Cancer Survivorship for the Primary Care Provider

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Associate Clinical Professor of Medicine
UCSF Helen Diller Family Cancer Center

Cancer Survivors 2012 (U.S.)

Figure 1. Estimated Numbers of US Cancer Survivors by Site

Source: Data Modeling Branch, Division of Cancer Control and Population Sciences, National Cancer Institute
Trends in 5-Year Relative Survival Rates by Year of Diagnosis, All Cancers, United States

![Bar graph showing trends in 5-year relative survival rates.]


High Rates of Long-term Survival Among Breast Cancer Survivors

![Bar graph showing survival rates for breast cancer survivors.]

There are an estimated 2.5 million breast cancer survivors in the United States

Survivorship Issues

• What is the impact on health of being a long-term cancer survivor?

• What is the cost of being a survivor—physically, emotionally, spiritually and financially?

• Is our healthcare system prepared to handle the growing number of people diagnosed with cancer, and the treatment and follow up needed for quality of life?

Differences in cancer follow up care - A world perspective

• In many countries, access to subspecialists is limited

• Primary care MDs and “physician extenders” play a bigger role in health care in general

• Studies in UK and Canada have demonstrated equivalent outcomes when follow up care is provided by a primary care provider
2005 Institutes of Medicine Guidelines on Survivorship

Key Recommendations:
1. **All** cancer stakeholders should work to raise awareness of cancer survivorship and to establish this as a distinct phase of cancer treatment.
2. Each patient should be given a Survivorship Care Plan reimbursed by insurers.
3. Plan components should be developed and refined using evidence-based clinical practice guidelines and assessment tools.


ASCO Treatment Plan and Summary

- Name, age, contact information
- Breast cancer diagnosis
- Surgery (type/dates)
- Patient history, including comorbid conditions
- Adjuvant chemotherapy/radiation therapy (planned and received)
  - Details on agents/doses prescribed (dates initiated/completed)
  - Toxicities (anticipated, experienced)
- Overview of page 2 (not shown)
  - Hormonal therapy (agent, duration, date to be initiated)
  - Trastuzumab (dates, ejection fraction)
  - Provider contacts (including referrals)
  - Pre- and posttreatment comments (eg, baseline assessments, patient counseling, follow-up recommendations)

Reproduced with permission from the American Society of Clinical Oncology. 
<table>
<thead>
<tr>
<th>Follow-Up Care</th>
<th>Providers to Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history and physical examination</td>
<td>• First 5 years</td>
</tr>
<tr>
<td></td>
<td>• Year 6+</td>
</tr>
<tr>
<td>Posttreatment mammography</td>
<td>• First 5 years</td>
</tr>
<tr>
<td></td>
<td>• Year 6+</td>
</tr>
<tr>
<td>Breast self-examination</td>
<td>• N/A</td>
</tr>
<tr>
<td>Pelvic examination</td>
<td>Ob/gyn</td>
</tr>
<tr>
<td>Coordination of care</td>
<td>• First 5 years</td>
</tr>
<tr>
<td></td>
<td>• Year 6+</td>
</tr>
<tr>
<td>Genetic counseling</td>
<td>If indicated, based on risk factors</td>
</tr>
</tbody>
</table>

### Follow-Up Care Visit Frequency

<table>
<thead>
<tr>
<th>Follow-Up Care</th>
<th>Visit Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history and physical examination</td>
<td>• Years 1 to 3: every 3 or 6 months (including key notes for 1st-year visits)</td>
</tr>
<tr>
<td></td>
<td>• Years 4 to 5: every 6 or 12 months</td>
</tr>
<tr>
<td>Mammography</td>
<td>• Every 6 or 12 months as indicated</td>
</tr>
<tr>
<td>Notes</td>
<td>• May include any relevant patient notes and/or recommendations</td>
</tr>
</tbody>
</table>

Breast Cancer Survivorship Care Plan. v1.0 09/07.

Essential Components of Survivorship Care

- **Recurrence, new cancers, late effects**
- **Treating the consequences of cancer and its treatments**
- **Surveillance**
  - Recurrence, second cancers, and assessing medical and psychosocial late effects
- **Prevention**
- **Intervention**
- **Coordination**
  - Interdisciplinary coordination between PCPs and specialists

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Optimal Post-Treatment Surveillance in Cancer Survivors: Is More Better?

