Strategies in Integrative Oncology during Active Treatment

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Biases & Disclosures

- VP of Quality and Education, Emerson Ecologics.
  - Emerson Ecologics distributes brands of professional dietary supplements to healthcare professionals.
- Independent contractor, Naturopathic Specialists
  - Naturopathic Specialists is an outpatient naturopathic oncology practice based in Scottsdale AZ with a remote clinic in Bedford NH (where I practice)
- Diagnosed with breast cancer 2008.
  - I utilized an integrative approach [surgery, chemotherapy, radiation, tamoxifen AND diet, exercise, supplements, acupuncture, shamanic work]
Outline

• Context for Integrative Oncology
  – Cancer specific considerations

• Lifestyle interventions during treatment: focus on diet and exercise

• Antioxidants with chemotherapy and radiation

• Selected co-management interventions
Active conventional treatments (and/or monitoring) by conventional oncologists

 +

Active integrative treatment:
Psychospiritual interventions, nutritional counseling, dietary supplements, acupuncture, manual therapies

 +

Whole person-focused care

= Integrative Oncology
Considerations

• Oncology is highly evidence based
• High stakes: cancer is the 2nd leading cause of death in the U.S.
• People with cancer are emotionally vulnerable to ill-informed hopes, but, conversely, are highly motivated to make significant lifestyle changes.
• Given this context, integrative interventions should be evidenced-based.
Integrative Oncology

• Nearly 70% of those diagnosed with cancer are not satisfied with treatments offered within conventional medicine and utilize complementary and alternative treatments in addition to receiving conventional care.

• Other surveys have estimated the use of CAM among people diagnosed with cancer to be approximately 85%.

Integrative Oncology

• *Integrative medicine* has the potential to be the dominant form of treatment for people diagnosed with cancer

• Supplements are largely under-investigated in the context of oncology.
Chemoprevention

Co-management

Focus of this presentation

Anti-neoplastic

Therapeutic Potential of Natural Medicine in Oncology
Goals of Co-management

- Maintain/Improve Nutritional Status
- Manage side effects of treatment
- Improve Response to Conventional Treatment
- Treat Co-Morbidities and Improve Quality of Life
- Provide additional Anti-neoplastic actions
- Empower the patient through education and options
- Reduce risk of Recurrence
Overwhelmed by Cancer

- Survey conducted in 2006 by the American Association of Cancer Research and the National Cancer Institute
  - Nearly 50% felt “it seems like almost everything causes cancer”
  - Nearly 30% felt that “there’s not much people can do to lower their chances of getting cancer”
  - More than 70% said “there are so many recommendations for preventing cancer, it’s hard to know which ones to follow”
  - Those who are overwhelmed and feel “almost everything causes cancer” end up doing nothing to create a “self-fulfilling prophecy”
- This confusion continues into active treatment.
Take Control of Cancer

- Adoption of lifestyle changes and incorporation of integrative therapies is empowering.
- Empowered patients are less victimized by the disease and its treatments.
- Empowerment engenders hope and optimism, which, in turn, supports health.
- One of the most powerful ways to empower patients is via healthy lifestyle changes.
Lifestyle: Exercise and Prostate Cancer


- In men 65 years or older, a lower risk in the highest category of vigorous activity was observed for advanced (RR=0.33; 95% CI, 0.17-0.62) and for fatal (RR=0.26; 95% CI, 0.11-0.66) prostate cancer.

- No associations were observed in younger men.

- Regular vigorous activity may slow the progression of and reduce mortality from prostate cancer.

Arch Intern Med 2005;165:1005-1010
Lifestyle: Exercise and Breast Cancer

- Women who got the equivalent of at least two to three hours of brisk walking each week in the year before they were diagnosed with breast cancer were 31% less likely to die of the disease than women who were sedentary before their diagnosis. [multivariable hazard ratios (HR) = 0.69 (95% CI, 0.45 to 1.06; P = .045)]

- Compared with women who were inactive both before and after diagnosis, women who increased physical activity after diagnosis had a 45% lower risk of death (HR = 0.55; 95% CI, 0.22 to 1.38), and women who decreased physical activity after diagnosis had a four-fold greater risk of death (HR = 3.95; 95% CI, 1.45 to 10.50).

