine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Your pain at its WORST?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>2.</td>
<td>Your fatigue (tiredness) at its WORST?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>3.</td>
<td>Your nausea at its WORST?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>4.</td>
<td>Your disturbed sleep at its WORST?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>5.</td>
<td>Your feelings of being distressed (upset) at its WORST?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>6.</td>
<td>Your shortness of breath at its WORST?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>7.</td>
<td>Your problem with remembering things at its WORST?</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>
## Most Prevalent Severe Symptoms in Patients with Cancer

(7-10/10, N = 507, MD Anderson, 2000)

<table>
<thead>
<tr>
<th>31-40%</th>
<th>21-30%</th>
<th>11-20%</th>
<th>5-10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Disturbed sleep</td>
<td>Pain</td>
<td>Nausea</td>
</tr>
<tr>
<td>Weakness</td>
<td>Distress</td>
<td>Shortness of breath</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Nothing done</td>
<td>Lack of appetite</td>
<td>Difficulty remembering</td>
<td>Cough</td>
</tr>
<tr>
<td></td>
<td>Sickness</td>
<td>Difficulty paying attention</td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td>Drowsiness</td>
<td>Irritability</td>
<td>Bleeding</td>
</tr>
<tr>
<td></td>
<td>Worry</td>
<td>Constipation</td>
<td>Mouth sores</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
<td>Sadness</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nervousness</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bloat</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Numbness</td>
<td></td>
</tr>
</tbody>
</table>
Consistency of Symptom Burden?

1. Individual patient differences? Disease, comorbidity, sex, age...
2. Aggressive therapies induced sickness. Such as chemoradiation, allogeneic and autologous hematopoietic stem cell transplant.
Lowess curves illustrate a gradual increase in symptom severity (on a 0–10 scale) during the accumulated dose of CXRT (Day 0=start of therapy)

Selected symptoms from MDASI included:
- Fatigue
- Pain
- Lack of appetite
- Distress
- Drowsiness
- Sleep disturbance
- Diarrhea
- Difficulty swallowing
- Shortness of breath
- Coughing

Lowess Curves of Most Severe Transplant-Induced Symptoms on MDASI

1. Sample: N=63, multiple myeloma. Received cycles induction therapy
2. Fatigue remained worst symptom, as for chemoradiation and allogeneic transplant
3. Cluster of worst symptoms over time, relative to other MDASI symptoms
4. Symptom peak fits WBC nadir, sickest period during stem cell transplant

Wang, et al, submitted
Sickness Behavior: An Animal Model for Psychoneuroimmunology Studies

- **Physiological components**
  - Fever, pain, wasting, increased HPA, autonomic activity

- **Behavioral components**
  - Somnolence, hyperalgesia, impaired learning, and decreased social interaction, exploration, and eating

- Inflammatory cytokines/chemokines and neurotransmitters may play central mechanistic role
Fundamental Considerations of Inflammation for Cancer Symptoms in Human Studies

- Does the animal sickness behavior model fit cancer-related symptoms in humans?
  - Hypothesis: Cytokines are a common denominator or initiator of different pathophysiological symptom-development processes.

- To what degree and by what pathways are these cytokines crucial for the emergence of symptoms (or symptom clusters) from cancer or cancer therapy?
  - Hypothesis: Pro-inflammation represents a relatively nonspecific, overlapping mechanism underlying various clinical manifestations.

- Accordingly, could modulation of these cytokines reduce or prevent the prevalence and severity of symptoms?
  - Hypothesis: Cytokine antagonists will significantly reduce targeted inflammation processes and have an even greater impact on symptom outcomes.
Examples of Inflammation-Related Cancer and Treatment Symptoms

- **Anorexia/Cachexia:** Elevated serum IL-6, TNF-α is confirmed to affect animals; TNF-α is important but not exclusively responsible for anorexic effects of tumor.

- **Pain:** IL-1β, IL-6 and TNF-α are increased in neuropathic pain, hyperalgesia, and extreme sensitivity to pain.

- **Cognitive Dysfunction:** Elevated IL-6 is associated with cognitive deficits in AML/MDS and LMD patients.

- **Sleep:** IL-6, TNF-α are increased in sleep deprivation.

- **Paraneoplastic syndrome in SCLC or metastatic RCC:** IL-6–related fever, fatigue, weight loss, cognitive impairment.
Cancer-Related Fatigue and Inflammatory Cytokines: Quantitative Review of Association

- PubMed, PsychINFO, BIOSIS search through July 2006
- 18 studies, N=1037
- Heterogeneous nature
- No publication bias
- Conservative meta analysis
- A significant association with IL-1RA, IL-6 and neopterin
- No evidence of IL-1β, TNF-α
- Limited by single sampling, fatigue measures, sample storage or processing
- Preliminary results

Serum IL-6 Fluctuates with Symptom Peak at Nadir: Allogeneic HSCT

AML/MDS patients, N=30
Mixed effect modeling

Baseline to 8 days
- IL-6: est=1.112, p=.006

Baseline to 30 days
- IL-6: est=1.05, p<.0001
- sTNF-R1: est=1.367, p=.036

Covariates: Age, sex, race, disease status, infusion cell service and dose, conditioning regimen

Serum assay: IL-6, IL-8, sTNF-R1, IL-1RA, IL-12p40p70

Component score of most severe symptoms: Pain, fatigue, disturbed sleep, drowsiness, poor appetite, dry mouth

Nadir Day 8; Symptom peak Day 11

Wang et al, Cancer, 2008
Mixed Effect Modeling: IL-6, sTNF-RI, IL-8, and Symptom Severity (Component Scores)

8 Weeks CXRT, NSCLC (N=62)

Changes in serum cytokines related to changes in symptom severity over eight weeks of CXRT (estimate\(^*\) (SE)).