Published on Cancer Network (http://www.cancernetwork.com)
Colon Cancer Follow Up – Evidence for recommendations

<table>
<thead>
<tr>
<th>Table 2: Colorectal Cancer Post-Treatment Surveillance: Common Practices, Data, and Author</th>
</tr>
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<tr>
<td><strong>Recommendations</strong></td>
</tr>
<tr>
<td><strong>Colonoscopy</strong></td>
</tr>
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| **Author Recommendations** |
| Colorectal cancer patients at high risk for developing second primary, particularly within 2 yr[55,36] |
| CEA detected most recurrences, particularly in second year[54] |
| Recommended at year 1 and, if normal, at 5-yr intervals thereafter (shorter interval if high-risk polyps found at year 1) |
| Recommended annually for 5 yrs, for those with stage II or III disease denied at high risk for recurrence |

56 year old postmenopausal woman is diagnosed with a Stage I invasive ductal carcinoma

- 1.5 cm grade 2 IDC
- ER positive, PR positive, HER2 negative
- She is treated with a lumpectomy, SLND, and radiation to the breast
- She has recently started on an aromatase inhibitor

She comes to see her primary care MD for routine health care and is extremely worried about breast cancer recurrence. She wants to have lab tests and scans to “make sure her cancer hasn’t come back”.

 Colon Cancer Follow Up – Evidence for recommendations

Table 2: Colorectal Cancer Post-Treatment Surveillance: Common Practices, Data, and Author

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What are the chances that this patient will experience a distant recurrence of breast cancer in the next 10 years?

1. < 10%
2. 10-20%
3. 20-30%
4. Depends on genomic profiling characteristics of her tumor

Should you order any lab tests or scans to follow up on her cancer?

Breast Cancer Follow Up: What to do and What NOT to do

- American Society of Clinical Oncology 2013 Update of the Breast Cancer Follow-Up and Management Guidelines in the Adjuvant Setting (JCO March 1 2013)
  - Routine labs, CT scans, bone scans are not necessary or indicated

- American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast (JCO Nov 20 2007: 5287-5312)
  - TUMOR MARKERS ARE NOT RECOMMENDED
Breast Imaging Recommendations

- NCCN, ACSO, and ACS guidelines recommend follow up mammograms every 6-12 months for affected breast in the setting of breast conserving surgery.

- Breast MRI only indicated for the following:
  - Pts with equivocal mammography and/or US at primary diagnosis
  - Pts presenting with malignant axillary adenopathy and unknown site of primary tumor
  - Patient with extensive or locally advanced cancer undergoing chemotherapy
  - Screening of women at increased (20% to 25%) lifetime risk
    - Known BRCA1 or BRCA2 gene mutation carrier
    - Pt with first-degree relative with a BRCA1 or BRCA2 gene mutation who has not had genetic testing themselves
    - Radiation therapy to the chest between the ages of 10-30 yo
    - Genetic disease such as Li-Fraumeni or Cowden syndrome or one of these syndromes in first-degree relatives

Orel S, JCO Feb 2008

Spectrum of Potential Side Effects

- Hot flashes/night sweats
- Depression
- Weight gain
- Cardiovascular effects
- Chronic fatigue
- Cognitive dysfunction
- Sexual dysfunction
- Genitourinary symptoms
- Arthralgia/joint symptoms
- Other 2nd-malignancy (ie, endometrial cancer)
- Osteoporosis/ bone fractures

Early breast cancer treatments including:
- Radiation therapy
- Chemotherapy
- Monoclonal antibody
- Hormonal therapy

Cardiovascular and Thrombotic Effects in Breast Cancer Survivors

- Many early breast cancer survivors receive a combination of treatments associated with cardiovascular and/or thrombotic side effects

Radiation Therapy  Anthracycline-Based Chemotherapy  Trastuzumab  Hormonal Therapy

Potential Cardiovascular or Thrombotic Adverse Effects


Thrombotic Effects of Cancer Treatment

- Tamoxifen increases the risk of thromboembolic events and cerebrovascular disease by approximately threefold

- A meta-analysis indicated a 29% increase in risk of stroke in women randomized to tamoxifen vs placebo or other therapies

- Concurrent combination of chemotherapy and tamoxifen has been associated with a further increased risk of thromboembolism

Cardiotoxicity Overview

• Extensive data regarding anthracycline mechanism for cardiac injury, but little data regarding treatment

• Over 50% of children with cancer will be exposed to anthracycline based therapy

• Tyrosine Kinase inhibitors (Sunitinib, Imatinib, Dasatinib, etc) have been in use <10 yrs
  – Extensive number of TKI trials ongoing
  – >50% of these trials have pathways that are shared in cardiac signaling

Role of Cancer Treatment in Long-Term Overall and Cardiovascular Mortality After Childhood Cancer

Tukenova M et al. JCO.2010;28:1308-1315
**Doxorubicin: Dose-Relationships**

- Retrospective review of 4018 patients who received doxorubicin
- Definition of doxorubicin-induced CHF: Clinical signs/symptoms of CHF believed to be secondary to doxorubicin by the clinician
- Findings:
  - Overall incidence: 2.2% (n=88).
  - ‘Inflection point’ at 550 mg/m² (7%)


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**A More Recent Look at the Data…**