The Combination Counts

- A combination of diet and exercise cuts risk of dying of breast cancer in half among early stage breast cancer patients.
  - At least eat five servings of vegetables and fruits daily and
  - Walking 30 minutes six days a week

Lifestyle: Obesity and Cancer

- Being overweight or obese is responsible for one in six cancer deaths in the United States.

- In the U.S., obesity accounts for 14% of deaths from cancer in men and 20% in women.
  - Excess weight increases the chance of dying of prostate cancer by 34%.
  - Being overweight more than doubles the risk of dying of breast cancer.

- The current Western diet promotes excess weight with the predominance of refined sugar, simple carbohydrates, fat and meat.
  - These foods add weight, weaken immunity, and promote inflammation – all of which favor cancer growth.

Magheli et al. Urol. 2008
Does a Healthy Diet Really Make a Difference?

- In a small (n = 24) controlled trial over 24 months, daily consumption of vegetable soup increased the median survival time of people with advanced lung cancer from 4.5 months to 15.5 months. (p<0.01)

- In a retrospective study of 239 patients diagnosed with bladder cancer, consumption of at least 1 cup of raw broccoli per month reduced risk of dying of bladder cancer by 57%.

Tang et al. Cancer Epidemiol Biomarkers Prev. 2010
Vegetable soup

• The median survival time and mean survival of stage III and IV patients:
  • control group patients were 4 and 4.8 months
  • vegetable soup group patients were 15.5 and 15 months
  • (p < 0.01).
• No clinical signs of adverse toxicity were found in the 24-month study period.

Figure 1. Survival times of stage III and IV non-small cell lung cancer patients with and without selected vegetables (SV). Patient information is described in Tables 2 and 3 and in Results. MST, median survival time; CI, 95% confidence interval; CG, control group; SVG, group treated with SV. Log-rank test comparing control and treatment groups with respect to their survival time yielded p < 0.01.
Speaking of vegetables, what about antioxidants?

- So-called ‘antioxidants’ have diverse mechanisms of action, the cumulative effect of which may be cytotoxic or reparative to mutated cells.

- Actions of ‘antioxidants’ in cancer cells include:
  - Enhanced clearance of reactive carcinogens via up regulation of cyp and phase II conjugation
  - Decreased DNA oxidation
  - Stimulation of DNA repair
  - Caspase activation (apoptosis)
  - Blocked signal transduction (TK pathways)
  - Blocked metastasis (inhibit MMP enzymes)

- Net effect of antioxidants compounds on cancer cells varies by compound, dosage, and cancer cell type.
Antioxidant Cautions

- Concern about antioxidants stems from their free radical scavenging activity interfering with cytotoxic chemotherapy.
- Cytotoxic therapies that include, though not exclusively, oxidative mechanisms:
  - Platinums (cisplatin, carboplatin, oxaliplatin)
    - Electrophile generation and nucleophilic substitution → DNA damage and alkylating agent
  - Anthracyclines (doxorubicin, epirubicin)
    - Anthracyclines produce ROS production from their redox cycling
  - Alkylating agents (cyclophosphamide, ifosfamide)
    - Intercalate and cross-links DNA, preventing replication; activation is an oxidative process
  - Taxanes (paclitaxel, docetaxel)
    - Promotes ROS generation through enhancing the activity of NADPH oxidase associated with plasma membranes – disrupts cell proliferation of cancer bystander cells
Antioxidants: Friend or Foe?

- **Friend**: During cancer chemotherapy, oxidative stress-induced lipid peroxidation generates numerous electrophilic aldehydes that can attack many cellular targets: slow cell cycle progression of cancer cells and cause cell cycle checkpoint arrest
  - These effects that may interfere with the ability of anticancer drugs to kill cancer cells.
  - The aldehydes may also inhibit drug-induced apoptosis (programmed cell death) by inactivating death receptors and inhibiting caspase activity. The use of anti-oxidants during chemotherapy may enhance therapy by reducing the generation of oxidative stress-induced aldehydes.

