The Rational Use of Nutritional Supplements/ Nutraceuticals for Cancer Supportive Care

Mary Hardy, MD
Medical Director, Simms/Mann-UCLA Center for Integrative Oncology
Why Nutraceuticals?

• Patients with cancer desire to be active participants in their care

• Patients with cancer want to:
  – Combat the cancer
  – Manage cancer symptoms
  – Cope with cancer treatment side effects

• Patients with cancer have access to OTC vitamins, minerals, and herbal supplements
Patient with Too Many Bags

- Asked by oncologist to see patient
- Being treated for early stage E+ breast cancer on Tamoxifen
- Recent increase in LFT’s (2-3x’s ULN)- concerned that Tamoxifen may be cause
- Patient admitted on direct questioning to taking some dietary supplements
- Arrived at our meeting with 3 shopping bags full
Unsupervised Use of Nutritional Supplements by Patients With Cancer

237 of 820 patients (29.1%) receiving chemotherapy or radiation therapy use nutritional supplements NOT prescribed by their physician.

- **Minerals**: 28.2%
- **Botanicals/biologics**: 43.8%
- **MVI**: 58.6%
- **Vitamins**: 86.5%

MVI, multivitamin.

Safety of Herbal Products

If what is on the label of an herbal medicine is what is in the container, “toxicity” is rarely encountered.

Norman R. Farnsworth, Ph.D. (1999)
## Launch Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Positioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>CogniQOL</td>
<td>Improvement of cognitive function; Lymphedema</td>
</tr>
<tr>
<td>DaxibeQOL</td>
<td>Cachexia, Sarcopenia</td>
</tr>
<tr>
<td>FemQOL</td>
<td>Hormone suppression induced night sweats</td>
</tr>
<tr>
<td>FolaQOL</td>
<td>Anti-folate induced toxicity</td>
</tr>
<tr>
<td>InflaQOL</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>LymphaQOL</td>
<td>Breast cancer-associated upper extremity lymphedema</td>
</tr>
<tr>
<td>MucosaQOL</td>
<td>Stomatitis, lower GI toxicity, Taxane induced neuropathy</td>
</tr>
<tr>
<td>MyoQOL</td>
<td>Anthracycline induced cardiotoxicity; Fatigue</td>
</tr>
<tr>
<td>NeuroQOL</td>
<td>Chemo induced neurotoxicity; Fatigue</td>
</tr>
<tr>
<td>NutraQOL</td>
<td>Immune-balancing, physical and mental well being; Febrile Neutropenia</td>
</tr>
<tr>
<td>RadoQOL</td>
<td>Post radiation cerebral edema</td>
</tr>
</tbody>
</table>
## Launch Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Positioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>ProbioQOL</td>
<td>Correction of imbalance in intestinal flora in cancer patients due to antibiotics and chemo; Diarrhea</td>
</tr>
<tr>
<td>ErythroQOL</td>
<td>Cancer associated anemia</td>
</tr>
<tr>
<td>VitaQOL</td>
<td>Cancer associated vitamin and mineral deficiency or support</td>
</tr>
</tbody>
</table>
Breast Cancer: Case One

• 45 y/o pre-menopausal female has recently intentionally lost 15# and palpated a mass in LUQ of her breast

• Tumor characteristics imaging & biopsy
  – E 3+  P2+  Hr2-
  – 1.5 cm MBR 7/9
  – Questionable peri-neural invasion

• Lumpectomy w/ SN biopsy
  – 1/3 nodes +
  – Surgical specimen similar to biopsy
Breast Cancer: Case One

• PE: unremarkable except for
  – BP 145/80
  – Ht Wt BMI 28
  – Well healing scars in left breast and axilla

• Social Hx: Married, Teaches music (violin)

Chemotherapy selected Taxotere Cytoxan in the usual doses followed by 5 years tamoxifen

What side effects do you anticipate for this patient during chemo and with tamoxifen?
Mucositis/Stomatitis: Burden of Disease

Grade 3 or 4 oral mucositis in patients with solid tumors associated with increased healthcare costs and dose reductions

TPN, 22% of patients

2-fold increase in ER visits

Additional 7 days of hospitalization/chemotherapy cycle

Chemotherapy dose reduction in 28% of cycles

TPN, total parenteral nutrition.
Radiation-induced Diarrhea: Burden of Disease

Radiation induced bowel injury causes diarrhea acutely and late effects may cause severe impacts on QOL.

- 80% of pelvic radiation patients acutely
- Dehydration and/or hospitalization
- Late term patients may require surgery
- Chronic effects can manifest after 6-24 months
- 30-50% pelvic radiation patients chronically

Modulation of Intestinal Function by Dietary Factors.