- Analysis of the placebo-arms of three dexrazoxane trials
- In all trials: Normal LVEF at start
- MUGA performed at baseline & after every 50 mg/m² of doxorubicin
- Examined rate of significant EF drop or symptomatic HF
- Almost identical data later shown in post-anthracycline echos in breast cancer patients in B-31 & N-9831 trials

Adapted from Swain et al. Cancer. 2003;97:2869-79.
Prevention of High-Dose Chemotherapy–Induced Cardiotoxicity in High-Risk Patients by Angiotensin-Converting Enzyme Inhibition

Daniela Cardinali, MD; Alessandro Colombo, MD; Maria T. Sandri, MD; Giuseppina Lamantia, MD; Nicola Colombo, MD; Maurizio Civelli, MD; Giovanni Martinelli, MD; Fabrizio Veglia, PhD; Cesare Fiorentini, MD; Carlo M. Cipolla, MD

Primary end-point:
LVEF decrease >10 percent units + <50%

Circulation 2006

Troponin I Early Positivity

443 pts
High-dose CT
TnI + = 114 pts (24%)

Enalapril
✓ n = 56 pts
✓ started 1 month after HDC
✓ continued for 1 year
✓ physical examination, ECG, ECHO: b,1,3,6,12 months

Controls
✓ n = 58 pts
Secondary end-points
follow-up 12 months

<table>
<thead>
<tr>
<th>Event</th>
<th>Total n=112</th>
<th>ACEI n=54</th>
<th>Controls n=58</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden death</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
<td>2 (3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>4 (2%)</td>
<td>0 (0%)</td>
<td>4 (3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart failure</td>
<td>14 (12%)</td>
<td>0 (0%)</td>
<td>14 (22%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Life-threatening arrhythmias</td>
<td>11 (10%)</td>
<td>1 (2%)</td>
<td>10 (16%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

CUMULATIVE EVENTS
31 (28%) 1 (2%) 30 (52%) 0.001

Cardinale et al. Circulation 2006

Efficiency of Atorvastatin in the Protection of Anthracycline Induced Cardiomyopathy

Table 1
Comparison of Echocardiographic Parameters in the Study Group Between Baseline and Follow-Up Values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statin Group (n = 20)</th>
<th>Control Group (n = 20)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>61.3 ± 7.9</td>
<td>62.9 ± 7.0</td>
<td></td>
</tr>
<tr>
<td>After 6 months</td>
<td>62.6 ± 9.3</td>
<td>55.0 ± 9.5</td>
<td></td>
</tr>
<tr>
<td>Mean change</td>
<td>1.3 ± 3.8</td>
<td>-7.9 ± 8.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>46.5 ± 7.2</td>
<td>47.2 ± 5.2</td>
<td></td>
</tr>
<tr>
<td>After 6 months</td>
<td>46.3 ± 6.8</td>
<td>49.2 ± 6.2</td>
<td></td>
</tr>
<tr>
<td>Mean change</td>
<td>-0.15 ± 4.0</td>
<td>2.0 ± 3.3</td>
<td>0.021</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>30.9 ± 7.2</td>
<td>30.3 ± 5.4</td>
<td></td>
</tr>
<tr>
<td>After 6 months</td>
<td>29.6 ± 6.1</td>
<td>32.3 ± 5.4</td>
<td></td>
</tr>
<tr>
<td>Mean change</td>
<td>-1.35 ± 4.0</td>
<td>2.1 ± 1.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter.
High Mortality Rates Associated with Withdrawal of Beta Blockers and Ace Inhibitors in Chemotherapy-Induced Heart Failure

![Diagram showing LVEF changes upon BB & ACE/I Withdrawal](image)

\[ LVEF \text{ changes upon BB & ACE/I Withdrawal} \]

<table>
<thead>
<tr>
<th>DRUG</th>
<th>HYPERTENSION (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>Hypertension (23% to 34%)</td>
</tr>
<tr>
<td>Sunitinib (Sutent)</td>
<td>Hypertension (&gt;15%)</td>
</tr>
<tr>
<td>Alemtuzumab (Campath)</td>
<td>Hypertension (11%)</td>
</tr>
<tr>
<td>Gemtuzumab (Mylotarg)</td>
<td>Hypertension (&gt;5%)</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>Hypertension (10%)</td>
</tr>
<tr>
<td>Muromanoab-CD3 (Orthoclone® OKT 3)</td>
<td>Hypertension (&lt; 1%)</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>Hypertension (6%)</td>
</tr>
</tbody>
</table>

