Clinical Considerations of Herbal Product Utilization within the Oncology Patient Population

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FLASCO Fall Session
Disclosures

- I have no conflicts of interest
- Off-label indications for herbal products will be discussed
Objectives

- Review literature regarding the use of dietary and herbal supplements in cancer patients
- Discuss potential effects of common herbal products on treatment safety and efficacy
- Identify barriers in patient and provider education on appropriate use of herbal products
Natural Is Safe

http://threesixtygh.com
Natural Is Also Cytotoxic

http://nativeplantspnw.com

http://meanderingwa.blogspot.com
Definitions

• Complementary Alternative Medicine
  • A group of diverse medical and healthcare systems, practices, and products that are not generally considered part of conventional medicines
  • Includes herbs, dietary supplements, spiritual therapies, biofeedback, hypnosis, acupuncture, homeopathy, naturopathy, Chinese medicine, chiropractic massage, *tai chi*, yoga, electromagnetic therapy, kinesiology, *reiki*, and *qigong*

• Dietary Supplements
  • Herbs, vitamins, minerals, and probiotics

• Herbal Products
  • Supplements containing whole plant or plant extracts consumed as powder, capsule, tablet, or liquid formulations
Herbal Medicines in Cancer

- Prevalence of herb use in cancer patients ranges from 60-80% depending on geographic region and culture
- Role of herbs in cancer
  - Primary or secondary prevention
  - Enhance immune system
  - Reduce side effects from traditional therapies
  - Alternative form of or complement to conventional treatment
Most Common Herbs in the US

- American ginseng
- Asian ginseng
- Black cohosh
- Cranberry
- Echinacea
- Garlic
- Ginger
- Gingko
- Goldenseal
- Green tea extract
- Kava kava
- Milk thistle
- Saw palmetto
- St. John’s wort
- Turmeric
- Valerian

Turmeric

- Overall sales exceed $50 million with 30% growth in the herbal/natural product industry
- Potential benefits as anti-angiogenic, anti-inflammatory, antioxidant, antimicrobial and antiviral
- Evidence in favor
  - Improvement in cachexia and health in patients with colorectal cancer\(^1\)
  - Reduction in PSA rise with polyphenol-rich diet in prostate cancer\(^2\)
  - Decreased proliferation of glioblastoma multiforme\(^3\)
  - Potential reduction in radiation-induced dermatitis\(^4,5\)

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\(^1\)He ZY. Cancer Invest 2011; 29 (3): 208-13
\(^2\)Thomas R. Prostate Cancer Prostatic Dis 2014; 17 (2): 180-6
\(^3\)Gersey ZC. BMC Cancer 2017; 17-99
\(^4\)Ryan JL. Radiat Res 2013; 180 (1): 34-43
\(^5\)Palatty PL. Br J Radiol 2014; 87: 20130490
Turmeric

- Evidence against
  - Over 120 studies yet no successful conclusions exist
  - Poor pharmacokinetic properties and chemical instability make for poor drug candidate
  - Drug-drug interactions: inhibit CYP1A2 2D6 3A4, P-glycoprotein, and anti-tumor activity of doxorubicin and cyclophosphamide
  - Antiplatelet effects


Obervational studies suggest vitamins, minerals, and dietary substances reduce the risk of certain cancers

Clinical trial results do not always support these claims

The 7-year follow up of the SELECT trial observed statistically significant increase risk of prostate cancer in 35,500 healthy males who received 400 IU/day of vitamin E (HR: 1.17; 99% CI: 1.004–1.36 P=0.008)

Anticipating results of large randomized controlled VITAL study using vitamin D and omega-3 for prevention of cancer and cardiovascular disease

More research needed for curcumin, green tea, probiotics, and medicinal mushrooms

Current guidelines recommend against the use dietary supplements in cancer prevention based on current evidence

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1Greenlee H Semin Oncol Nurs 2012; 28 (1): 29-44
2Klein EA et al. JAMA 2011;306(14):1549-1556
3Pradhan AD Manson JE. J Steroid Biochem Mol Biol. 2016;155(10)
Many in vitro and in vivo studies in animals demonstrate herbs and supplements may be used synergistically with anticancer therapy to overcome chemoresistance. 