- **Foe**: Simultaneous use of antioxidants and chemotherapeutic agents has the potential to attenuate the efficacy of chemotherapy by inducing the expression of enzymes that can detoxify cytotoxic agents.

De Larco et al. Cancer Biol Ther. 2010
Indications for Antioxidants

- More than 100 citations of human studies
- Results differ due to study design, type of malignancy, intervention protocol, and chemotherapy regimen
- Inconsistencies preclude a definitive conclusions
- Total antioxidant status declines during chemotherapy
- Low antioxidant status may be associated with neoplastic activity and subsequent poor health
- Antioxidant supplements may reduce the frequency and severity of toxicity associated with chemotherapy

Safety of Antioxidants and Chemotherapy

- 16 randomized clinical trials that studied the concurrent use of antioxidant supplements and chemotherapy; 6 of those trials included a placebo control.
  - Although no decrements in tumor response rates or survival rates were observed in the studies that reported response data, none of those studies were powered to evaluate these endpoints.
- Simone et al. reviewed 53 studies, of which 36 were observational, on the use of antioxidants and chemotherapy.
  - Conclusion: antioxidants do not adversely effect survival.
  - Note: of the 16 randomized controlled trials reviewed, 10 included fewer than 50 patients, a sample size too small to inspire confidence in findings of equivalent survival.

Systematic Reviews by Block et al: Antioxidants & Chemotherapy

- RCTs only that reported data on chemotherapy toxicity, response or survival
- All oxidative chemotherapy agents were included.
  - Exclusions included radiation therapy
- All cancer types
- Supplements taken concurrently with chemotherapy.
  - Included (not an inclusive list): vitamin C, vitamin E, vitamin A, melatonin, glutathione, curcumin, green tea catechins, lycopene, selenium, carnitine...
  - No whole herb or multi-ingredient supplements

Studies Included

• Chemotherapy and Efficacy
  – 33 RCTs included representing 2446 patients
  – Updated since 2007 with 297 studies screened and 2 RCTs and 420 patients added

• Chemotherapy and Interference
  – 845 articles screened (inception to 2006)
  – 19 RCTs included representing 1554 patients
  – Updated since 2006 with 224 additional studies screened and 5 RCTs and 489 patients added

• Jadad scores evaluated and included in final analysis (majority had Jadad scores of 2/5 and 1/5)

# Results

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NHL = Lymphoma; GSH = glutathione; MLT = melatonin; EA = ellagic acid; NAC = n-acetyl cysteine

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Antioxidants on Response to Chemotx & Survival

Response to Treatment

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* Ascorbic acid (3), Vitamin A (2), Vitamin E (1), NAC (1), ellagic acid (1)

Survival

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* Ascorbic acid (3), Vitamin A (2), Vitamin E (1), NAC (1), ellagic acid (1), lycopene (1)

Antioxidants and Chemotx Toxicity

Effects on Toxicity: AOX vs Control Arm; Combined Data with Updates

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There was consistent evidence of a decrease in toxicity from the addition of antioxidants.

Limitations to Block Reviews

• Poorer quality studies (lower Jadad scores)
• Small sample sizes
• Not standardized for cancer type, stage or intervention
Recent observational studies

• Systematic review of antioxidants in breast cancer
  – Twenty-two observational studies and trials
  – Conclusion: Insufficient evidence to support or negate the value of antioxidants concurrent with chemotherapy.

• However, the observational studies demonstrated that there was reduced recurrence for patients who used vitamins C and E and increased recurrence for those who used combination carotenoids.

Vit. E Interference with Radiation

- RCT (n = 540) patients with head and neck cancer undergoing radiation.

- Patients were given either placebo or a combination of antioxidants (alpha-tocopherol 400 IU, beta-carotene 30 mg) daily throughout radiation therapy and for 3 years afterwards.

- Acute side effects of radiation were significantly less in the antioxidant group, quality of life was not improved significantly, and the rate of local recurrence was higher in the supplemented group (OR 1.37; CI 0.93 to 2.02).

- Long-term follow-up of these subjects showed that at a median follow-up of 6.5 years, all-cause mortality was significantly higher in the treated group (HR 1.38 CI 1.03-1.85).

