ALTERNATIVE AND COMPLEMENTARY THERAPIES

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Cancer Survivorship

• Currently 12 million+ cancer survivors in the US

• Cancer survivors want to know what they can do beyond conventional treatment to:
  • Improve recurrence and survival rates
  • Prevent and treat side effects of conventional therapies
  • Increase efficacy of conventional therapies
  • Meet needs not addressed by conventional therapies, e.g. stress reduction
  • Treat other comorbidities, e.g. heart disease, diabetes
  • Wellness promotion
Complementary and alternative medicine (CAM) use

**CAM use by US adults**
- 1990: 34% using CAM, 10% seeing CAM provider
- 2007: 38% using CAM, 17% seeing CAM provider

**CAM healthcare costs (2007)**
- 1.5% of US healthcare expenditures ($33.9 billion)
- 11.2% of out-of-pocket health care costs
- $22 billion: Self-care – products, classes, materials
- $11.9 billion: ~354.2 million practitioner visits

**Intended uses of CAM:**
- Health promotion / wellness
- Prevent specific diseases
- Treat specific diseases
- Prevent & treat side effects of conventional therapies
- Meet needs not addressed by conventional therapies

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

**Traditional therapies**
- *Culturally-based health practices*

**Alternative therapies**
- *Used in place of conventional medicine*

**Complementary therapies**
- *Used with conventional medicine*

**Integrative medicine**
- *Evidence-based use of complementary and supportive therapies in conjunction with conventional therapies*
Founded: 1990
Membership: 51 academic medical centers & affiliate institutions in N America

Integrative Medicine:
The practice of medicine that reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic approaches, healthcare professionals and disciplines to achieve optimal health and healing.

www.imconsortium.org
Integrative Oncology

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

**Natural products** – vitamins, minerals, botanicals, fish oil, glucosamine

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

**Body-based therapies** – acupuncture, massage

**Energy therapies** – reiki, qigong, therapeutic touch

**Diet / Physical activity**
Society for Integrative Oncology Evidence-based guidelines

STRONG RECOMMENDATIONS ON USE AFTER DIAGNOSIS

<table>
<thead>
<tr>
<th>Modality</th>
<th>Indication</th>
<th>Quality of Evidence</th>
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<tbody>
<tr>
<td>Natural Products</td>
<td></td>
<td></td>
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<tr>
<td>Dietary supplements</td>
<td>Do not take for prevention</td>
<td>High</td>
</tr>
<tr>
<td>Supplement counseling</td>
<td>Prevent side effects &amp; interactions</td>
<td>Moderate</td>
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<tr>
<td>Mind-Body</td>
<td></td>
<td></td>
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<tr>
<td>Mind-body techniques</td>
<td>Anxiety, pain, QOL</td>
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<tr>
<td>Support groups</td>
<td>Anxiety, pain, QOL</td>
<td>High</td>
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<tr>
<td>Body-Based</td>
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<td></td>
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<tr>
<td>Massage</td>
<td>Anxiety, pain</td>
<td>Low</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>Pain, side effects</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Radiation xerostomia</td>
<td>Moderate</td>
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<tr>
<td>Energy Therapies</td>
<td></td>
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<tr>
<td>Reiki, healing touch</td>
<td>Anxiety</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Pain, fatigue, symptoms</td>
<td>Low</td>
</tr>
</tbody>
</table>

www.nccam.nih.gov/health/providers/clinicalpractice
Deng J SIO 2009
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
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
NATURAL PRODUCTS
Adverse Effects of Supplements

• There are NO FDA controls over herbal and dietary supplements

• Contents are not listed, and descriptions may not be accurate

• The lay press has popularized the belief that herbs and dietary supplements are safer than conventional medicines.
Ginseng

- Genus: Panax, Araliaceae family. perennial plant
- Used in Traditional Chinese Medicine
- Requires 4+ years of growing;
- Active constituents: ginsenosides
Brief Fatigue Inventory at 8 Weeks

Placebo | 750 mg | 1,000 mg | 2,000 mg
--- | --- | --- | ---

Activity interference

Usual fatigue

Barton, DL J. Sup Care 2010
Schema

Randomization

Panax quinquefolius 2,000 mg (ground root Wisconsin ginseng) by mouth BID for 8 weeks

Matching Placebo by mouth BID for 8 weeks

Ginseng was provided in capsules
Both doses taken before noon
Standardized to 3% ginsenoside content
Salivary cortisol and plasma cytokines collected

Barton, DL JNCI 2013
Fatigue Endpoints
Change from baseline, 0-100, higher is better

- Fatigue/Inertia 4 wks:
  - Ginseng: P = .08
  - Placebo

- Fatigue/Inertia 8 wks:
  - Ginseng: P = .008
  - Placebo
What Is Flaxseed?

- Annual plant
- Seeds have physiologic properties
- Contains
  - Lignans (phytoestrogen)
  - Alpha-linoleic acid (omega 3 fatty acid)
  - Fiber
- Estrogen agonist and antagonist effects
**Pilot Flaxseed Study**

Mean percentage of baseline hot flash score and frequency over 6 weeks.

