Complementary and Alternative Medicine in Breast Oncology

Hope S. Rugo, MD
Professor of Medicine
Director, Breast Oncology and Clinical Trials Education
University of California San Francisco Comprehensive Cancer Center
Chinese Plant Compound Wipes out Cancer in 40 Days, Says New Research

The Lei Gong Teng plant compound led to no signs of tumors after a 40 day period — even after discontinuing the treatment. Published in the journal *Science Translational Medicine* and funded by the National Institutes of Health, even the scientists working on the project were stunned by the anti-cancer properties of the compound.
Why Study CAM?

• 29 - 42% of Americans use some sort of CAM (Eisenberg, 1997, 1999 NHIS survey of 30,801 adults)
  – 629 million visits (> than the number of visits to all primary care providers)
  – Total out-of-pocket expenditures relating to CAM estimated at $27 billion
  – 83% of patients with cancer (Richardson, JCO 2000)

• Fewer than 40% of patients who use CAM told their physicians
  – Nondisclosure related to lack of interest and knowledge on the part of the physician
Alternative Medicine Treatments Go Mainstream (NBC Nightly News (10/12))

- NBC's Brian Williams reported that alternative medicine "is actually so common that now it has a new name. It is called complementary medicine, to compliment the usual practice," and "a lot of it has simply been demanded by patients of their doctors." Dr. Nancy Snyderman introduces Diane Miller, who turned to exercise and acupuncture to help cope with "lymphedema a painful arm swelling caused by invasive treatment."

- Dr. Barrie Cassileth is shown saying: "Acupuncture doesn't cure cancer, but it is extremely helpful in the cancer setting, because it can control multiple symptoms, some of which are not even treatable with mainstream means. Which is why the oldest cancer treatment center in the world offers hypnosis, mind-body therapies and tai-chi. Complementary medicine has gone mainstream."
Definitions

• **Alternative therapy**
  – Treatments outside of conventional medical practice that are designed to treat cancer
  – ‘Alternative Programs of Medical Practice’
    • Direct tumoricidal effects
    • Immune effects

• **Complementary therapy**
  – Treatment given along side of standard medical treatment to:
    • Reduce side effects (includes homeopathy)
    • Enhance the effects of standard therapy
    • ‘Stimulate’ the immune system

• **CAM**: Diverse medical and health care systems, practices and products not generally considered to be part of conventional medicine (www.nccam.nih.gov)
Who uses Complementary and Alternative Medicine (CAM?)

- Review of 26 surveys from 13 countries
  - Up to 64% (ave 31%) used CAM at some point (Ernst 1998)
- Most common in breast cancer patients
  - 63 – 83% use at least one form of CAM
- Most common types of CAM
  - Vitamins, supplements, herbs, acupuncture, massage, chiropractic techniques, mind-body approaches
- Type may vary with ethnicity (Lee, 2000)
  - African American – spirituality
  - Chinese – herbal remedies
  - Latino – dietary therapies and spiritual healing
Why do Patients use CAM?

• Expectations
  – Improve QOL
  – Alleviate symptoms
  – Prolong life
  – Cure disease
  – Boost immune system
  – Reduce toxicity of systemic therapy
  – More ‘natural’

• Benefits
  – More control
  – Lack of known toxicity
  – Added hopefulness

• Disadvantages
  – Cost
  – Interaction with chemo or hormonal therapy
  – GI upset
  – Possible limitation in effective therapy
Implications

• Breast cancer patients who use CAM tend to have higher levels of psychosocial distress

• Use associated with:
  – Younger age, higher socioeconomic level, higher education
  – Higher risk disease

• Treatment typically not reimbursed by insurers
  – Adds to stress from out of pocket costs for approved meds

Burstein 1999, Ganz 2002
Challenges to Interpretation of Published Data

- Lack of standardization of treatment
- Lack of randomized controlled trials
  - A review of > 1000 studies in the world’s literature found only 17 randomized controlled trials
    - Majority are phase II
  - Major shortcomings in trials included
    - Lack of informed consent
    - Small sample size
    - Heterogeneity and lack of details regarding participants
    - No adverse event reporting
    - Measurement of outcomes variable
    - Role of adherence to therapy
Cochrane Review: Homeopathic Medicines for the Adverse Effects of Cancer Treatment

- Evaluated 8 RCT with 664 pts
  - 3 chemotherapy
  - 3 radiation therapy
  - 2 menopausal symptom control

- Conclusions
  - Calendula ointment improved acute dermatitis compared to trolamine and should be explored
  - Traumeel S mouthwash may reduce stomatitis
  - Trials are small and often have some degree of bias
  - Lack of control population
  - Adverse events are rare

Problems with Studies of CAM

• Why is there so little data?
  – Bias against unconventional approaches
  – Difficulty in studying individualized therapy
  – Lack of funding sources and difficulty in publishing results
  – Lack of standardized formulations and knowledge about content

• Lack of research training as well as bias in practitioners limits reporting and research design
What do our Patients Know?