<table>
<thead>
<tr>
<th></th>
<th>Five most severe symptoms(^b)</th>
<th>All 15 symptoms</th>
<th>Esophagitis-related symptoms(^b)</th>
<th>Affective symptoms(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>3.68 (3.34)</td>
<td>2.48 (2.51)</td>
<td>6.04 (2.87)(^c)</td>
<td>5.94 (3.07)</td>
</tr>
<tr>
<td>Days of radiation therapy</td>
<td>0.03 (0.01)(^c)</td>
<td>0.02 (0.01)(^d)</td>
<td>0.04 (0.01)(^d)</td>
<td>0.005 (0.008)</td>
</tr>
<tr>
<td>sTNF-R1</td>
<td>1.51 (0.93)</td>
<td>1.74 (0.69)</td>
<td>1.15 (1.02)</td>
<td>1.87 (1.00)</td>
</tr>
<tr>
<td>IL-1RA</td>
<td>−0.86 (0.68)</td>
<td>−0.34 (0.51)</td>
<td>−1.40 (0.81)</td>
<td>−0.38 (0.77)</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.32 (0.16)(^c)</td>
<td>0.09 (0.12)</td>
<td>0.77 (0.19)(^c)</td>
<td>−0.06 (0.19)</td>
</tr>
<tr>
<td>IL-8</td>
<td>−0.15 (0.14)</td>
<td>−0.10 (0.11)</td>
<td>−0.49 (0.17)(^d)</td>
<td>−0.18 (0.16)</td>
</tr>
<tr>
<td>IL-10</td>
<td>0.65 (0.34)</td>
<td>0.42 (0.26)</td>
<td>0.43 (0.36)</td>
<td>−0.22 (0.36)</td>
</tr>
<tr>
<td>IL-12</td>
<td>0.19 (0.25)</td>
<td>0.01 (0.18)</td>
<td>0.17 (0.26)</td>
<td>0.02 (0.26)</td>
</tr>
</tbody>
</table>

CXRT, concurrent chemoradiation therapy; SE, standard error; sTNF-R1, soluble receptor 1 for tumor necrosis factor; IL, interleukin; RA, receptor antagonist.

\(^a\) Age, sex, race, recurrence of cancer, dose of radiotherapy, BMI, previous chemotherapy, and type of radiotherapy were adjusted in all models.

\(^b\) The five most severe symptoms: pain, fatigue, lack of appetite, disturbed sleep, sore throat. Esophagitis-related symptoms: pain, sore throat. Affective symptoms: distress, sadness.

\(^c\) \(p < .05\).

\(^d\) \(p < .01\).

\(^e\) \(p < .0001\).

\(^*\) The estimate for a predictor indicates how many units the outcome (symptom severity) changed on a 0–10 scale when the predictor changed one unit.

Double increase in IL-6 concentration associated with an average increase of 0.32 in mean of top 5 most severe symptoms on 0-10 scale on any week during CXRT.

\(Sx = \text{intercept} + \text{other factors} + 0.32 \times \log(\text{IL-6})\)

Wang et al, *Brain Behav Immun*, 2010
Colorectal and Esophageal Cancer: IL-6, sTNF-R1 related to CXRT Symptoms

- Fatigue (darker line)
- **Component score** of 5 most severe symptoms (fatigue, pain, distress, drowsiness, disturbed sleep)
- Serum assay on IL-6, IL-8, IL-10, IL-1RA, VEGF, sTNF-R1

Fatigue: **sTNF-R1** (P<.001)
Component score:
  - **IL-6** (P<.0001)
  - **sTNF-R1** (P<.0001)

Etanercept Effective for Fatigue and Depression Reduction in Psoriatic Arthritis

- N=618, double blind, placebo controlled Phase III RCT
- Etanercept – a tumor necrosis factor (TNF-α) inhibitor
- Improvements in fatigue were independent, significant, clinically meaningful by 12 weeks (ES=0.27)
- Etanercept treatment relieved fatigue and symptoms of depression associated with this chronic disease

Figure 3: Improvement from baseline in FACIT-F over time
p values for comparison between etanercept and placebo groups.

Summary

- Sickness symptoms of fatigue, pain, disturbed sleep, drowsiness, and poor appetite co-occur over time during acute phase of aggressive curative cancer therapies.
- Symptoms developed in parallel for an increase in severity in response to these therapies, then decrease immediately after therapy; measurable by MDASI in longitudinal study.
- Serum IL-6 and sTNF-R1 are significant inflammatory markers positively related to the cluster of symptoms.
- Results suggest components of systemic inflammation mediate symptoms of sickness, regardless of patient and disease factors.
- Etiologic studies are challenging, but much needed for mechanism-driven symptom management. Need empirical evidence for other pathways/markers, and for other symptoms/clusters.