**GLUTAMINE**
- Preferred fuel for enterocytes
- Precursor GSH
- Modulate Heat Shock Protein response
- Regulate apoptosis/proliferation signaling
- Modulate intestinal & systemic immunity

**OMEGA 3 FATTY ACIDS**
- Attenuate inflammatory injury
- Modulate intestinal immunity
- Modify lymphocyte number
- Improve gut barrier function
- Modulate gut microbiota

**PRO/PRE-BIOTICS**
- Reverse microbiota disruption
- Modulate intestinal immune system
- Enhance production of SCFA
- Enhance production of intestinotrophic hormones
- Boost gut barrier function
- Modulate drug metabolism via modification key bacteria

**INTESTINAL INJURY**

**DECREASING INJURY**

Xue H et al. JPEN J Parenter Enteral Nutr 2011;35:74-90
Glutamine Effect on Oral Mucositis

TABLE 4
Oral Mucositis Assessment Scale

<table>
<thead>
<tr>
<th>Treatment Cycle 1 Intervention</th>
<th>Saforis (n = 163)</th>
<th>Placebo (n = 163)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral mucositis score, mean (SD)</td>
<td>0.22 (0.29)</td>
<td>0.26 (0.34)</td>
<td>.200</td>
</tr>
<tr>
<td>Worst ulceration score, mean (SD)</td>
<td>0.23 (0.39)</td>
<td>0.32 (0.45)</td>
<td>.013*</td>
</tr>
<tr>
<td>Ulceration score &gt; 0, n (%)</td>
<td>63 (30.7)</td>
<td>81 (49.7)</td>
<td>.025†</td>
</tr>
</tbody>
</table>

SD indicates standard deviation.
* From analysis of variance with terms for center and treatment.
† From Cochran-Mantel-Haenszel test adjusted for center.

TABLE 3
Maximum Severity of Oral Mucositis by Treatment Group in Treatment Cycle 1

<table>
<thead>
<tr>
<th>Maximum WHO grade</th>
<th>Patients, n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saforis (n = 163)</td>
<td>Placebo (n = 163)</td>
</tr>
<tr>
<td>0</td>
<td>52 (31.9)</td>
<td>50 (30.7)</td>
</tr>
<tr>
<td>1</td>
<td>48 (29.4)</td>
<td>32 (19.6)</td>
</tr>
<tr>
<td>2</td>
<td>61 (37.4)</td>
<td>70 (42.9)</td>
</tr>
<tr>
<td>3</td>
<td>2 (1.2)</td>
<td>11 (6.7)</td>
</tr>
</tbody>
</table>

WHO indicates World Health Organization.
* Overall shift in the distribution of maximum oral mucositis grade using the Wilcoxon rank-sum test, adjusted for center.
† Cochran-Mantel-Haenszel test, adjusted for center.

FIGURE 4. Percentage of patients with World Health Organization (WHO) grade ≥ 2 oral mucositis at each time point during Treatment Cycle 1 by treatment group.

with the placebo group (97.5% vs 91.9%; P = .039). No treatment differences were observed with respect to
Glutamine & Chemotherapy Diarrhea

Figure 1. Meta-analysis of the duration of diarrhea in randomized controlled trials comparing glutamine and placebo. The results revealed a benefit of glutamine in reducing the duration of diarrhea, particularly in the oral glutamine subgroup. CI, confidence interval. Chi^2, Chi-square.
Support for Mucositis & Enteritis

- Glutamine 20 gm/day 1-7 chemotherapy cycle
- Fish oil containing 750-1200 mg EPA + DHA
  - Hold for platelets less than 75,000
  - Caution using with anti-platelet or anticoagulant drugs
- Probiotics 1 or 2 doses per day
- Include prebiotic & probiotic foods in diet
Black Cohosh Extract

For Management of Hot Flashes, Sweating, Other Symptoms Related to Hormonal Suppression
Black Cohosh & Breast Cancer: Safety & Efficacy

• 136 breast cancer pts after surgery, radiation & adjuvant chemotherapy (age 35-50); Groups equivalent for tumor stage & therapy
• Open label trial
• Tamoxifen +/- BCE (Klimadynon) 20 mg/d
• Assessment: HF number & severity
• Outcome (1 yr):
  – 50% patients free of hot flashes
  – Severe hot flashes (24% BCE vs 74% Us care)
  – No significant ADE occurred in either group