_Circulation_. 2008;118:S_797
**Drug-Induced HF of FDA Approved Targeted Cancer Therapies**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approval</th>
<th>Action</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib (Nexavar)</td>
<td>2007</td>
<td>VEGF1,2,3/PDGF</td>
<td>1%</td>
</tr>
<tr>
<td>Dasatinib (BMS-354825)</td>
<td>2006</td>
<td>BCR-ABL/SRC C-Kit, PDGF</td>
<td>4%</td>
</tr>
<tr>
<td>Sunitinib (Sutent)</td>
<td>2006</td>
<td>VEGF/PDGF/C-KIT</td>
<td>3-14%</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>2004</td>
<td>VEGF</td>
<td>2-14%</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>2000</td>
<td>ErbB-2/TKI</td>
<td>3-27%</td>
</tr>
<tr>
<td>Imatinib (Gleevec)</td>
<td>2001</td>
<td>C-ABL, C-Kit</td>
<td>1%</td>
</tr>
</tbody>
</table>

**Chemotherapy-induced Neuropathy: Natural History, Prevention, and Treatment**
Persistent Peripheral Neuropathy in Breast Cancer Survivors Treated With Taxane Chemotherapy

• Study design:
  – 35 pts receiving adjuvant paclitaxel for breast cancer followed for a median of 14 months following taxane therapy.
  – Quantitative sensory testing, FACT-Tax and Neuropathic Pain Scale assessments, and serum levels of nerve growth factor were evaluated.

• Results:
  – Overall, significant peripheral neuropathy (> 60%) was seen a year or more after taxane therapy completion

<table>
<thead>
<tr>
<th></th>
<th>Patients With Neuropathy (%)</th>
<th>Patients With Moderate-to-Severe Neuropathy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbness in Hands</td>
<td>66%</td>
<td>34%</td>
</tr>
<tr>
<td>Numbness in Feet</td>
<td>64%</td>
<td>36%</td>
</tr>
<tr>
<td>Pain in Hands</td>
<td>68%</td>
<td>41%</td>
</tr>
<tr>
<td>Pain in Feet</td>
<td>65%</td>
<td>44%</td>
</tr>
</tbody>
</table>

Crew, SABCS 2007, Abstract 6089

Many cancer drugs cause neuropathy

• Paclitaxel
• Docetaxel
• Abraxane
• Ixabepilone
• Vinorelbine
• Oxaliplatin
• Eribulin

• Velcade (proteosome inhibitor)
Selected CIPN Clinical Trials

- Gabapentin
- Glutamine
- Omega 3 Fatty Acids
- Acetyl-L-Carnitine
- Scrambler therapy
- Photon Simulator (Near Infared Light)
Efficacy of gabapentin in the management of CIPN: a phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3).

Chemotherapy Induced Peripheral Neuropathy

N = 115 pts

6 wks Gabapentin 2700 mg/day Placebo

2 wks Washout

6 wks Placebo Gabapentin 2700 mg/day

Cancer 2007 Nov 1;110(9):2110-8.

Mean Pain Intensity

Mean Pain Intensity

Garabentin 2700 mg/day

Placebo

First period

Washout

Second period

P = 0.21

P = 0.37
Glutamine

- Glutamine is a nonessential AA thought to have a neuroprotective role, possibly due to the upregulation of nerve growth factor.
- Two non-randomized studies revealed that oral glutamine was effective in reducing neuropathy associated with high-dose paclitaxel
  - Reduction in numbness, dysesthesias, and motor weakness, as well as a smaller loss of vibratory sensation
- Another study found that glutamine effectively reduced peripheral neuropathy in patients with colorectal cancer being treated with oxaliplatin
- Data are limited by small sample sizes in these studies and the lack of placebo-controlled, randomized clinical trials.

Omega-3 fatty acids are protective against paclitaxel-induced peripheral neuropathy: a randomized double-blind placebo controlled trial.

- Breast cancer patients were randomized to take a placebo or omega-3 fatty acid pearls (640 mg tid) during and one month after paclitaxel chemotherapy
- Clinical and electrophysiological studies were performed before chemo and one month after therapy to evaluate PIPN
- 21/30 pts (70%) assigned to omega-3 fatty acids did not develop PN as compared to 40.7% (11/27 pts) in the placebo group.
- There was a non-significant trend for differences of PIPN severity between the two study groups but the frequencies of PN in all scoring categories were higher in the placebo group ( p = 0.054).