Bairati, J Clin Oncol, 2005;23(24):5805
Bairati, Int J Cancer, 2006;119(9):2221
Vit E and radiation: smokers

- However, a subgroup analysis of these patients showed that the interactions between antioxidant supplementation and cigarette smoking during radiation therapy were associated with:
  - an increase in both disease recurrence (hazard ratio [HR] = 2.41, 95% confidence interval = 1.25 to 4.64) and
  - cancer-specific mortality (HR = 3.38, 95% CI = 1.11 to 10.34).
- And accounted for all of the increase in mortality risk seen in the original study.
- There was no increase in either of these outcome measures for the nonsmokers.

Bottom line?

- Overall, the evidence is suggestive of a beneficial effect of antioxidant use concurrent with chemotherapy.
- There is no clinical trial evidence of harm from, or interference by, antioxidants during chemotherapy.
- Antioxidants appear to have deleterious effects in smokers receiving radiation and so should be avoided in this population.
- The use of supplemental carotenoids is associated with increased mortality risk and should be avoided in smokers and during active treatment.
Conservative guidelines

- Avoid high dose antioxidant supplementation during days of administration + ½ life of oxidative chemotherapy and radiation unless:
  - Specific antioxidant compound has been studied with specific chemotherapeutic agent or radiation and has known quality of life and survival benefits.
  - Chemotherapy agent does not exert its effects via oxidative mechanism.
  - Quality of life outweighs survival benefit – i.e. palliative chemotherapy.
  - Individual depletion of antioxidants may reduce efficacy of chemotherapy.
Let’s get specific:
Selected co-management interventions

• Ginger and chemotherapy induced nausea [breast cancer]
• DHA and anthracycline chemotherapy [breast cancer]
• Zyflamend & Pomegranate during ‘watchful waiting’ for prostate cancer
• Activated charcoal and CPT-11 [colon cancer]
• Melatonin and NSCLC
• Astragalus and –platin chemotherapy [lung cancer]
• Glutamine and Taxane chemotherapy
Ginger for Nausea and Vomiting

- Meta-analysis in 2000 of RCTs regarding efficacy of ginger for N/V collectively favored ginger over placebo.
  - Gingerols may increase gastric motility, absorb toxic compounds, and block nausea feedback.
  - Galanolactone is a competitive antagonist of 5-HT3 receptors.
- Ginger has anti-nausea properties in cisplatin-induced nausea in both rats and dogs.
  - Cisplatin inhibits gastric emptying, thus causing nausea.
  - Ginger increases gastric motility.


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Breast Cancer: Ginger and chemotherapy induced nausea

• Multisite phase 2/3 randomized trial assessed the efficacy of ginger for chemotherapy-related nausea in cancer patients at member sites of the University of Rochester–affiliated Community Clinical Oncology Program.

• The cohort consisted of 644 primarily female patients (90%) who were randomly assigned to receive a placebo or 0.5 g, 1.0 g, or 1.5 g of ginger in capsule form, which was divided into 2 doses given each day for 6 days.

• Breast cancer was the most common type of malignancy among the participants (66%), followed by alimentary (6.5%) and lung (6.1%) cancers.

Julie Ryan, MD PhD, presented at 2009 Annual Meeting of the American Society of Clinical Oncologists (ASCO)
Ginger and nausea

- All of the patients received 5-HT$_3$ receptor antagonist antiemetics — ondansetron (Zofran, GlaxoSmithKline) or granisetron (Kytril, Roche) — starting on day 1 of all cycles, and began supplementation with either ginger or placebo 3 days before the first day of a chemotherapy cycle.

- All doses of ginger significantly reduced nausea more than the placebo, with the 0.5 g and 1.0 g doses having the greatest effect. That dose is the equivalent of 1/4 to 1/2 a teaspoon of ground ginger.
  - The highest dose might not have worked as well as the lower doses because the patients may have reached the saturation point with the lower doses.
Breast Cancer: DHA and Anthracyclines

• Open-label single-arm phase II study evaluated the safety and efficacy (response rate) as primary end points.
• Intervention was the addition of 1.8 g DHA daily to an anthracycline-based chemotherapy (FEC) regimen.
• Participants were breast cancer patients (n = 25) with rapidly progressing visceral metastases.
• The secondary end points were time to progression (TTP) and overall survival (OS).