## Black Cohosh Laboratory Studies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Week 0 (mean ± SD)</th>
<th>Week 52 (mean ± SD)</th>
<th>Difference (mean ± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hormones</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17β-estradiol (pg/mL)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19.86 ± 9.38</td>
<td>22.66 ± 50.35</td>
<td>2.81 ± 50.38</td>
<td>Sig.</td>
</tr>
<tr>
<td>FSH (mU/mL)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>75.05 ± 27.36</td>
<td>68.86 ± 33.44</td>
<td>−6.19 ± 29.45</td>
<td>Sig.</td>
</tr>
<tr>
<td>LH (mU/mL)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>31.79 ± 11.48</td>
<td>29.64 ± 13.26</td>
<td>−2.15 ± 11.85</td>
<td>Sig.</td>
</tr>
<tr>
<td><strong>Lipids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol total (mg/dL)</td>
<td>202.91 ± 26.41</td>
<td>216.06 ± 36.07</td>
<td>13.15 ± 37.28</td>
<td>Sig.</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>64.28 ± 12.60</td>
<td>71.38 ± 15.52</td>
<td>7.11 ± 12.65</td>
<td>Sig.</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>124.14 ± 22.59</td>
<td>132.10 ± 30.25</td>
<td>7.96 ± 31.47</td>
<td>Sig.</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>110.47 ± 38.75</td>
<td>138.93 ± 85.03</td>
<td>28.46 ± 84.55</td>
<td>Sig.</td>
</tr>
<tr>
<td><strong>Clinical chemistry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGOT (U/L)</td>
<td>21.78 ± 10.37</td>
<td>31.47 ± 11.67</td>
<td>9.69 ± 13.77</td>
<td>Sig.</td>
</tr>
<tr>
<td>SGPT (U/L)</td>
<td>25.21 ± 11.53</td>
<td>28.48 ± 35.22</td>
<td>3.27 ± 35.53</td>
<td>Sig.</td>
</tr>
<tr>
<td>γ-GT (U/L)</td>
<td>26.61 ± 17.47</td>
<td>27.44 ± 31.54</td>
<td>0.83 ± 32.84</td>
<td>NS</td>
</tr>
<tr>
<td>Bilirubin total (mg/dL)</td>
<td>0.51 ± 0.25</td>
<td>0.56 ± 0.29</td>
<td>0.05 ± 0.25</td>
<td>Sig.</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>4.42 ± 1.19</td>
<td>4.42 ± 1.10</td>
<td>0.00 ± 1.12</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>98.46 ± 13.42</td>
<td>100.62 ± 27.78</td>
<td>2.16 ± 28.84</td>
<td>NS</td>
</tr>
<tr>
<td>INR</td>
<td>1.01 ± 0.11</td>
<td>0.96 ± 0.26</td>
<td>−0.05 ± 0.27</td>
<td>Sig.</td>
</tr>
</tbody>
</table>

FSH, follicle-stimulating hormone; LH, luteinizing hormone; HDL, high-density lipoprotein; LDL, low-density protein; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; γ-GT, gamma-glutamyl transferase; INR, international normalized ratio; Sig., significant; NS, not significant.

<sup>a</sup>Values below the lower limit of quantification were replaced by lower limit of quantification value.

<sup>b</sup>Values above the upper limit of quantification were replaced by upper limit of quantification value.

Breast Cancer Case Two

• How would your dietary supplement recommendations change if the patient in case one was 65 with a history of diabetes and sciatica?

• What would you recommend to reduce the toxicity of her radiation?
Chemotherapy Induced Neuropathy: Burden of Disease

Often results in dose reductions or early discontinuation of therapy

Taxanes: 50-
80% overall
Up to 33% with serious symptoms
Pre-existing conditions increase risk
Results may be permanent

Platinum based drugs: up to 100%
Reduce ADL’s
Impair exercise capacity
Contributes to falls

# Glutamine: Clinical Study

## Adult Oxaliplatin and 5-FU: Beneficial Effects

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients &amp; Design</th>
<th>Glutamine Dose</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang et al 2007</td>
<td><strong>Randomized study</strong>&lt;br&gt;Metastatic colon or rectal cancer patients in Taipei&lt;br&gt;(N = 86 patients; glutamine=42, control=44)&lt;br&gt;Excluded patients with pre-existing neuropathy or diabetes&lt;br&gt;No calcium or magnesium infusion allowed&lt;br&gt;Primary outcomes:&lt;br&gt;• Prevention or decrease of neuropathy&lt;br&gt;Chemo: Oxaliplatin 85 mg/m² days 1 and 15 + folinic acid 20 mg/m² and 5-FU 500 mg/m² bolus days 1, 8, and 15 every 28 days</td>
<td><strong>15 g BID x 7 days every 2 wks beginning on day of oxaliplatin infusion</strong></td>
<td>Glutamine decreased&lt;br&gt;• Grade 1–2 sensory neuropathy after 2 cycles (16.7% vs 38.6%; P=.04)&lt;br&gt;• Grade 1–2 sensory neuropathy (26.2% vs 36.4%) and grade 3–4 (4.8% vs 18.2%; P=.05) after 4 cycles&lt;br&gt;• Grade 3–4 sensory neuropathy (11.9% vs 31.8%; P=.04) after 6 cycles&lt;br&gt;• Incidence of acute, transient peripheral nerve hyperexcitability (33.3% vs 56.8%; P=.03)&lt;br&gt;• Interference with ADL (16.7% vs 40.9%; P=.02)&lt;br&gt;• Percentage of patients requiring dose reductions (7.1% vs 27.3%; P=.02)</td>
</tr>
</tbody>
</table>