• Little scientific evidence with which to base decisions regarding treatment
• Role of complementary providers in educating patients on efficacy of specific CAM treatment (and about toxicities of ‘Western’ therapies)
• Other sources of information (non peer reviewed!)
  – Internet
  – Health food stores
  – Family members
  – Books!
What Do We Know?
Benefits of CAM

• Potential reduction of side effects, effect on cancer
• Decision making related to use of CAM assists sense of regaining control during times of uncertainty
  – Improves security and sense of hope
• Physician support for decision making process important
Integrative Oncology

The evidence-based use of complementary and supportive therapies in conjunction with conventional cancer therapies

Diet / Physical activity

Mind-body modalities – yoga, meditation, art/music/dance therapy

Body-based therapies – acupuncture, massage

Energy therapies – reiki, qigong, therapeutic touch

Natural products – vitamins, minerals, botanicals, fish oil, glucosamine
Exercise and Dietary Interventions

• Large randomized trials have demonstrated that lifestyle modifications may reduce the risk of breast cancer recurrence
  – Moderate exercise
  – Reduction in dietary fat intake
  – Weight loss
Behavioral Interventions: Reduce Side Effects of Treatment/Psychosocial Distress

- Likely little impact on overall survival or response to therapy
- Mind/body methods of treatment
  - Massage and body therapy
  - Relaxation therapy
  - Guided imagery
    - Reduce pain and stress associated with treatment and diagnosis
    - Reduce distress associated with diagnosis following completion of acute therapy
  - Contemplative self-healing
    - Associated with improved QOL, reduced stress and disability (Loizzo et al, 2010)
Mindfulness-Based Stress Reduction in Breast Cancer Survivors

- 84 women within 18 months of completing treatment randomized to 6 week MBSR designed to reduce arousal to stress or symptoms
  - Intervention resulted in reduction in depression, anxiety, fear of recurrence, higher energy and physical functioning

Lengacher et al, Psychooncology 2009
Role of Support Groups

- Variable results in randomized, controlled trials
  - Initial positive results using support-expressive therapy in terminally ill patients (Speigel, 1989), not reproduced in subsequent studies
  - Clear psychosocial benefit with reduction in levels of distress, improved QOL
- Need for individualization for patients
- Integrated programs may be more successful
- We need to pay more attention to interventions that involve stress reduction techniques, cost and access remain a problem
Acupuncture and Acupressure: Nausea and Vomiting

• Acupuncture
  – Reduces nausea and vomiting associated with chemotherapy
  – May improve pain from cancer as an adjunct to pain medications
    • In conjunction with standard therapy, reduced acute V and often N, but not delayed symptoms

• NIH Consensus Panel in 1997 concluded:
  – ‘Needle acupuncture is effective for postoperative and chemotherapy induced nausea and vomiting’

• Small pilot studies support use of acupressure
Other Treatment Options for CINV

• **Progressive Muscle Relaxation**
  – Meta-analysis: 742 subjects with malignancies receiving highly-emetogenic chemorx (mostly women), trained in Progressive Muscle Relaxation (PMR)
  – Clinically significant reductions in nausea and other symptoms.

• **Music Therapy**
  – Often used with other behavioral techniques, little information

*Luebbert K et al. Psychooncology. 2001:10;490-502.*
Randomized Placebo-Controlled Trial of Acupuncture for AI-related Joint Symptoms

- 43 patients with early stage breast cancer randomized to acupuncture vs sham acupuncture 2x weekly x 6 wks
  - Taking an AI for > 6 mo
  - Worst joint pain score ≥ 3
- Primary outcome
  - Change in joint pain score
    - 43 randomized, 38 evaluable at 6wks
    - > 2 pt improvement in worst BPI-SF
    - 80% TA vs 22% sham (p<0.001)
    - 2/3 found acupuncture to be relaxing
    - 74% wanted to continue
    - 91% would recommend to a friend
    - 59% were willing to pay for acupuncture

