Health Issues in Breast Cancer Survivors

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UCSF Helen Diller Family Cancer Center

Trends in 5-Year Relative Survival Rates by Year of Diagnosis, All Cancers, United States


Cancer Survivors 2012 (U.S.)

High Rates of Long-term Survival Among 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 physicians and other “physician extenders” play a bigger role in health care in general

GREAT BRITAIN

- In a randomized trial of 296 women with a history of breast cancer, transfer of routine oncology follow-up care to a family physician did not result in an increase in the time to diagnosis of recurrence
  - Patient satisfaction was greater
  - Health service costs were less
  - Anxiety and health related quality of life were unaffected


CANADA

- 968 early-stage breast cancer patients who had completed adjuvant treatment were randomized to follow up in a cancer center or with their own family physician
  - No differences in number of recurrences, deaths, recurrence related serious clinical events
  - No difference in patient reported health-related quality of life

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 Survivorship Care Plan

<table>
<thead>
<tr>
<th>Follow-Up Care</th>
<th>Providers to Contact</th>
</tr>
</thead>
</table>
| Medical history and physical examination | Year 5+  
| Posttreatment mammography       | Year 6+  
| Breast self-examination          | N/A  
| Pelvic examination               | Gyn  
| Coordination of care             | Year 5+  
| Genetic counseling               | If indicated, based on risk factors  

Follow-Up Care Visit Frequency

| Medical history and physical examination | Every 3 to 6 months (including key notes for 1st year visits)  
| Mammography                             | Every 6 to 12 months as indicated  

Notes: May include any relevant patient notes and/or recommendations.


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, data to be initiated)
  - Trastuzumab (dates, ejection fraction)
  - Provider contacts (including referrals)
  - Pre- and posttreatment comments (eg, baseline assessments, patient counseling, follow-up recommendations)


Essential Components of Survivorship Care

- Recurrence, new cancers, late effects
- Recurrence, second cancers, and assessing medical and psychosocial late effects

Treating the consequences of cancer and its treatments

Interdisciplinary coordination between PCPs and specialists

Optimizing Survivorship Care: Practice Considerations and Barriers in the Community

1. Fragmented system of care
2. Lack of training
3. Absence of agreed-upon standards of care
4. Reimbursement
5. Communication


What are the chances that this patient will die of breast cancer in the next 10 years?

1. < 5%
2. 5-10%
3. 10-20%

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

• 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”.

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  - ER positive, PR positive, HER2 negative
  - She is treated with a lumpectomy, SLND, and radiation to the breast
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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”.

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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 mammographic 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

Critical Issues in Cancer Survivorship

- Cancer survivors are at risk for a range of late physical effects and emotional and practical issues due to their primary treatment.

- Physical Effects
  - Fatigue
  - Chronic pain or neuropathy
  - Organ damage
  - Cognitive dysfunction
  - Sexual dysfunction
  - Premature menopause or infertility
  - Osteoporosis
  - Lymphedema

- Emotional Issues
  - Increased concerns about the future and health
  - Sadness, depression, and sense of loss
  - Coping with stopping treatment
  - Relationship issues

- Practical Issues
  - Financial issues and insurance coverage
  - Employment/workplace discrimination
  - Obtaining future medical or life insurance


Symptom/Side-Effect Management

Spectrum of Potential Side Effects

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

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

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\(^1,2\).
- A meta-analysis indicated a 29% increase in risk of stroke in women randomized to tamoxifen vs placebo or other therapies\(^3\).
- Concurrent combination of chemotherapy and tamoxifen has been associated with a further increased risk of thromboembolism\(^4\).


**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.

**Late Mortality Among 5 Year Survivors of Childhood Cancer (CCSS)**

Frequency of Deaths by Different Causes in the Childhood Cancer Survivor Study

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence/progressive disease</td>
<td>1,469</td>
<td>58.0</td>
</tr>
<tr>
<td>Medical Causes of Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Subsequent neoplasm</td>
<td>470</td>
<td>18.5</td>
</tr>
<tr>
<td>- Diseases of the circulatory system</td>
<td>176</td>
<td>6.9</td>
</tr>
<tr>
<td>- Diseases of the respiratory system</td>
<td>67</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Armstrong GT et al. JCO.2009;27:2328-2338

**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%)


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.