Support for Peripheral Neuropathy

- **Glutamine** 20 gm/ day 1-7 of chemotherapy cycle
  - Can increase to maximum of 30 grams QD
- **Acetyl-L-carnitine** 500 mg-1 gm TID
- **Alpha-lipoic acid** 600 mg BID to TID
- **B complex** (low doses often contained in multivitamins)
Glutamine Safety

- Hepatic encephalopathy & renal insufficiency - limit protein
- Glutamine precursor of glutamate (excitatory neurotransmitter) theoretically contribute mania
- MSG hypersensitivity - theoretical interaction
- Warburg effect - paradoxical response cellular level vs. whole organism
MucosaQOL

Indications: Mucositis, Neuropathy, Enteritis

L-Glutamine

5-gram stick-packs, peach flavor

Recommended Use: 1-2 stick-packs in water TID—swish and swallow

4-7 days during chemotherapy

May increase to every day for symptom relief
Advanced Cancer: Case Three

• 78 y/o woman presents with NSCC of lung metastatic to liver
• She is currently undergoing salvage chemotherapy with carboplatin
• Her major complaint now is fatigue
• She reports a recent 20# weight loss
• She never smoked
Cancer Related Fatigue: Burden of Disease

Cancer related fatigue causes marked impacts on QOL and is often under recognized or considered inevitable.

The multifactorial pathophysiology of cancer-related fatigue is not fully understood

- **Poor Nutrition**: Anorexia, Nausea, Vomiting, Diarrhea, Sarcopenia
- **Energy Metabolism Imbalance**: Disease- or treatment-related
- **Dysregulation**: Metabolic homeostasis, Muscle function
- **Hypoxia**:
- **Sleep and Mood Disorders**:
Advanced Cancer: Case Three

Correlation between isokinetic (60° /s) quadriceps extension strength (QS) and the Brief Fatigue Inventory (BFI) in male (dotted line, n=33) and female (solid line, n=24) patients with newly diagnosed advanced cancer.
# Carnitine: Clinical Studies

## Effect on Fatigue/QOL/Nutrition/Function

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients &amp; Design</th>
<th>Carnitine Dose</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Gramignano et al 2006  | Open-label, non-randomized study Patients with advanced cancer who developed fatigue, high ROS blood levels, or both (N = 12) | Oral L-carnitine 2 g, TID x 4 wks | Fatigue decreased  
  • MFSI-SF: $t_0$, 25.40 vs wk 4, 12.05; $P < .001$  
  Quality of life improved  
  • QOL-OS: $t_0$, 54.30 vs wk 4, 36.80; $P < .05$  
  • EQ-5D$_{vas}$: $t_0$, 50.58 vs wk 4, 73.33; $P < .001$  
  Nutrition/function improved  
  • LBM: $t_0$, 38 kg vs wk 4, 40.39 kg; $P < .05$  
  • Significantly improved appetite  
  • No difference in grip strength  
  Laboratory variables  
  • Reduced CRP: $t_0$, 0.97 ng/mL vs wk 4, 0.59 ng/mL; $P = .05$  |

CRP, C-reactive protein; EQ-5D$_{vas}$, EuroQol visual analog scale; IL, interleukin; LBM, lean body mass; MFSI-SF, Multidimensional Fatigue Symptom Inventory-Short Form; PIC, proinflammatory cytokines (IL-6, IL-1, TNF-$\alpha$); QOL, quality of life; QOL-OS, quality of life-oxidative stress questionnaire; ROS, reactive oxygen species; $t_0$, baseline; TID, thrice daily; TNF-$\alpha$, tumor necrosis factor-alpha. Gramignano G, et al. *Nutrition*. 2006;22:136-145.
Support for Cancer Fatigue

- Acetyl-L-carnitine 2 gm BID to TID
- Co-enzyme Q 10 100 mg BID
- Branch chain amino acids 6.6 grams BID
- Dietary changes to stabilize blood sugar
- Additional protein
- Normalize sleep (melatonin 3-10 mg QHS)
- Exercise
- Yoga
Carnitine: Safety