- Turmeric with cisplatin-resistant lung cancer
- Black cumin with gemcitabine and oxaliplatin in pancreatic cancer
- Asian ginseng metabolite with paclitaxel in multidrug resistance breast cancer
- Milk thistle in doxorubicin-related apoptosis in breast cancer and sensitization of etoposide and doxorubicin in drug-resistant small cell lung cancer

Large human in vivo confirmatory studies are needed.
Intravenous Vitamin C

RESEARCH ARTICLE

CANCER

High-Dose Parenteral Ascorbate Enhanced Chemosensitivity of Ovarian Cancer and Reduced Toxicity of Chemotherapy

Yan Ma,1,2 Julia Chapman,3 Mark Levine,4 Kishore Polireddy,1,2 Jeanne Drisko,2* Qi Chen1,2*

• Phase 1/2a randomized controlled clinical trial in patients with newly diagnosed stage III or IV ovarian cancer
• Twenty seven patients randomized to receive ascorbate or placebo in combination with conventional treatment with carboplatin and paclitaxel
  • Two patients withdrew because they wanted to receive ascorbate
Intravenous Vitamin C

Ma Y et al. Sci Transl Med 6, 222ra18 (2014)
Ascorbate alone demonstrated inhibition of mTOR, enhanced AMPK phosphorylation, and reduced tumor burden in rodent xenograft models.

Greater cell killing was observed when combined with chemotherapy.
Reduced Chemotherapy Toxicity

- Grade 1 and 2 toxicities substantially decreased which was observed in almost all categories of toxicity evaluated.
• Trend toward improvement in overall survival and longer median time to progression or relapse
Acetyl-L-Carnitine

• Endogenous amino acid involved in neuronal protection through acetylation of tubulin
• Reduced incidence and severity of sensory neuropathy in animal models and human trials in diabetes and HIV\(^1,2,3\)
• Small non-controlled pilot studies in cancer patients showed reduction in paclitaxel and cisplatin-induced neuropathy\(^4,5\)

\(^4\)Bianchi G et al. Eur J Cancer 41:1746-1750, 2005
\(^5\)Maestri A et al. Tumori 91:135-135, 2005
409 women with stage I-III breast cancer undergoing adjuvant taxane-based chemotherapy

Excluded patients with pre-existing diabetes, neuropathy or receiving medications known to reduce neuropathy

Randomized to placebo or acetyl-L-carnitine (ALC) 3000 mg per day at start of taxane
• Study Results¹
  • Primary endpoint: absolute difference between arms in FACT-NTX from baseline to 12 weeks
  • FACT-NTX scores were 0.9 lower (95% CI, −2.2 to 0.4; \( P = .17 \)) at week 12 and 1.8 lower (95% CI, −3.2 to −0.4; \( P = .01 \)) at week 24 with ALC than placebo
  • Grade 3 and 4 neurotoxicity observed in 8 patients taking ALC versus 1 with placebo
  • Decrease in functional status in ALC arm
  • No difference in fatigue
  • Breast Cancer Integrative Therapy Guidelines do not recommend ALC due to potential for harm²

# Management of Toxicities

## Symptoms and Herbs with Potential Benefit

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Supplements and Herbs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>Ginger</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Guarana, ginseng, coenzyme q10, acetyl-L-carnitine</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Melatonin, valerian</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Echinacea, bovine colostrum</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>B vitamins, calcium/magnesium, acetyl-L-carnitine, glutathione, glutamine, alpha-lipoic acid</td>
</tr>
</tbody>
</table>
Drug-Drug Interactions

• Major concern in oncology with use of potent and toxic drugs with narrow therapeutic index\textsuperscript{1}

• Retrospective studies observed 27-58% of all patients had at least one drug-drug interaction (DDI)\textsuperscript{2,3}

• Prospective study revealed herbal products were frequently involved in a DDI leading to a clinical intervention\textsuperscript{1}