Prognostic Value of Troponin I in Cardiac Risk Stratification of Cancer Patients Undergoing High-Dose Chemotherapy

Daniela Cardinale, MD; Maria T. Sandri, MD; Alessandro Colombo, MD; Nicola Colombo, MD; Marina Boeri, MD; Giuseppina Lamantia, MD; Maurizio Civelli, MD; Fedro Peccatori, MD; Giovanni Martinelli, MD; Cesare Fiorentini, MD; Carlo M. Cipella, MD

• 703 patients (216 males)
• Age 47±12 years
• Treated with HDC for poor prognosis malignancies
• Follow-up = 48 months
• MACE (Major Adverse Cardiac Event) incidence

✓ Tn I serum determination:
  • Baseline = before HDC
  • Early = soon after HDC (0,12,24,36,72 hours)
  • Late = 1 month after HDC

Circulation 2004

Results

\[ \begin{array}{ccc}
\text{TnI }+/- & n = 495 \text{ pts (70\%)} \\
\text{TnI }+/- & n = 63 \text{ pts (9\%)} \\
\text{TnI }+/- & n = 145 \text{ pts (21\%)}
\end{array} \]
Left ventricular ejection fraction

Cardinale et al. Circulation 2004

Cardiac Events
3.5 year-follow-up

Sudden death
Cardiac death
Acute pulmonary edema
Heart failure
Asymptomatic ↓ LVEF >25%
Life-threatening arrhythmias
Conduction disturbances requiring PM implantation

* = p<0.01 vs. TnI -/-; # = p<0.01 vs. TnI +/-.

Prevention of High-Dose Chemotherapy–Induced Cardiotoxicity in High-Risk Patients by Angiotensin-Converting Enzyme Inhibition

Daniele Cardinale, MD; Alessandro Colombo, MD; Maria T. Sandri, MD; Giuseppina Lamiunio, MD; Nicoletta Colombo, MD; Maurizio Cividelli, MD; Giovanni Martinelli, MD; Fabrizio Veglia, PhD; Cesare Fionomini, MD; Carlo M. Ghezzi, MD

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

Troponin I Early Positivity

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

Enalapril

Controls

✓ n = 56 pts
✓ started 1 month after HDC
✓ continued for 1 year
✓ physical examination, ECG, ECHO: b,1,3,6,12 months
**Secondary end-points follow-up 12 months**

<table>
<thead>
<tr>
<th></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

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**Valsartan for Prevention of Cardiotoxicity**

- 40 patients with NHL randomized to receive CHOP with or without 80 mg/day of valsartan.
- Acute cardiotoxicity evaluated before and on days 3, 5, and 7 after CHOP.
- CHOP induced transient increases in the LVETD on ECHO, the QTc interval and QTc dispersion on EKG, and in the plasma BNP. All changes returned to nearly normal levels within a week after CHOP (P < 0.001).
- Valsartan significantly prevented all these changes except for the elevation in BNP (P < 0.05).

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**Protective Effects of Carvedilol Against Anthracycline-Induced Cardiomyopathy**

- 25 pts in whom ANT therapy was planned were randomized to carvedilol or control. Carvedilol was given 12.5 mg qd for 6 months during chemo.
- Pts were evaluated with ECHO before and after chemotherapy.
- At the end of 6 months of follow-up, 1 patient in the carvedilol group and 4 in the control group had died.
- Control EF was below 50% in 1 patient in the carvedilol group and in 5 in the control group.
- Mean EF of the carvedilol group was similar at baseline and f/up echocardiography (70.5 vs. 69.7, respectively; p = 0.3), but in the control group the mean EF at f/up ECHO was significantly lower (69.0 vs. 52.3; p = 0.001).

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**Efficiency of Atorvastatin in the Protection of Anthracycline Induced Cardiomyopathy**

<table>
<thead>
<tr>
<th>Table 1 Comparison of Echocardiographic Parameters in the Study Group Between Baseline and Follow-Up Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin Group (n = 20)</td>
</tr>
<tr>
<td>LVEF (%)</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>After 6 months</td>
</tr>
<tr>
<td>Mean change</td>
</tr>
<tr>
<td>LVETD (mm)</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>After 6 months</td>
</tr>
<tr>
<td>Mean change</td>
</tr>
<tr>
<td>LVESD (mm)</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>After 6 months</td>
</tr>
<tr>
<td>Mean change</td>
</tr>
</tbody>
</table>

LVEF = left ventricular ejection fraction; LVETD = 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

Drug-Induced Hypertension with FDA Approved Cancer Therapies

<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>

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)

Paclitaxel-Associated Acute Pain Syndrome: Natural History Study N08C1

Patients scheduled to receive IV paclitaxel at one of 2 dose/schedules
  ➢ 175+ mg/m² Q 3 wks
  ➢ 70-90 mg/m² weekly

Patient questionnaires looking at the incidence and severity of paclitaxel-associated acute pain and sensory neuropathy.

EORTC CIPN-20 Data (Weekly)

Baseline values (%)

P < 0.0001
EORTC CIPN-20 Tingling, Numbness and Pain Scores – Hands (Weekly)

Selected CIPN Clinical Trials
- Gabapentin
- Scrambler therapy
- Photon Simulator (Near Infared Light)

Gabapentin Study Schema

Mean Pain Intensity

Cancer 110(9):2110, 2007
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
Massey Cancer Center of Virginia Commonwealth University

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

Unadjusted CIPN "pain now" scores

Characterization and Treatment of Chemotherapy Neuropathy (CIN)

- 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 the standard of care 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>
</tr>
<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)

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.