Trial supplementation

- 0.5 g capsules of DHASCO containing DHA enriched triglyceride oil of algal origin (44% DHA providing 0.2-g DHA). [Martek Biosciences Corp.]
- Patients received nine capsules of DHASCO daily (representing 1.8g DHA/day), as three capsules at each meal.
- DHA was administered from inclusion before initiation of chemotherapy (a 7–10-day loading period) and then for the 5 months of chemotherapy (except on day of chemo.)
- Patients were explicitly asked to avoid any intake of anti-oxidants.
- FEC chemotherapy (cyclophosphamide, fluorouracil, epirubicin q 3 weeks.)
Study results

• In terms of survival, frontline FEC chemotherapy in this setting normally induces a median TTP ranging from 6 to 13 months and a median OS ranging from 18 to 23 months.

• In this study, the median TTP was 6 months and median OS was 22 months – consistent with expected results.

• However, in the sub-population of patients (n =12) with the highest plasma DHA incorporation, median TTP was 8.7 months and median overall survival reached 34 months.

• Neutropenia was the most common adverse toxicity.
DHA

- This highly unsaturated fatty acid incorporates into cell membrane phospholipids, particularly in fast growing or proliferating cells such as tumor cells.
- DHA enhances the tumor cell chemosensitivity, specifically to anthracyclines.
  - This is likely the result of anthracyclin induced peroxidation of membrane-enriched DHA.

• This increased chemosensitivity applies preferentially to aggressive tumor cells.

• Aggressive tumor cell lines lack glutathione peroxidase induction in response to ROS compared to less aggressive cancer cell lines and are therefore more susceptible to the peroxidizing effects of the DHA.

• Normal cells are even less chemosensitized from DHA incorporation due to their intact glutathione peroxidase antioxidative defenses.
DHA incorporation

Survival and DHA incorporation

Time to Progression

Overall Survival


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Inflammation: The criticality of anti-inflammatory interventions

- Interleukin-6 (IL-6), tumor necrosis factor (TNF), vascular endothelial growth factor (VEGF), and fibroblast growth factors (FGF) are among the inflammatory substances believed to contribute to the growth and progression of cancer.
  - Inflammatory T-cell infiltrates accompany prostate cancer.
- The liberation of multiple proinflammatory cytokines, including IL-1, IL-6, and TNF-a from the tumor microenvironment eventually results in the induction of CRP synthesis from the liver and other tissues.

Central role of NF-κB in Inflammation and Cancer

A self-perpetuating activation cycle leading to sustained oxidant production and chronic inflammation and cancer.
Prostate Cancer & Zyflamend
[manufactured by New Chapter]

• Serving size: 2 Softgels Servings Per Container: 60
  – Rosemary (leaf), 150 mg extract
  – Turmeric, (rhizome), 110 mg extract
  – Ginger, (rhizome), 100 mg extract
  – Holy Basil, (leaf), 100 mg extract
  – Green Tea, (leaf), 100 mg extract
  – Hu Zhang, (Polyganum cuspidatum)(root & rhizome), 80 mg extract
  – Chinese Goldthread, (root), 40 mg extract
  – Barberry, (root), 40 mg extract
  – Oregano, (leaf), 40 mg extract
  – Scutellaria baicalensis, (root), 20 mg extract
Zyflamend – mechanisms of action

- COX-1 and COX-2 inhibition
- Induces apoptosis in LNCaP and PC-3 prostate cancer cell lines
- Affects signaling pathways including JAK-STAT and NF-kB
- Exerts COX-2 independent anti-inflammation
Zyflammend for hgPIN

- Safety and tolerability study (n=29)
- All participants had high grade PIN
- Dose = 3 capsules daily (780mg) x 18 months
- 48% experienced a 25%-50% reduction of PSA
- 22% experiences a >50% reduction of PSA
- Significant reduction in NF-kB associated with decreased PSA.
- No significant adverse toxicity
- By 18 months, conversion to PCa similar to literature (30%) however regression to benign prostate better than reported literature (55% v 18%-22%)