• Potential for reduced treatment efficacy or toxic adverse effects

\textsuperscript{1}Van Leeuwen RW et al. Ann Oncol 2015; 26: 992-997
\textsuperscript{3}Riechelmann RP et al. J Natl Cancer Inst 2007; 99: 592-600
Drug-Drug Interactions

• Pharmacokinetic
  • Impact on drug absorption, distribution, metabolism, and excretion
  • Primarily through alteration of enzyme systems and drug transporters
  • Adjust drug dosing to counteract interaction

• Pharmacodynamic
  • Additive, synergistic, or antagonistic effect
  • Anticoagulant/antiplatelet, QTc prolongation, CNS depression

Herb-Drug Interactions

• Pharmacokinetic interactions
  • Enzyme inhibition (CYP and UGT)\textsuperscript{1,2,3}
    • St. John’s wort and irinotecan: 42% reduction in levels of SN-38, myelosuppression worsened in absence of SJW
    • St. John’s wort and imatinib: 43% greater imatinib clearance
    • Beware of other supplements shown to reduce bioavailability and efficacy of etoposide, paclitaxel, vinblastine, vincristine
  • Drug transporter inhibition (P-glycoprotein)\textsuperscript{3}
    • Inhibition of P-glycoprotein: curcumin, ginsenosides, green tea, quercetin, silymarin
    • Potentially negative effects on bortezomib, irinotecan, etoposide, methotrexate, paclitaxel, tamoxifen
  • Oral oncolytics!

\textsuperscript{1}Asher GN et al. Am Fam Physician 2017;96(2):101-107
\textsuperscript{2}Yeung KS et al. ASCO Post 2013;4
\textsuperscript{3}Ben-Arye E et al. Cancer 2016; 122: 598-610.
## Herb-Disease Interactions

<table>
<thead>
<tr>
<th>Additive anticoagulant and/or antiplatelet effects</th>
<th>Herbal products with hormonal properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilberry</td>
<td>Soy</td>
</tr>
<tr>
<td>Garlic</td>
<td>Ginseng</td>
</tr>
<tr>
<td>Ginger</td>
<td>Red clover</td>
</tr>
<tr>
<td>Gingko</td>
<td>Licorice</td>
</tr>
<tr>
<td>Dong quai</td>
<td>Dong quai</td>
</tr>
</tbody>
</table>
Antioxidants

• Benefits
  • Reduction in reactive oxygen species leading to decreased cancer progression and adverse effects
  • Chemosensitization and pro-oxidative activity
  • Modest decrease in treatment-related adverse effects

• Risks
  • Possible tumor protection and reduced survival
  • Decreased effectiveness of radiotherapy
  • Insufficient data to recommend use

Fuchs-Tarlovski V. Nutrition 29(2013):15-21
Classes of chemotherapy with highest likelihood of interaction with antioxidants

- Anthracyclines
- Alkylating agents
- Platinum analogs
- Topoisomerase-1 inhibitors
- Topoisomerase-2 inhibitors
- Anti-microtubule agents
- Proteasome inhibitors
Federal Regulation

• 1994 Dietary Supplement Health and Education Act (DSHEA)
  • Defined herbal and botanical products as dietary supplements
  • Experts argue this protects companies more than consumers
  • Exempted them from more rigorous standards used by the FDA for food, drugs, and medical devices
  • Prior to marketing, evidence of safety and claims of efficacy are not required to be submitted to the FDA
  • FDA has authority to remove product from market if it demonstrates a “significant or unreasonable risk”
Federal Regulation

- Health-related claims on labeling describe relationship with supplement and reduced risk of disease or condition
  - Required disclaimer "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease"
- Manufacturers must follow current good manufacturing practices
  - Guidelines for manufacturers to ensure product identity, purity, strength, and composition through manufacturing policies and procedures
  - Does not always ensure quality
- Independent organizations perform quality testing

https://well.blogs.nytimes.com/2015/02/12/107141/
Product Barriers

- Lack of consistent and reliable sources of herbs
  - Species verification, authentication, cultivation
- Lack of definitions and preparation of ingredients
- General safety considerations, i.e. dosing
- Proof of efficacy in specific populations and diagnoses
- Complex and personalized formulations (Chinese medicines)
- Criminal “spiking” of other drugs into herbal products (adulteration)
Clinical Barriers