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


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

Musculoskeletal Events: Joint Symptoms

- AIs are associated with significantly higher rates of joint symptoms/arthralgias vs tamoxifen
  - Typical onset within 2 months of treatment initiation
  - Symptoms may resolve over time
  - The true etiology and the optimal treatment is not known

ATAC Substudy: Risk Factors for Developing Joint Symptoms

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Joint Symptoms, n (%)</th>
<th>Multivariate OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastrozole</td>
<td>1040 (37.2)</td>
<td>1.31 (1.16-1.47)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Previous HRT</td>
<td>840 (42.3)</td>
<td>1.52 (1.35-1.72)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>485 (38.9)</td>
<td>1.20 (1.04-1.38)</td>
<td>.01</td>
</tr>
<tr>
<td>HR negative</td>
<td>130 (27.7)</td>
<td>0.76 (0.60-1.08)</td>
<td>.02</td>
</tr>
<tr>
<td>Region of origin (vs rest of world)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• UK</td>
<td>563 (30.2)</td>
<td>1.19 (1.01-1.37)</td>
<td>.04</td>
</tr>
<tr>
<td>• North America</td>
<td>803 (47.7)</td>
<td>2.1 (1.81-2.43)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>BMI &gt; 30 kg/m² (vs &lt; 25)</td>
<td>555 (39.3)</td>
<td>1.36 (1.17-1.57)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

- Use of previous HRT led to greater difference in joint symptoms between patients on anastrozole vs tamoxifen

**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)

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### Venlafaxine for Hot Flashes

Loprinzi et al, Lancet 2000

### Gabapentin for Hot Flashes

40% to 100% of cancer survivors report some form of sexual dysfunction (i.e., vaginal dryness, painful intercourse)\(^1\)

- Multiple dimensions\(^2\):
  - Psychological/body image
  - Hormonal treatment effects
- After primary treatment with mastectomy and chemotherapy\(^3\):
  - 34% of women lacked sexual interest
  - ~25% of women report difficulty with arousal, orgasm, or lubrication

Estrogen Deprivation: Sexual Dysfunction Symptoms

- Non-estrogenic vaginal lubricants (Replens)
- Vaginal estrogens (ESTRING or Vagifem)
- Vaginal Testosterone Cream or DHEA

Replens for vaginal dryness

Are vaginal estrogens safe in breast cancer patients? The jury is still out…

Vagifem - Controversial

- Prospectively measured the serum E levels in 6 women on adjuvant AI therapy for early breast cancer using Vagifem
- All were prescribed Vagifem 25 mcg tablets administered qd for 2 wks then twice wkly
- Serum was analyzed for E, FSH and LH at baseline then 2, 4, 7–10 and 12 weeks since commencement of vaginal estradiol
- Serum E levels rose from baseline levels ≤5 pmol/l consistent with AI therapy to a mean 72 pmol/l at 2 weeks. By 4 weeks this had decreased to <35 pmol/l in the majority (median 16 pmol/l) although significant further rises were seen in two women


Transdermal Testosterone in Female Cancer Survivors with Decreased Libido – NCCTG N02C3

4 weeks

Testosterone* 10 mg/day

4 weeks

Placebo**

R

Placebo**

Testosterone* 10 mg/day

*In Vanicream

** Vanicream

JCO 24:469S, 2006 ASCO abstract #8507

Mean Change from baseline:

Free testosterone concentrations

Testosterone

ng/dl

P<.0001

(Norms: 0.3-1.9 ng/dl)

P=0.58

P=0.71

Libido Change from Baseline

Placebo
testosterone
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?

Potential Impact of Lifestyle Factors on Survivorship

| Diet and Weight | • Weight and weight gain may be associated with higher rates of breast cancer recurrence and mortality
|                | • One study suggests that a low fat diet high may be associated with a decreased risk of recurrence
| Exercise       | • Regular moderate exercise may improve survival, particularly in women with hormone receptor-positive tumors
| Alcohol        | • Limited alcohol consumption is recommended by the NCCN to promote a healthy lifestyle

Takeaway Messages for HCPs of Breast Cancer Survivors

- Cancer patients face many long term complications and symptoms from their treatment

- 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

What Are the Most Essential Aspects Required to Optimize Survivorship Care?

- Monitoring for recurrence
- Managing treatment-related side effects
- Adherence to therapy
- Overall wellness promotion
- Emotional health
- Coordination of care
- Monitoring late effects of treatment
- Patient/caregiver counseling/education about recurrence risk
- Referrals
- Other


Diet and Weight

3. Holmes MD et al. JAMA. 2009;293:2479-2486