Jillian Capodice, Ph.D. (Ctr for Holistic Urology, Columbia University), Results of a prospective, open-labeled clinical trial of a novel herbal amalgam in men with PIN, presented at Society for Integrative Oncology, November 2008
Prostate cancer: Pomegranate juice and PSA

• A phase II clinical trial for men with rising PSA after surgery or radiotherapy.
• Eligible patients had a detectable PSA > 0.2 and < 5 ng/mL and Gleason score < or = 7.
• Patients were treated with 8 ounces of pomegranate juice daily (Wonderful variety, 570 mg total polyphenol gallic acid equivalents) until disease progression.

Results:
• Mean PSA doubling time significantly increased with treatment from a mean of 15 months at baseline to 54 months post-treatment (P < 0.001).
• In vitro assays comparing pretreatment and post-treatment patient serum on the growth of LNCaP showed a 12% decrease in cell proliferation and a 17% increase in apoptosis (P = 0.0048 and 0.0004, respectively).

 Colon cancer: Phase II Study of Activated Charcoal to Prevent Irinotecan-Induced Diarrhea

• The dose-limiting toxicity of irinotecan (CPT-11; Camptosar) is delayed-onset diarrhea, with an incidence at the grade 3 to 4 level of 20% to 35%.
  • SN38, its active moiety, is responsible by a direct effect on mucosal topoisomerase-I.
  • Activated Charcoal adsorbs free lumenal SN38, thus decreasing toxicity.

• Patients with advanced colorectal cancer received irinotecan 125 mg/m² intravenously once a week.
  • In cycle 1, patients received irinotecan plus charcoal (5 mL aqueous Charcodote [1,000 mg charcoal] plus 25 mL water) given the evening before the irinotecan dose and then tid for 48 hours after the dose.
  • In cycle 2, no activated charcoal was given.
### Table 1. NCI Grading of Diarrhea in Cycles 1 (Ir + AC) and 2 (Ir − AC)

<table>
<thead>
<tr>
<th>NCI Grade Diarrhea</th>
<th>Cycle 1 (Ir + AC) (n = 28)</th>
<th>Cycle 2 (Ir − AC) (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>%</td>
</tr>
<tr>
<td>0</td>
<td>13</td>
<td>46.4</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>32.1</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>14.3</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>7.1</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: NCI, National Cancer Institute; Ir, irinotecan; AC, activated charcoal.
Activated charcoal

Table 2. Loperamide Consumption in Cycles 1 (Ir + AC) and 2 (Ir − AC)

<table>
<thead>
<tr>
<th>Loperamide Consumption (No. of tablets/6-week cycle)</th>
<th>Cycle 1 (Ir + AC) (n = 28)</th>
<th>Cycle 2 (Ir − AC) (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>%</td>
</tr>
<tr>
<td>0</td>
<td>14</td>
<td>50</td>
</tr>
<tr>
<td>1-10</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td>11-20</td>
<td>2</td>
<td>7.1</td>
</tr>
<tr>
<td>21-40</td>
<td>2</td>
<td>7.1</td>
</tr>
<tr>
<td>41-60</td>
<td>1</td>
<td>3.5</td>
</tr>
<tr>
<td>61-80</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>81-100</td>
<td>2</td>
<td>7.1</td>
</tr>
</tbody>
</table>

Abbreviations: Ir, irinotecan; AC, activated charcoal.
Fig 1. Dose intensity (dose delivered/500 mg/m²) of irinotecan (Ir) delivered in cycles 1 (Ir + activated charcoal [AC]; n = 28; solid bars) and 2 (Ir – AC; n = 24; open bars).
Lung cancer: Melatonin and NSCLC

NSCLC
- Metastatic
- Untreated
n = 100

Follow-up x 72 mo

<table>
<thead>
<tr>
<th>Clinical Response</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Chemotherapy alone: Cisplatin 20mg/m/day + Etoposide 100mg/day for 3 consec days q 21 days</td>
<td>51</td>
</tr>
<tr>
<td>Same Chemotherapy + Melatonin: 20 mg given 7 days prior and qd throughout</td>
<td>49</td>
</tr>
</tbody>
</table>