- Increased patient demand
- Lack of patient disclosure
- Limited well-designed studies
- Risk versus benefit still unknown
- Optimal timing and integration
- Interaction with oral chemotherapy
- Lack of comprehensive education and experience for providers
- Availability of integrative medicine programs

http://busseltondoctors.com.au
Take Home Points

• Perform thorough medication reconciliation
  • Specifically ask about use of over-the-counter products, herbs, and dietary supplements
• Evaluate for drug interactions, avoid supplements with potential harm
• Discuss evidence-based recommendations
  • i.e. healthy diet, exercise, smoking cessation, limit alcohol intake
• Recommend supplements in the form of food, not a pill
• Explain problems of authenticity, labeling, and contaminants
  • Recommend products with quality testing seal of approval
• Refer to integrative medicine
### Clinical Resources

<table>
<thead>
<tr>
<th>Resource</th>
<th>Website</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>About Herbs, Botanicals &amp; Other Products</td>
<td><a href="https://www.mskcc.org/cancer-care/treatments/symptom-management/integrative-medicine/herbs">https://www.mskcc.org/cancer-care/treatments/symptom-management/integrative-medicine/herbs</a></td>
<td>Dietary supplement monographs and interaction checker from Memorial Sloan Kettering Cancer Center</td>
</tr>
<tr>
<td>The Allied and Complementary Medicine Database*</td>
<td><a href="https://www.ebscohost.com/academic/amed-the-allied-and-complementary-medicine-database">https://www.ebscohost.com/academic/amed-the-allied-and-complementary-medicine-database</a></td>
<td>Bibliographic records for more than 600 journals dating back to 1995</td>
</tr>
<tr>
<td>ConsumerLab.com*</td>
<td><a href="https://www.consumerlab.com/">https://www.consumerlab.com/</a></td>
<td>Quality testing of many dietary supplements</td>
</tr>
<tr>
<td>Facts &amp; Comparisons eAnswers*</td>
<td><a href="http://online.factsandcomparisons.com/index.aspx">http://online.factsandcomparisons.com/index.aspx</a></td>
<td>Drug and dietary supplement monographs</td>
</tr>
<tr>
<td>Indiana University Clinical Pharmacology</td>
<td><a href="http://medicine.iupui.edu/clinpharm/ddis/clinical-table">http://medicine.iupui.edu/clinpharm/ddis/clinical-table</a></td>
<td>Lists of drugs metabolized by common cytochrome P450 enzymes</td>
</tr>
<tr>
<td>Lexi-Natural Products*</td>
<td><a href="http://webstore.lexi.com/Store/Individual-Databases/Lexi-Natural-Products">http://webstore.lexi.com/Store/Individual-Databases/Lexi-Natural-Products</a></td>
<td>Software for dietary supplement monographs</td>
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<td><a href="http://micromedex.com/">http://micromedex.com/</a></td>
<td>Drug and dietary supplement monographs with interaction checker</td>
</tr>
<tr>
<td>Natural Medicines*</td>
<td><a href="https://naturalmedicines.therapeuticresearch.com/">https://naturalmedicines.therapeuticresearch.com/</a></td>
<td>Dietary supplement database with interaction checker</td>
</tr>
<tr>
<td>NIH’s National Center for Complementary and Integrative Health</td>
<td><a href="https://nccih.nih.gov/">https://nccih.nih.gov/</a></td>
<td>Evidence-based information on many complementary therapies</td>
</tr>
<tr>
<td>NIH’s Office of Dietary Supplements</td>
<td><a href="https://ods.od.nih.gov/">https://ods.od.nih.gov/</a></td>
<td>Fact sheets and information on many dietary supplements</td>
</tr>
<tr>
<td>NSF International</td>
<td><a href="http://www.nsf.org/services/by-industry/dietary-supplements">http://www.nsf.org/services/by-industry/dietary-supplements</a></td>
<td>Dietary supplement safety information and testing</td>
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Thank you!