BMC Cancer 2012 Aug 15;12:355
Randomized Double-Blind Placebo-Controlled Trial of Acetyl-L-Carnitine for the Prevention of Taxane-Induced Neuropathy in Women Undergoing Adjuvant Breast Cancer Therapy

- Acetyl-L-carnitine (ALC) is a natural compound involved in neuronal protection.
- 24-week randomized double-blind trial comparing ALC (3,000 mg per day) with placebo in women undergoing adjuvant taxane-based chemo
- Primary objective: To determine if ALC prevents CIPN as measured by the neurotoxicity NTX component of the FACT–Taxane scale at 12 weeks
- Secondary objectives: Changes in 24-week end points, functional status (measured by FACT-Trial Outcome Index [TOI]), fatigue, and NTX grade


Results

- 409 patients were evaluable
- In a multivariate linear regression, week-12 scores were 0.9 points lower (more CIPN) with ALC than placebo (P = .17), week-24 scores were 1.8 points lower with ALC (more CIPN) (P = .01)
- Patients receiving ALC were more likely to have a > 5-point decrease in FACT-NTX scores (38% v 28%; P = .05), and FACT-TOI scores were 3.5 points lower with ALC (P = .03).
- Grade 3 to 4 neurotoxicity was more frequent in the ALC arm (eight v one).
- No differences between arms were observed for FACIT-Fatigue or other toxicities.
Conclusions

• There was no evidence that ALC affected CIPN at 12 weeks
• ALC significantly increased CIPN by 24 weeks
• First study showing that a nutritional supplement increased CIPN
• Patients should be discouraged from using supplements without proven efficacy

Pilot trial of a Patient-specific Cutaneous Electro-stimulation Device (MC5-A Calmare®) for Chemotherapy Induced Peripheral Neuropathy

Thomas J. Smith MD, Patrick J. Coyne RN MSN, Patricia Dodson BSN MA, , Gwendolyn Parker RN MSN, V. Ramakrishnan, PhD

J Pain Symptom Manage 2010 Dec;40(6):883-91
**MC5-A Calmare™**

- Patient-specific *cutaneous* electro-stimulation similar to spinal cord stimulation, but non-invasive

- Creates "non pain" information in packets of rapidly varying impulses, given non-invasively using the patients own nerves

- 30 minute long sessions using EKG pads. Above and below pain, on dermatomes.

- Stinging, then tingling; adjust to tolerance.

- US FDA approved Feb 09.

**Results**

- 18 patients (4 men and 14 women, 16 evaluable)
- Duration of CIPN was three months to eight years
- Most common drugs were taxanes, platinums, and bortezomib

- At the end of the study (Day 10), a 20% reduction in pain scores was achieved in 15 of 16 patients
- Pain score fell 59% from 5.81±1.11 before treatment to 2.38±1.82 at the end of 10 days (P<0.0001).
- Four patients had their CIPN reduced to zero.

- No toxicity was seen. Some responses have been durable without maintenance.
Characterization and Treatment of Chemotherapy Neuropathy (CIN): UCSF Study

- Recruiting patients with (n=400) and without (n=200) chemo-induced neuropathy (CIN) whom received taxanes, platinum-based, or both classes of CTX agents and completed therapy

- Pts will come to the CRS at Mt Zion once for an interview, neurological testing, and a blood collection for a candidate gene analysis
Characterization and Treatment of Chemotherapy Neuropathy: Intervention Arm

- Pts with CIN in their feet may enroll in a RCT of the photon stimulator, a device that delivers near-infrared light

- The LED diode wavelength for this study is 870 nanometers
  - When activated, the photon stimulator is preset to deliver 1800 Joules in a 7 minute treatment period.
  - Patients will receive a total of 8 treatments, to both feet simultaneously, within a 14 day period

What medications breast cancer patients might be taking

And what to worry about with these medications…
Tamoxifen

- Tamoxifen has been shown to decrease disease recurrence and increase overall survival
- Remains an option for pre-menopausal breast cancer patients
- CYP2D6 pharmacogenetics varies and results in different levels of therapeutic efficacy
  - Certain antidepressants should be avoided in patients on tamoxifen
- Tamoxifen use has been associated with endometrial cancer and thromboembolism


Acute effects of tamoxifen and AIs on menopausal symptoms in breast cancer patients

- Prospective study of 181 consecutive postmenopausal women starting hormonal therapy
- Both first line tamoxifen and AIs increased occurrence and severity of hot flashes
- Musculoskeletal pain and dyspareunia significantly increased with AIs
- Sexual interest decreased significantly with tamoxifen
- Younger age was associated with more hot flashes and vaginal dryness

Morales et al, Anti-Cancer Drugs 2004
## Changes in Menopausal Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>AI (Baseline)</th>
<th>AI (3 mo)</th>
<th>TAM (Baseline)</th>
<th>TAM (3 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flashes</td>
<td>54/46/0</td>
<td>23/69/8</td>
<td>52/44/4</td>
<td>13/64/23</td>
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<tr>
<td>Musculoskeletal Pain</td>
<td>36/57/7</td>
<td>18/46/36</td>
<td>56/40/4</td>
<td>40/53/6</td>
</tr>
<tr>
<td>Vaginal Dryness</td>
<td>67/32/0</td>
<td>50/46/4</td>
<td>65/27/8</td>
<td>53/32/15</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>68/21/11</td>
<td>37/37/25</td>
<td>74/18/8</td>
<td>50/38/12</td>
</tr>
<tr>
<td>Decreased sexual interest</td>
<td>63/21/16</td>
<td>31/37/31</td>
<td>53/37/10</td>
<td>21/32/47</td>
</tr>
<tr>
<td>Emotional disturbance</td>
<td>45/50/5</td>
<td>53/47/0</td>
<td>35/56/8</td>
<td>27/64/9</td>
</tr>
</tbody>
</table>