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

* P < 0.05 vs. chemotherapy alone  ** P < 0.01 vs. chemotherapy alone

Lissoni, Chilelli et al., Pineal Res, 2003
Melatonin: NSCLC survival curves
Melatonin and Toxicity: NSCLC

<table>
<thead>
<tr>
<th>Patients</th>
<th>n</th>
<th>Neurotoxicity</th>
<th>Thrombocytopenia</th>
<th>Weight loss &gt; 10%</th>
<th>Asthenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotx</td>
<td>51</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>Chemotx + Mlt</td>
<td>49</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

P < 0.01
P < 0.01
P < 0.001
P < 0.005
• *Astragalus membranaceus* may potentiate host immune function by
  – stimulating macrophage and natural killer cell activity
  – enhancing immune recognition of lung cancer cells by inhibiting production of T-helper cell type 2 cytokines (T-helper cell subsets implicated in the development of immunological tolerance to tumor progression)

• Meta-analysis: Of 1,305 potentially relevant publications, 34 randomized studies representing 2,815 patients met inclusion criteria.

Astragalus and NSCLC

Six-month survival with *Astragalus-based herbs and platinum-based chemotherapy* versus platinum-based chemotherapy alone.
12-month survival with *Astragalus-based herbs and platinum-based chemotherapy* versus platinum-based chemotherapy alone.
### Astragalus and NSCLC

24-month survival with *Astragalus-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.*
36-month survival with Astragalus-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.
Stable/improved Karnofsky performance status with Astragalus-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.
One more for the road:
Glutamine and Paclitaxel-induced neuropathy

- 10 grams po TID L-glutamine for 4 days starting 24 h after completion of paclitaxel
- Statistically significant reduction in severity of peripheral neuropathy [development of moderate to severe dysesthesias and numbness in the fingers and toes (P < 0.05)].
- The degree and incidence of motor weakness was reduced (56% versus 25%; P = 0.04) as well as deterioration in gait (85% versus 45%; P = 0.016) and interference with activities of daily living (85% versus 27%; P = 0.001)

Clin Cancer Res 2001;7(5):1192-7
Table 4  Evaluation of acute peripheral neuropathy symptoms after paclitaxel

<table>
<thead>
<tr>
<th>Moderate-to-severe symptoms</th>
<th>Without glutamine</th>
<th>With glutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n = 33$ (%)</td>
<td>$n = 12$ (%)</td>
</tr>
<tr>
<td>Dysesthesias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fingers</td>
<td>13 (40)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Toes</td>
<td>14 (42)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Numbness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fingers</td>
<td>24 (73)</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Toes</td>
<td>27 (82)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Paresthesias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fingers</td>
<td>18 (56)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Toes</td>
<td>21 (64)</td>
<td>6 (50)</td>
</tr>
</tbody>
</table>

$^a$ NS, not significant.
Fig. 1 Gait evaluated pre- and postpaclitaxel in the glutamine and nonglutamine groups.
Fig. 2 ADL evaluated pre- and postpaclitaxel in the glutamine and nonglutamine groups.
The Future: Integrative Oncology

• Natural therapies combined with active conventional treatment is a rational and effective treatment strategy.
• Clinically proven effective natural therapies exist within an Oncology context.
• An integrative approach to cancer treatment can positively transform cancer care and reduce the suffering caused by this illness.
The Five to Thrive™ Plan
At a glance, here are the secrets to successful THRIVING!

DIET
- Engage your senses
- Eat organic
- Whole foods
- More color
- Spice it up

SPIRIT
- Love
- Laughter
- Joy
- Service
- Soul

MOVEMENT
- Exercise daily
- Strength
- Stretch
- Cardio
- Nature

REJUVINATION
- Rhythm
- Rest
- Relax
- Replenish
- Rehydrate

DIETARY SUPPLEMENTS
- Omega-3
- Probiotics
- Polyphenols
- Antioxidants
- Vitamin D

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www.EmersonEcologics.com/ADAoncology (for Dr. Alschuler’s recommended sources of supplemental nutrients discussed in this webinar)
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