• Adults: no toxicity at doses up to 30 g/day\textsuperscript{1,2}
  – Pediatrics: appears safe in doses up to 0.65g/kg/day in children ages 2–21 years\textsuperscript{3}

• No significant side effects reported in any study
  – One report of insomnia\textsuperscript{1}
  – Four patients reported mild nausea\textsuperscript{2,3}

• Warfarin
  – Due to the known interaction between L-carnitine and acenocoumarol, L-carnitine and acetyl-L-carnitine should be used cautiously in patients taking warfarin

• L-carnitine inhibits thyroid hormone uptake by target cell nuclei\textsuperscript{4}
  • An increase in seizure frequency or severity has been reported in people with a history of seizures who have received oral or intravenous L-carnitine\textsuperscript{5}

NeuroQOL (acetyl-L-carnitine)

Indications: Neuropathy, Fatigue, QOL

500 mg per capsule
Recommended Use: 2 capsules TID
May be used up to 6g/day
FemQOL:
Indications: Menopausal symptoms

Standardized Isopropanolic Black Cohosh Extract
20 mg per capsule
Recommended Use: 1 capsule BID
Pancreatic Cancer: Case Four

• Patient is a 55 y/o male presenting initially with a 20 pound unintentional weight loss. He weighed 235 three months ago and now weighs 216 pounds.
• He was diagnosed with a locally advanced pancreatic tumor
• He is starting on FOLFIRI
Cachexia & Sarcopenia: Burden of Disease

Cachexia, anorexia and sarcopenia impair patient response to treatment and significantly affect prognosis.

Effect of Weight Loss on Median Survival in Cancer Patients

- The clinical course of cancer is adversely affected by weight loss
- Results from case record analysis (N = 3047) of 12 ECOG chemotherapy trials

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Median Survival (Wk)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No WL</td>
<td>0–5% WL</td>
</tr>
<tr>
<td>NSCLC</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Prostate</td>
<td>46</td>
<td>30</td>
</tr>
<tr>
<td>Colorectal</td>
<td>43</td>
<td>27</td>
</tr>
</tbody>
</table>

Cachexia Syndrome

• In and of itself, weight loss does not fully describe or define cachexia

• Three factors relate to adverse patient function and prognosis:
  – Weight loss (≥ 10%)
  – Reduced food intake (≤ 1500 kcal/day)
  – Systemic inflammation (C-reactive protein ≥ 10 mg/L)

# Nutritional/Functional and Quality of Life Before and After Treatment With AA Supplementation

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>Post-treatment</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grip strength (kg)</td>
<td>28.2 ± 9.5</td>
<td>30.4 ± 9.2</td>
<td>.0001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>53.1 ± 10.6</td>
<td>54.2 ± 11.1</td>
<td>.056</td>
</tr>
<tr>
<td>BMI</td>
<td>19.7 ± 2.8</td>
<td>19.8 ± 2.9</td>
<td>.119</td>
</tr>
<tr>
<td>Lean body mass (kg) (bioimpedence)</td>
<td>41.2 ± 8.3</td>
<td>42.6 ± 6.7</td>
<td>.221</td>
</tr>
<tr>
<td>Fatigue (MFSI-SF)</td>
<td>25 ± 8.1</td>
<td>22 ± 7.3</td>
<td>.181</td>
</tr>
</tbody>
</table>

<sup>a</sup>Calculated by Student t test for paired data.

BMI, body mass index; MFSI-SF QoL, multidimensional fatigue symptom inventory-short form quality of life.

Nonsignificant Changes Before VS After Amino Acid Supplementation

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>After Treatment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.7 ± 1.5</td>
<td>11.2 ± 1.6</td>
<td>.894</td>
</tr>
<tr>
<td>Absolute lymphocyte count (1 μl⁻¹)</td>
<td>1473 ± 559</td>
<td>1673 ± 872</td>
<td>.284</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>24.7 ± 18.1</td>
<td>17 ± 11.4</td>
<td>.066</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>21.3 ± 16.4</td>
<td>13.7 ± 4</td>
<td>.157</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>22.1 ± 11.9</td>
<td>19.5 ± 7.6</td>
<td>.526</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>3.6 ± 4.5</td>
<td>10.8 ± 11.7</td>
<td>.052</td>
</tr>
</tbody>
</table>

Differences between means calculated by Student t test for paired data; P
IL-6, interleukin 6; TNF-α, tumor necrosis factor alpha.
Support for Cachexia

- Branch chain amino acids 6.6 gm BID to TID
- Curcumin
  - 3-6 gm BID (unformulated to improve absorption)
  - 1-2 gm BID (formulated to improve absorption)
- Fish oil 1200 – 2000 gm EPA + DHA BID
- Appetite stimulation
- Increase oral protein intake
Safety of Oral Amino Acid in Cancer Patients