A: BPI worse pain score
B: BPI pain severity
C: BPI pain related interference

% change in Brief Pain Inventory Scores

Crew...Hershman. J Clin Oncol; 28:1154-1160 2010
Eligibility:
Age > 45 years
Postmenopausal
Stage I-III breast cancer
Taking an AI for > 3 mo
Worst joint pain score ≥ 4
N=228

Primary Outcome: Change in BPI-SF at 6 weeks
Secondary Outcomes: Change in joint pain, stiffness, function, analgesic use, serum inflammatory biomarkers, Grip strength, Timed Get up and Go, cost, adherence

6, 12, 24, 52 week follow-up

Other Sites: USC; U. of Washington (Fred Hutch); KPNC; Oregon; Beaumont CCOP
Acupuncture for Fatigue Following Adjuvant Chemotherapy for Breast Cancer

- 6 week data
- Significant improvements seen in
  - General fatigue
  - Other aspects of fatigue
    - Physical and mental fatigue
    - Anxiety and depression
  - Quality of life

Molassiotis et al, JCO 2012
Treatment of Hot Flashes

• Cimicifuga racemosa (Black Cohosh)
  – Phytoestrogen and antiestrogenic activity, does not bind to ER$_{\alpha}$
• Randomized trial of Black Cohosh or placebo in patients completing primary therapy for breast cancer +/- tamoxifen (Jacobson, 2001)
  – Treatment period of 2 months
  – No difference in hot flashes in treatment or placebo group
    • Effect of duration of treatment?
    • Doesn’t seem to do any harm….
Yoga

• Ancient Eastern spiritual discipline
• One of the most widely used mind-body therapy in U.S.
• Based in physical postures, breathing, meditation
  – Mastery of body and breath to achieve mastery of the mind.
  – Non randomized data associated yoga with improved QOL, emotional well-being, physical symptoms, distress
Iyengar Yoga* for Persistent Fatigue in Breast Cancer Survivors

- Screened 255 women, randomized 31
  - Completed chemotherapy ≥ 6 mo.
  - Randomized to 12 weeks of Iyengar yoga or health education

- Fatigue severity declined significantly from baseline to post RX and over 3 months of follow-up relative to controls
  - Also noted increase in vigor

- Both groups noted improvement in depression and perceived stress

*A form of Hatha Yoga, focusing on the structural alignment of the physical body through the development of asanas, aims to unite the body, mind and spirit for health and well-being

Bower et al, Cancer 2012
Multicenter, Randomized Controlled Trial of Yoga for Sleep Quality Among Cancer Survivors (YOCAS)

410 survivors suffering from moderate or greater sleep disruption

Mustian K M et al. JCO 2013;31:3233-3241
Evaluation of Supplements for the Treatment of Cancer: Examples

• Pomegranate
  – Polyphenols and oil inhibit aromatase activity
  – Antiproliferative activity of oil and fermented juice
  – Inhibit experimental cancers
Curcumin

- Yellow pigment present in the rhizome of turmeric
- Curcumin has been shown to suppress NF-κB activation induced by various inflammatory stimuli (paclitaxel does not)
- NF-κB activation may play a role in taxane resistance
- In a nude mouse model, the combination of both agents suppressed tumor growth more than each agent alone
- In vitro models support effect

He Joon Kang et al, Breast J, 2009
Soy Products – What is the Data?

- Phyto-estrogens have weak estrogen agonist/antagonist properties
  - Isoflavones
    - Soy beans and other legumes
  - Lignans
    - Cereals, fruit, vegetables, seeds
  - Coumestans
    - Alfalfa and other sprouting vegetables
- Content varies, unpredictable bioavailability
- Bind primarily to Erβ
- Quantification of food intake for prevention unclear
- Data from observational and population studies
Shanghai Soy Study

- 5042 female breast cancer survivors
- Soy intake associated with reduced risk of recurrence and death (11 vs 8% 4 yr recurrence risk; 10 vs 7% MV 4 yr mortality)

Table 3. Soy Food Intake and Tamoxifen Use in Association With Total Mortality and Recurrence Among Women With Estrogen Receptor–Positive Breast Cancer in the Shanghai Breast Cancer Survival Study