- **Score**
- **Frequency**

Pruthi S et al: J of Soc for Integrative Oncology, 2007
Percent Change from Baseline Hot flash Score

Mean percent change from baseline HF score

Week

Flaxseed
Placeb

Pruthi S et al. Menopause, 2012
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% 4 yr mortality)

<table>
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<tr>
<th>Quartile of Intake</th>
<th>No. of Participants</th>
<th>No. of Events</th>
<th>HR (95% CI)</th>
<th>No. of Participants</th>
<th>No. of Events</th>
<th>HR (95% CI)</th>
<th>No. of Events</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>Soy protein, g/d</td>
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<td>0.90 (0.52-1.57)</td>
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<td>32</td>
<td>0.79 (0.45-1.39)</td>
<td>24</td>
<td>0.73 (0.41-1.32)</td>
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<td>9.46-15.31</td>
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<td>24</td>
<td>1.24 (0.69-2.22)</td>
<td>554</td>
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<td>0.62 (0.35-1.12)</td>
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<td>1.10 (0.65-1.88)</td>
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<td>&gt;15.31</td>
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<td>18</td>
<td>0.65 (0.33-1.29)</td>
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<td>0.61 (0.34-1.08)</td>
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<td>Isoflavones, mg/d</td>
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<td>253</td>
<td>20</td>
<td>1 [Reference]</td>
<td>560</td>
<td>37</td>
<td>0.92 (0.53-1.60)</td>
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<td>36.51-62.68</td>
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<td>26</td>
<td>1.15 (0.63-2.09)</td>
<td>559</td>
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<td>0.74 (0.42-1.29)</td>
<td>21</td>
<td>0.71 (0.39-1.28)</td>
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</table>

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

Soy food intake was treated as a time-dependent variable. Hazard ratios were adjusted for age at diagnosis, TNM stage, chemotherapy, radiotherapy, type of surgery received, body mass index, progesterone receptor status, education level, income, cruciferous vegetable intake, total meat intake, vitamin supplement use, tea consumption, and physical activity. P values for interaction between tamoxifen use and soy food intake were as follows: for soy protein intake, P=0.18 for total mortality and P=0.26 for recurrence or breast cancer-specific mortality; for isoflavone intake, P=0.40 for total mortality and P=0.39 for recurrence/breast cancer-specific mortality.

Shu et al, JAMA 2009
Chemotherapy Induced Peripheral Neuropathy (CIPN)

- Prevention
  - Acetyl L Carnitine
  - Calcium/Magnesium
  - Glutamate/Glutamine
  - Omega 3
  - Vitamin E

- Treatment
  - Acetyl L Carnitine
  - Menthol
Randomized Placebo-Controlled Trial Of Acetyl L-Carnitine For The Prevention Of Taxane Induced Neuropathy (S0715)

History of stage I, II, or IIIA, About to initiate taxane-based chemotherapy

- Paclitaxel at 175 mg/m2 QOW x 4
- Paclitaxel at 80 mg/m2 x 12 w
- TAC (docetaxel 75 mg/m2) q3weeks x 6
- TC 4 or 6

Enrolled: 410/380

Baseline data collection: FACT TAX; Fatigue
NCI CTC - Pill Diaries
Serum + DNA

Follow-up data collection: FACT TAX ; Fatigue
NCI CTC – Pill Diaries
Serum + DNA

Follow-up: 12** weeks, 24 weeks, 36 weeks; 1 year; 2 years

Main Outcome: Change in Taxane subscale of the FACT-TAX

RANDOMIZE

ALC
1 gm (2 pills) TID x 24 weeks

Placebo
2 pills TID x 24 weeks
**Observed Mean FACT-Neurotaxane Subscale Scores (low score=worse CIPN)**

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Observed Baseline*</th>
<th>Observed Week 12</th>
<th>Fitted Week 12</th>
<th>P-value***</th>
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<tbody>
<tr>
<td>ALC</td>
<td>40.6</td>
<td>35.4</td>
<td>35.4</td>
<td>.17</td>
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<td>Placebo</td>
<td>40.9</td>
<td>36.4</td>
<td>36.3</td>
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**Week 24 Analysis**

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<th>Assignment</th>
<th>Observed Baseline**</th>
<th>Observed Week 24</th>
<th>Fitted Week 24</th>
<th>P-value***</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALC</td>
<td>40.6</td>
<td>35.3</td>
<td>35.5</td>
<td>.01</td>
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<tr>
<td>Placebo</td>
<td>41.1</td>
<td>37.5</td>
<td>37.3</td>
<td></td>
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</tbody>
</table>
Cumulative probability of neurotoxicity for ALC and Placebo at 12 & 24 weeks

Hershman et al, JCO 2013
Aromatase Inhibitor Arthralgias

- Glucosamine
- Omega 3
- Vitamin D

- Acupuncture
Phase II study of glucosamine/chondroitin for AI-induced arthralgias (n=46)

**Eligibility Criteria:**
- Postmenopausal
- Stage I-IIIA breast cancer
- AI therapy > 3 mo
- Pain/stiffness in hands/knees ≥ 4/10
- Pain worse after initiating AIs