- Madeddu, 2010¹
  - No toxicity of any grade nor adverse events for any patient observed

- Cangiano, 1996²
  - No discontinuations related to trial
  - Authors conclude that BCAAs may be used safely in cancer patients with anorexia

- May provide an additional hypoglycemic effect in patients receiving anti-diabetic medications

- Toxicity in rare diseases
  - Amyotrophic lateral sclerosis
  - Branched-chain ketoaciduria

DaxibeQOL

Indications: Cachexia; Anorexia; Sarcopenia

Essential Amino Acid Supplement
For Musculoskeletal Support

6.6 g per Sachet
Recommended Use: 1-2 sachets daily
Curcumin Phytosome
500 mg per capsule
Suggested Use: 2-3 capsules bid
Colon Cancer: Case Five

• 62 y/o African American male with iron deficiency anemia discovered on routine physical required for work (commercial truck driver)

• FHx: MGF developed colon cancer at 70 yrs

• Pt has never had colonoscopy & “hates doctors”

• Pt is asymptomatic but stool guiac + for blood
Colon Cancer: Case Five

- Colonoscopy reveals fungating mass in Right ascending colon
- Surgery reveals 5.5 cm adenocarcinoma partially through the muscularis
- Lymph nodes: 5/10 local nodes positive
- Stage III B
- FolFox chemo therapy for 6 months
Colon Cancer: Case Five

• What would improve this patient's response to chemotherapy?
• What side effects do you anticipate from his chemotherapy?
• What issues are you concerned about based on his race?
• What would you recommend to reduce his risk of recurrence?
Use of Freeze-dried Wheat Germ Extract for the Supportive Care of Cancer Patients
FWGE Mechanism: How Does It Work?

- Decreased glucose carbon flow towards nucleic acid synthesis
- Decreased availability of NADPH, inhibition of dNTP synthesis, inhibition tumor cell proliferation, slowing down disease progression, decreased glucose consumption of the tumor leads to a metabolic harmony with the host and weight gain in patients with even advanced cancers
- Inhibition pentose cycle reactions in cancer cells, inhibition the formation of ribose, inhibition the synthesis of the carbon skeleton of nucleic acids, inhibition the formation of ribosomes, inhibition polypeptide synthesis in cancer cells
- Inhibition of glycolysis, reduced energy supply at both aerobic and anaerobic conditions
- Glucose uptake -> reduced intracellular glucose availability
- Glu -> inhibition of glucose activation
- ICAM-1 -> efficient leukocyte infiltrate of the tumor
- COX-1, COX-2 -> anti-inflammatory activity
- MHC-I -> NK lysis of cancer cells
- PARP (active) -> apoptosis of cancer cells
## Squamous Cell Carcinoma of the Oral Cavity
### 1 and 5 Year FWGE Treatment Results

<table>
<thead>
<tr>
<th>1-Year</th>
<th>FWGE</th>
<th>Control</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0.0%</td>
<td>1</td>
</tr>
<tr>
<td>Local relapse</td>
<td>1</td>
<td>4.3%</td>
<td>12</td>
</tr>
<tr>
<td>Metastasis</td>
<td>1</td>
<td>4.3%</td>
<td>4</td>
</tr>
<tr>
<td>Disease Progression</td>
<td>2</td>
<td>8.7%</td>
<td>13</td>
</tr>
</tbody>
</table>

### 5-Year Survival

FWGE: 17 Patients (74%)
Control: 10 Patients (45.5%)

$P<.05$

FWGE, fermented wheat germ extract.
Adjuvant FWGE (NutraQOL) Improves Overall Survival in High Risk Skin Melanoma Patients

Figure 2. Kaplan-Meier estimate of the cumulative probability of overall survival in stage III skin melanoma patients. Log-rank test: chi-square [1] = 4.72; p = 0.0298.

FWGE, fermented wheat germ extract.
Colorectal Cancer: Point Analysis

In colorectal cancer, following surgery, compared with SOC alone, SOC plus FWGE results in:

- 82% reduction in new recurrences ($P<.01$)
- 67% reduction in metastasis ($P<.01$)
- 62% reduction in deaths ($P<.01$)

“FWGE has supportive value in the treatment of the colorectal cancer”

FWGE, fermented wheat germ extract; SOC, standard of care.