<table>
<thead>
<tr>
<th>Quartile of Intake</th>
<th>Soy protein, g/d</th>
<th>No. of Participants</th>
<th>No. of Events</th>
<th>HR (95% CI)</th>
<th>Soy protein, g/d</th>
<th>No. of Participants</th>
<th>No. of Events</th>
<th>HR (95% CI)</th>
<th>Soy protein, g/d</th>
<th>No. of Participants</th>
<th>No. of Events</th>
<th>HR (95% CI)</th>
<th>Soy protein, g/d</th>
<th>No. of Participants</th>
<th>No. of Events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soy protein, g/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5.31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.32-9.45</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.46-15.31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;15.31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoflavones, mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20.01-36.50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36.51-62.68</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;62.68</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

Shu et al, JAMA 2009
Soy Products

• Possible therapeutic uses
  – Hot flashes
    • Dietary phyto-estrogens, soy-protein, soy extract, isoflavone supplement from red clover
    • No differences compared to placebo in randomized studies
  – Prevention
    • Unknown benefit

• What do we tell our patients?
  – Soy in the diet seems to be safe
  – The risks and benefits of pharmacologic doses of soy are unknown
Risks of Alternative and Complementary Treatments

• Herbs
  – Adverse pharmacologic interactions with standard medications
  – Direct toxicity
  – Stimulation of cancer cell proliferation

• Other
  – Delay or deter conventional medical treatment
  – Alter treatment regimens without evidence base
Adverse Effects Associated with Herbal Therapies

• Aristolochia fangchi used to replace a similar herb in a weight loss clinic in Belgium
  – Nephrotoxic with rapidly progressive renal failure in treated patients
  – Carcinogenic with increased uroepithelial cancers (Nortier, NEJM 2000)

• Other examples
  – Comfrey and hepatic veno-occlusive disease
  – Germander and acute hepatitis
  – Ephedra and cardiovascular death
  – Hydrazine and hepatorenal failure

• And others – but overall these are very rare occurrences
Lessons Learned: St. John’s Wort

• Hypericum Perforatum
  – References to use date to early Greeks, over a period of 2,000 years
  – Over the counter herbal product widely used for the treatment of depression
  – Variable results in clinical trials
    • Probably effective in mild to moderate depression
    • Not more effective than placebo in moderate to severe depression
  – Broad mechanism of action
    • Likely mediated by serotonergic, noradranergic and dopaminergic systems
    • Contains large array of biologically active compounds
St. John’s Wort

- Possible drug-drug interactions
  - Inhibition then induction of cytochrome P450 (CYP) 3A4 enzyme activity
  - May increase P-glycoprotein expression resulting in increased drug efflux

- CYP 3A4 substrates represent at least 50% of all marketed medications including
  - Estradiol (OCPs)
  - Cyclosporine, warfarin
  - Irinotecan, topo II inhibitors, others?
  - Simvastatin, SSRIs
  - Etc.....
Rigorous Scientific Studies of Herb/Drug Interactions

• Generally not available
• One study assessed CYP2D6 mediated herb-drug interactions in healthy controls
  – Tested 6 botanical extracts (milk thistle, black cohosh, goldenseal, kava kava, St. John’s wort, echinacea) in successive cohorts of 16 healthy volunteers
  – Randomized to receive extract for 14 days, and a CYP2D6 substrate before and at the end
  – Significant inhibition of CYP2D6 activity seen for goldenseal, but not others

Gurley et al, Mol Nutr Food Res 2008
Adverse Effects of Herbs

• There are NO controls over herbal and dietary supplements
  – Contents are not listed, and descriptions may not be accurate
  • PC-SPES and prostate cancer
    – Multiple contaminants including warfarin
  – The lay press has popularized the belief that herbs and dietary supplements are safer than conventional medicines.
Variation in the Amounts of Active Ginsenosides (Panax Species) and Eleutherosides (Eleutherococcus senticosus) in Ginseng Products in Relation to the Amounts Indicated on Their Labels. Adapted from Harkey et al. (Am J Clin Nutr 2001;73:1101-6), with the permission of the publisher.
Conclusions

• Many complementary therapies have been shown to be beneficial in patients with cancer for control of:
  – Stress, anxiety, depression, pain, nausea and vomiting, persistent fatigue, and likely more
• These approaches should be considered along with mainstream interventions
• It is critical to understand pharmacokinetic interactions between herbs and standard treatments for cancer
• Herbal therapies can and should undergo the same type of clinical testing as pharmaceutical agents
  – Benefits often unproven
  – Patients should exercise caution when combining herbs with chemotherapy