*(no symptom or mild/mod-severe/intolerable)*

## Aromatase Inhibitors

- AIs have been shown to decrease disease recurrence compared with tamoxifen
- Several regimens have been shown to be more effective than 5 yrs of tamoxifen alone
  - 5 yrs of adjuvant AI therapy
  - 2 to 3 yrs of tamoxifen, followed by 2 to 3 yrs of an AI
  - 5 yrs of tamoxifen, followed by 5 yrs of AI

Your breast cancer patient comes in to see you three months later and is complaining of pain in her right hip and also stiffness in her hands. She says she has tried acetaminophen without relief. What should you do?

1. Reassure patient that joint pains are a common side effect of the aromatase inhibitors.
2. Order plain films of her hands and/or hip
3. Order a bone scan
4. Suggest she try NSAIDS and exercise

Musculoskeletal Events: Bone Health

- During treatment, aromatase inhibitors (AIs):
  - Reduce estrogen
  - Are associated with a decline in BMD and an increased risk of fracture
  - Exacerbate the normal progressive loss of BMD in postmenopausal women
- In contrast, tamoxifen may preserve BMD
- Osteoporosis/increased fracture risk are serious health issues for breast cancer survivors
- Patients with osteopenia/osteoporosis prior to initiation of AI therapy may be at the greatest risk

BMD=bone mineral density.
Monitoring of bone density while on an aromatase inhibitor

- Most patients should have a bone density tested within one year of starting an AI
- Recommend patients with normal BMD at baseline to take calcium, vit D, and pursue weight bearing exercise
- Patients with osteopenia should have BMD rechecked one year later to assess change
- Patients with osteoporosis at baseline or during follow up should consider bisphosphonate therapy
- Osteoporosis is not a contraindication to taking an aromatase inhibitor

Aromatase Inhibitors and Bone Loss

IV bisphosphonates may decrease AI-associated bone loss

Z-FAST study evaluated 36-month safety and efficacy of upfront vs delayed IV ZA in decreasing AI-associated bone loss in postmenopausal women with early breast cancer

Brufsky et al. *J Clin Oncol* 25:829-836
Estrogen Deprivation: Vasomotor Symptoms

- Chemotherapy can induce ovarian failure
- Hormone therapy can exacerbate vasomotor symptoms
- Hot flashes and sleep disturbances are common
- May lead to additional physical and psychosocial symptoms including mood lability


Management of hot flashes in breast cancer

- Placebo effect
  - Several placebo controlled studies have shown that placebo can decrease hot flashes by 25% over 3-4 week period
  - 10% of women may >75% reduction
  - 10% will have a 50-75% reduction

Loprinzi et al, Lancet Oncol 2001
Phyto-estrogens

- NCCTG found no evidence of efficacy or toxicity from soy phyto-estrogen equivalent of 3 glasses of soy milk
- Small placebo controlled randomized trial found 50 mg of soy isoflavone equivalent to reduce hot flashes by 45% (c/w 25% in control arm)
- Larger randomized trial of soy preparation found statistically significant decrease in hot flashes at 6 weeks (p=0.03) but not at 12 wks

Quella et al, JCO 2000; Scambia et al, Menopause 2000; Upmalis et al, Menopause 2000

Progestational Agents

- Megestrol acetate (Megace) tested in placebo controlled, double-blinded, randomized crossover trial in men and women
  - Megace reduced hot flashes by 75-80% c/w 20% with placebo
  - Women on tamoxifen had transient increase in hot flashes, resolving in 2-3 wks
  - Well tolerated but many pts d/c’d treatment due to perceived side effects (weight gain)
- Attractive option in metastatic breast cancer pts due to anti-cancer effects of Megace

Other “Safe” Options

- **Vitamin E**
  - Double blind placebo controlled trial in breast cancer survivors
  - 800 IU/day was slightly more effective than placebo, decreased hot flash frequency by one per day

- **Black Cohash**
  - Herb, *Cimicifuga racemosa*, approved in Germany for menopausal symptoms
  - Ongoing trials in US and Europe with mixed results

- **Bellergal**
  - Several small studies showed decrease in hot flash frequency (at 2 wks only) and severity (retrospective)
Venlafaxine for Hot Flashes