FWGE Safety & Use

- No adverse effects reported in studies
- Clinical experience
  - Occasional mild gastroenteritis distress
  - No increased distress in gluten intolerant patients
- Separate dose from all medication
- Take on a completely empty stomach for one hour before and after dose
- Do not expose to heat or take with hot beverages

FWGE, fermented wheat germ extract
NutraQOL

Indications: QOL, Febrile Neutropenia

Fermented Wheat Germ Extract
Orange flavor
5.5 gram sachets
Recommended Use: 1 sachet daily
Inflammation and Cancer
Inflammation & Prognosis

- **Adenocarcinoma of Pancreas after surgery**
  - CRP < 10 = median survival 21.5 months; > 10 = 8.4 months (p=0.015)\(^1\)
- **Prostate cancer survival 10 yrs after intitial dx & trx**
  - CRP predicted overall survival & prostate cancer specific survival (HR 1.80 [1.01-3.52] p < 0.05)\(^2\)
- **Gastro-esophageal cancer survival after surgery**
  - CRP < 10 = median survival 79 months; > 10 = 19 months (HR:3.53 [1.88-36.64]; p<0.001); \(^3\)
- **Breast cancer survival in HEAL study**
  - CRP decreased overall survival HR 2.27 [1.27-4.08; p=.002] & trend towards decreased disease free survival (p=.07)\(^4\)

Molecular Targets of Curcumin
## Curcumin: Anticancer Studies

### Pancreatic Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients &amp; Design</th>
<th>Curcumin Dose</th>
<th>Curcumin Outcomes</th>
</tr>
</thead>
</table>
| Kanai et al 2011¹   | Phase I/II study in patients with GEM-resistant advanced disease (N = 21)         | 8 g/d              | • Well tolerated  
  • 100% treatment completion rate  
  • Stable disease rate: 28%  
  • Median survival: 161 d (95% CI, 109–223 d)  
  • One-year survival: 19% (95% CI, 4.4%–41.4%)  
  • Improvement in patient-reported cancer- or CT-related symptoms (eg, fatigue, pain, constipation) |
|                     | Chemo: GEM-based                                                                 |                    |                                                                                                                                                  |
|                     | Outcomes: Efficacy, safety, and feasibility                                       |                    |                                                                                                                                                  |
| Epelbaum et al 2010²| Open-label phase II in patients with untreated locally advanced or metastatic disease (N = 17) | 4 g/d BID until disease progression, death, or severe toxicity | • Grade 2–3 GI toxicity in 8 patients  
  • Toxicity-related discontinuation: 29%  
  • CBR: 40%  
  • Local control rate: 45.5%  
  • Median TTP: 2.5 mo (range: 1–12)  
  • Median OS: 5 mo (range: 1–24) |
|                     | Chemo: GEM                                                                        |                    |                                                                                                                                                  |
|                     | Outcomes: Efficacy and safety                                                     |                    |                                                                                                                                                  |
| Dhillon et al 2008³ | Open-label phase II study in patients with histologically-confirmed disease (N = 21) | 8 g/d for ≥ 8 wk   | • No treatment-related toxic effects  
  • Stable disease for > 18 mo (n = 1)  
  • Dramatic but transient tumor response (n = 1)  
  • Stable weight and improved well being for 8 mo despite progression in nontarget lesions (n = 1) |
|                     | No chemo                                                                          |                    |                                                                                                                                                  |
|                     | Outcomes: Efficacy and safety                                                     |                    |                                                                                                                                                  |

BID, twice daily; CBR, clinical benefit response; CI, confidence interval; CT, chemotherapy; GEM, gemcitabine; GI, gastrointestinal; OS, overall survival; TTP, time to progression.

Phosphatidylcholine-Curcumin Complex: Pharmacokinetics

- In rat study, PC-curcumin complex Cmax and AUC were 5-times higher than unbound curcumin
- Small unpublished, single-dose trial demonstrated 450 mg of PC-curcumin complex absorbed as efficiently as 4000 mg unbound *C. longa* extract (95% curcumin)

AUC, area under the plasma concentration time curve; Cmax, maximum plasma concentration; PC-curcumin, phosphatidylcholine-curtcin complex.

## Curcumin

### Gastrointestinal Disorders: Ulcerative Colitis

<table>
<thead>
<tr>
<th>Patients &amp; Design</th>
<th>Dose</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, double-blind, placebo-controlled multicenter trial of curcumin as maintenance therapy for patients in Japan with quiescent UC (N = 89)</td>
<td>Curcumin 1 g BID (n=43) or placebo (n=39) x 6 mo Patients continued on SZ or mesalamine for an additional 6 mo</td>
<td>• Relapse rate lower in curcumin group vs control (4.6% vs 20.5%; P=.04)</td>
</tr>
<tr>
<td>All patients received: SZ (1–3 g/d; median 2 g/d) or mesalamine (1.5–3 g/d; median 2.25 g/d)</td>
<td></td>
<td>• Mean CAI in curcumin group improved from 1.3 at baseline to 1 at 6 mo (P=.038)</td>
</tr>
<tr>
<td>Outcomes:</td>
<td></td>
<td>• Mean CAI in placebo deteriorated from 1 at baseline to 2.2 at 6 mo (P=.0003)</td>
</tr>
<tr>
<td>• CAI</td>
<td></td>
<td>• Patients in curcumin group had improved EI (1.3 at baseline vs 0.8 at 6 mo; P=.0001)</td>
</tr>
<tr>
<td>• EI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BID, twice daily; CAI, clinical activity index; EI, endoscopic index; SZ, sulfasalazine; UC, ulcerative colitis.