**Data Collection:**  Clinic visits: 0, 6, 12, 18, 24 weeks

**Primary Endpoints (24 week):**
- Change in composite index of pain, function, and global assessment of disease (OMERACT-OARSI)

**Secondary Endpoints:**
- Change in knee symptoms (WOMAC)
- Change in hand symptoms (M-SACRAH)
- Change in quality of life (FACT-B)
- Change in grip strength
- Adverse events
- Change in estradiol levels (safety)

IND 79,502/S0005

PI: Dawn Hershman, MD, MS
**M-SACRAH: Hands/Wrists**
(Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands)

<table>
<thead>
<tr>
<th></th>
<th>Pain</th>
<th>Stiffness</th>
<th>Function</th>
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</thead>
<tbody>
<tr>
<td>Baseline</td>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
<td><img src="image3.png" alt="Graph" /></td>
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<tr>
<td>12 weeks</td>
<td><img src="image4.png" alt="Graph" /></td>
<td><img src="image5.png" alt="Graph" /></td>
<td><img src="image6.png" alt="Graph" /></td>
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<tr>
<td>24 weeks</td>
<td><img src="image7.png" alt="Graph" /></td>
<td><img src="image8.png" alt="Graph" /></td>
<td><img src="image9.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

≥ 20% Improvement from baseline

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td># patients:</td>
<td>23/36</td>
<td>15/32</td>
</tr>
<tr>
<td>% patients:</td>
<td>63.9%</td>
<td>46.9%</td>
</tr>
</tbody>
</table>
SWOG S0927: Randomized Placebo-Controlled Trial of Omega-3-Fatty Acid for the control of AI-Induced Musculoskeletal Pain

Eligibility:
- Age > 21 years
- Postmenopausal
- Stage I-III ER+ and/or PR+ breast cancer
- Taking an AI for > 3 mo
- Worst joint pain score ≥ 5/10
- N=~246

Follow-up: 0, 6, 12, 24 weeks

Primary Endpoint: Change in worst joint pain/stiffness at 12 weeks

Secondary Endpoints: 1) Dosage and frequency of analgesic use, 2) BPI-SF, 3) WOMAC, 4) M-SACRAH, 5) Global Rating of Change, 6) FACT-B, ES, 7) Hormonal levels, 8) Fasting lipid levels, 9) Adverse events, 10) Inflammatory markers (TNF, CRP), 11) DNA- CYP19, 12) Urine for CTX II

PI: Dawn Hershman, MD, MS
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 hepato-renal failure
• And others – but overall these are very rare occurrences
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 marked medications including
  • Estradiol (OCPs)
  • Cyclosporine, warfarin
  • Irinotecan, topo II inhibitors, others?
  • Simvastatin, SSRIs
  • Etc…..
Randomized trial of antioxidant vitamins to prevent acute adverse effects of radiation therapy in head and neck cancer patients.
BODY-BASED THERAPY

ACUPUNCTURE
ACUPUNCTURE

- Needles stimulate nerve fibers in muscle bed
- Modulation of pain signals in the CNS at level of spinal cord, midbrain and cortex via descending inhibitory pathway
  - Release of endogenous opiate
  - Release of neurotransmitter
- Anti-inflammatory effects
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
  • Meta-analysis (Ezzo et al, J Clin Oncol 23:2005)
    • 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
Acupuncture-Point Stimulation for Chemotherapy-Induced Nausea and Vomiting

Ezzo J et al. JCO 2005;23:7188-7198
Hot flash frequency for acupuncture and venlafaxine groups at pretreatment, post-treatment, and follow-up.

Walker E M et al. JCO 2010;28:634-640
Acupuncture for Pain and Dysfunction After Neck Dissection
Randomized Placebo-Controlled Trial of Acupuncture for AI-related Joint Symptoms

**Eligibility:**
- Age > 21 years
- English or Spanish-speaking
- Postmenopausal
- Stage I-IIIA ER+ and/or PR+ breast cancer
- Taking an AI for > 6 mo
- Worst joint pain score ≥ 3
- N=40

**Primary Outcome:** Change in joint pain score (BPI-SF)

**Secondary Outcomes:** Change in joint pain, stiffness, function (WOMAC,M-SACRAH), QOL (FACT-ES), analgesic use, serum inflammatory biomarkers

Randomization to:
- Acupuncture twice weekly x 6wks
- Sham Acupuncture twice weekly x 6wks
Percent change Brief Pain Inventory scores: 0, 3, 6 wks for true and sham acupuncture groups

- 43 were randomized and 38 were evaluable at 6 weeks
- 80% in the TA group reported >2-point improvement in the BPI-SF worst pain compared to 22% with 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
SWOG/R01: Multicenter Randomized Placebo-Controlled Trial of Acupuncture for AI-related Joint Symptoms

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
MIND-BODY MODALITIES
Mindfulness-Based Stress Reduction in Breast Cancer Survivors

- 84 women 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
Yoga

- Ancient Eastern spiritual discipline
- One of the most widely used mind-body therapy in U.S.
- Based in physical postures, breathing, meditation
  - Masterly 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
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.

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

• 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