Loprinzi et al, Lancet 2000

Gabapentin for Hot Flashes

### Symptoms Encountered

<table>
<thead>
<tr>
<th>Male Survivors</th>
<th>Female Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erectile Dysfunction</td>
<td>Dyspareunia</td>
</tr>
<tr>
<td>Ejaculatory Dysfunction</td>
<td>Vaginal Atrophy</td>
</tr>
<tr>
<td>Loss of Libido</td>
<td>Loss of Libido</td>
</tr>
<tr>
<td>Penile Deformities</td>
<td>Vaginal Dryness or Atrophy</td>
</tr>
<tr>
<td>Loss of Spontaneity</td>
<td>Vaginal Changes (Length, Stenosis)</td>
</tr>
<tr>
<td>Infertility</td>
<td>Infertility</td>
</tr>
<tr>
<td>Negative Body Image</td>
<td>Negative Body Image</td>
</tr>
<tr>
<td>Embarrassment</td>
<td>Embarrassment</td>
</tr>
<tr>
<td>Concerns Regarding Ostomy</td>
<td>Concerns Regarding Ostomy</td>
</tr>
<tr>
<td>Partner Distress</td>
<td>Partner Distress</td>
</tr>
<tr>
<td></td>
<td>Decreased Sensation (Vaginal, Breast)</td>
</tr>
<tr>
<td></td>
<td>Decreased Arousal</td>
</tr>
</tbody>
</table>


### Treatment Options

- **Male Erectile Dysfunction:**
  - Phosphodiesterase-5 Inhibitors (Sildenafil, Tadalafil)
  - Improve erectile dysfunction in up to 67% of prostate cancer and 78% of rectal cancer survivors

- **Female Sexual Dysfunction:**
  - Vaginal lubricants may transiently alleviate dyspareunia
  - Vaginal estrogens may improve urogenital atrophy in appropriate survivors
  - Pelvic floor muscle training and mindfulness-based cognitive interventions may help with pelvic muscle strength, arousal, and overall function

Yang L et al, *Urol Int* 2012, Epub ahead of print
Brollo L et al, *Gynecol Oncol* 2012, Vol 126, p. 328-335
Vaginal Dryness: Interventions Tested

- Non-estrogenic vaginal moisturizers
  - Replens
  - Hyalo Gyn
- Vaginal estrogens (Vagifem® or Estring®)
- Vaginal testosterone cream
- Vaginal DHEA

Do Vaginal Estrogens (Estring or Vagifem) Increase Serum Estradiol in BC pts on AIs?

- Initial study with Vagifem 25 mcg dose suggested yes¹
- Wills 2012 (10 Vagifem 25 mcg and 6 Estring pts on AI)²
  - Prior exposure to vaginal estrogen preparation for >3 months
  - Post-insertion estradiol levels were significantly higher in the Vagifem group than controls
    - 45 vs 3.72 pmol/L (P < .001)
  - No change in mean estradiol at 60d for pts using Estring (15 pmol/L)
- Goldfarb 2012 (26 pts Vagifem 10 mcg)³
  - Estradiol levels were measured by Cisbio RIA, high values were repeated
  - Median change in estradiol from baseline to week 12:
    - 0.2 (range - 3 to 14.6; p=.29)
    - 5/26 (19%) had a sporadic one time modest elevation in estradiol outside of the post-menopausal range

Absorption of Low Dose 10µg Intravaginal 17-β Estradiol (Vagifem®) in Postmenopausal Women with Breast Cancer on Aromatase Inhibitors

Distribution of FSH and Estradiol at Each Time Point
Goldfarb et al, SABCS 2012

Topical Testosterone for Breast Cancer Patients with Vaginal Atrophy Related to AIs: A Phase I/II Study

• 21 postmenopausal women with symptoms of vaginal atrophy
  – Treated with vaginal testosterone cream for 28 days (10 received 300 mcg/d, 10 received 150 mcg/d, 1 not evaluable)
  – Estradiol levels suppressed to < 8 pg/mL at baseline and at one month
  – Dyspareunia (p=.0014) and vaginal dryness improved (p<.001)
  – Improvement in total symptom score was similar for the two doses tested

Witherby et al, Oncologist. 2011;16(4):424-31
Vaginal DHEA for Vaginal Symptoms: A Phase II, Randomized, Double Blind, Placebo-Controlled Study

- PM women with a history of breast or gyn cancers
- Stratified by tamoxifen use, AI use, hysterectomy, cigarette smoking
- Primary endpoint: Effectiveness of twice daily DHEA in reducing vaginal dryness/dyspareunia over 12 weeks
- Fully accrued, preliminary results presented at ASCO 2014

Barton et al

UCSF Trial

A Phase II Study of Vaginal Testosterone Cream vs. ESTRING for Vaginal Dryness or Decreased Libido in Patients with Early Breast Cancer Patients Receiving AIs


Preliminary data presented at SABCS 2009
Manuscript in preparation
Treatment and Evaluation