Curcumin: General Safety

• Curcumin is well tolerated in patients at doses up to 12,000 mg/d\textsuperscript{1-8}
  – No maximum tolerated dose has been identified in humans\textsuperscript{1}
• Side effects primarily NCI CTCAE toxicity grade 1–2 nausea and diarrhea\textsuperscript{1-8}
  – May be secondary to bulky volume of tablets with higher doses
• Time of side effect onset varies by patient and could begin months after treatment initiation\textsuperscript{1-8}
• Caution using with anti-coagulants & anti-platelets\textsuperscript{9}

NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.
Curcumin: General Safety

Disease Interactions

Gallbladder Disease\textsuperscript{1,2}

- Turmeric can cause gallbladder contractions
- Use with caution in patients with gallstones or gallbladder disease

Surgery\textsuperscript{3}

- Due to its antiplatelet effects, turmeric may cause excessive bleeding if used perioperatively
- Consider discontinuing turmeric at least 2 weeks before elective surgical procedures
- No adverse event cases have been reported related to surgery

InflaQOL

Indications: Radiosensitizing; anti-inflammatory

Curcumin Phytosome

500 mg per capsule

Suggested Use: 2-3 capsules bid
Coenzyme Q10 in the Prevention of Anthracycline Toxicity & Cardiac Protection
Coenzyme Q10: Clinical Studies

Conclusions

- Randomized controlled trials with between-group analyses are lacking
- Optimum blood levels of CoQ10 for prevention of anthracycline-induced cardiotoxicity have not been defined
- An increase in serum CoQ10 levels requires supplementation with ~100 mg/d, but 3 studies used 90 mg/d
- CoQ10 may have a stabilizing effect on the heart
- CoQ10 effect on development of late or delayed cardiomyopathy unknown; no long-term follow-up
- Factors affecting bioavailability include
  - CoQ10 preparation used
  - Individual’s age, sex, race, diet, and nutritional status
  - Stomach contents and alcohol consumption
- CoQ10 not associated with any toxicity in clinical trials

Safety of Coenzyme Q10 in Cancer Patients

• No toxicities reported for daily intake up to 240 mg/d\textsuperscript{1,2}

• Safety not established in pregnant or lactating women\textsuperscript{2}

• Procoagulant effects; structurally similar to vitamin K\textsuperscript{2}

MyoQOL

Indications: Cardioprotective; Energy

Coenzyme Q10 - 100 mg per capsule
Crystal-free CoQ10 with superior absorption compared to other preparations.
Suggested use: 1 capsule BID
Xenoestrogen Free Personal Care Products
Enhancing Quality of Life
### DermaQOL

<table>
<thead>
<tr>
<th>Product</th>
<th>Positioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>DermaQOL</td>
<td>Current Thorne organics skin line- shampoo, conditioner, body lotion, and soaps will be relabeled under OncoQOL- DermaQOL line</td>
</tr>
<tr>
<td></td>
<td><strong>Positioning</strong></td>
</tr>
<tr>
<td></td>
<td>- For patients with breast cancer on anti-estrogens to minimize exogenous estrogens from skin products</td>
</tr>
<tr>
<td></td>
<td>- For patients with alopecia</td>
</tr>
<tr>
<td></td>
<td>- For patients with skin irritation due to disease or chemo</td>
</tr>
<tr>
<td>Shampoo, Conditioner, Lotion Shower gel, Lip balm, Aloe soap</td>
<td>Xenoestrogen free personal care products for patients with hormone receptor positive breast cancer or women at high risk for breast cancer</td>
</tr>
<tr>
<td>Sulfur Balsam soap</td>
<td>Cancer or chemo associated dermatitis</td>
</tr>
<tr>
<td>Aloe Spray</td>
<td>Acute Radiation dermatitis</td>
</tr>
<tr>
<td>Soothing Relief cream</td>
<td>Relief cream for rough skin areas. Use with Aloe Spray for radiation dermatitis</td>
</tr>
</tbody>
</table>
Summary & Discussion