- 76 patients randomized to 12 weeks of:
  - Testosterone Cream, 1% micronized in velvachol
    - 0.5 gm (5000 mcg) of cream vaginally 3x/week
  - OR
    - Estring 2mg ring inserted vaginally q 12 weeks
- Serum estradiol and testosterone
  - Baseline, weeks 4 &12
  - Testosterone measured in testosterone arm only
  - During treatment, if estradiol elevated > PM range, or 10pg/mL > baseline, value repeated within 1-2 weeks
- GYN exam at baseline and week 12
- Sexual QoL at baseline, week 4 & 12

Results

- 76 pts enrolled, 69 completed 12 wks of assigned treatment
  - 75 evaluable (one did not start rx)
  - 35 in EST arm and 34 in Test arm completed treatment

- Mean baseline estradiol levels for evaluable pts was 20 pg/ml (range <2 – 127 pg/ml) as measured by Quest LC/MS/MS
  - 28 pts (19 in Est arm and 9 in Test arm) had baseline estradiol >10 pg/ml by Quest lab (range 13-127 pg/ml)
  - 9 pts (all in Est arm) had baseline estradiol >16 pg/ml by Dowsett RIA (range 46-178 pg/ml)
  - Baseline Quest and Dowsett lab values were highly correlated (p<0.0001)
  - No association was found between age, weight, or body mass index (BMI) and baseline estradiol levels.
Elevation in Baseline Estradiol was Common

At baseline:
• 28/75 (37%) pts had elevated estradiol (>10 pg/ml) by Quest (Mass Spec)
• 9/63 (14%) pts had elevated estradiol (>16 pg/ml) by Dowset (RIA)

Study Timepoints

<table>
<thead>
<tr>
<th>Pgm/ml estradiol</th>
<th>Persistent Estradiol Elevations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm</td>
<td>Baseline</td>
</tr>
<tr>
<td>Testosterone</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Testosterone</td>
<td>&lt;2</td>
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<tr>
<td>Testosterone</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Testosterone</td>
<td>&lt;2</td>
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</tbody>
</table>

ND* - Not drawn since not required by protocol

End of Treatment
Transient Estradiol Elevations

<table>
<thead>
<tr>
<th>Arm</th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 6-8</th>
<th>Week 12</th>
<th>Week 14-16</th>
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</thead>
<tbody>
<tr>
<td>Estring</td>
<td>&lt;2</td>
<td>5</td>
<td>ND*</td>
<td>70</td>
<td>&lt;2</td>
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<tr>
<td>Estring</td>
<td>&lt;2</td>
<td>&lt;2</td>
<td>ND*</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Estring</td>
<td>&lt;2</td>
<td>29</td>
<td>5</td>
<td>&lt;2</td>
<td>ND*</td>
</tr>
<tr>
<td>Estring</td>
<td>3</td>
<td>20</td>
<td>ND†</td>
<td>ND†</td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>5</td>
<td>23</td>
<td>&lt;2</td>
<td>22</td>
<td>ND**</td>
</tr>
<tr>
<td>Testosterone</td>
<td>&lt;2</td>
<td>&lt;2</td>
<td>ND*</td>
<td>26</td>
<td>&lt;2</td>
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<tr>
<td>Testosterone</td>
<td>31</td>
<td>113</td>
<td>11</td>
<td>&lt;2</td>
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<tr>
<td>Testosterone</td>
<td>&lt;2</td>
<td>21</td>
<td>&lt;2</td>
<td>&lt;2</td>
<td>ND*</td>
</tr>
</tbody>
</table>

ND* - Not drawn since not required by protocol
ND** - Patient declined coming in for repeat blood
ND† - Patient dropped out of study after week 4 due to family emergency

End of Treatment

What we know…and what we need to know

- Urogenital atrophy is a significant concern among breast cancer survivors and impacts compliance and QOL
- Estradiol levels are more variable in PM women on AIs that previously realized
  - “Post-menopausal” range may not be accurate
  - Sporadic fluctuations may occur
- Data suggests that exposure to vaginal estrogens may result in transient increases in serum estradiol in some pts
- Are these elevations substantially more frequent or significant in pts exposed to vaginal estrogen than in control pts?
What other long term health and QOL issues may be in store for your breast cancer patient?

• Weight gain
• Unfavorable lipid profiles?
• Persistent cognitive complaints?
• Chronic fatigue?

Takeaway Messages for HCPs of Cancer Survivors

• Many cancer patients will be cured of their disease
  – Not every symptom is a recurrence of cancer!!
  – Before you order a scan or test, consider contacting patient’s treating oncologist to discuss what test would be best and what the implications will be

• Cancer patients face many long term complications and symptoms from their treatment
  – Take advantage of opportunities to learn about symptoms and side effect management