Overcoming side effects of aromatase inhibitors

Magdolna Solti, MD
February 12, 2014
ATLAS and aTTom

Update on final results

Adjuvant Tamoxifen Treatment: offer more?
10 years of tamoxifen vs 5

• 13,799 women with ER positive disease completed 5 years of tamoxifen, then were randomised to:
  
• CONTINUE to year 10, or
• STOP at year 5.
ER+ disease, 5 yrs tam. vs 0, and 10 yrs vs 5 yrs. Breast cancer death rate ratio (RR), by period

<table>
<thead>
<tr>
<th></th>
<th>5 yrs tam vs 0: meta-analysis (n=10,645)</th>
<th>10 yrs tam vs 5: ATLAS trial (n= 6846)</th>
<th>10 yrs tam vs 5: aTTom study (n=6953)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yrs 0-4</td>
<td>0.71</td>
<td>(1.0)</td>
<td>(1.0)</td>
</tr>
<tr>
<td>Yrs 5-9</td>
<td>0.66</td>
<td>0.97</td>
<td>1.03</td>
</tr>
<tr>
<td>Yrs 10+</td>
<td>0.73</td>
<td>0.71</td>
<td>0.77</td>
</tr>
</tbody>
</table>
In estrogen positive early breast cancer 10 yrs of tamoxifen...

- Reduces recurrence by 25%
- Reduces breast cancer mortality by 23-29%
Background

• Aromatase inhibitor (AI) therapy has superior disease free and overall survival compared to tamoxifen\(^1\)
• Early discontinuation due to toxicity occurs in 20-30% of patients\(^2\)
• Non-adherence to AI therapy has been associated with increased mortality\(^3\)

\(^1\) Burstein HJ et al JCO, 2010; \(^2\)Henry NL et al JCO 2012; \(^3\)Hershman DL et al BCRT 2011
Associations Between Baseline Patient-reported Symptoms and Discontinuation of Adjuvant Aromatase Inhibitor Therapy

NL Henry, KM Kidwell, DF Hayes, AM Storniolo, DA Flockhart, V Stearns, DJ Clauw, DA Williams for the Consortium on Breast Cancer Pharmacogenomics (COBRA)

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Background

- Early AI discontinuation is primarily due to musculoskeletal symptoms\(^1\)
- Breast cancer survivors have high rates of other reported symptoms\(^2\)
  - Mood disorders
  - Cognitive dysfunction
  - Insomnia
  - Fatigue

\(^{1}\) Henry N et al JCO 2012; \(^{2}\)Bower JE JCO 2008
Fatigue, depression, and sleep disturbance frequently co-occur in breast cancer patients and survivors.
Hypothesis

• Patient-reported symptoms present prior to AI initiation may impact persistence with AI therapy
Exemestane and Letrozole Pharmacogenetics (ELPh) Trial

- Postmenopausal
- Early Stage BC
- First line AI or after TAM
- N=503

R

- Exemestane
  - 25 mg PO qD x 2 years

- Letrozole
  - 2.5 mg PO qD x 2 years

0, 1, 3, 6, 12, 24 mo:
- QOL assessments
- Serum hormone concentrations

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Patient Characteristics: ELPh Trial

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>59 years</td>
</tr>
<tr>
<td>Mean body mass index</td>
<td>29.1 kg/m²</td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>44.5%</td>
</tr>
<tr>
<td>- Prior taxane</td>
<td>32.1%</td>
</tr>
<tr>
<td>Prior tamoxifen</td>
<td>36.5%</td>
</tr>
</tbody>
</table>
Rates of AI Treatment Discontinuation within 1 year: ELPh Trial

503 enrolled subjects

3 not randomized

Randomization

Letrozole (n=252)

172 continued AI (74.1%)

20 discontinued for other reasons

Discontinued for toxicity (140/449, 31.2%)

Letrozole 60

Exemestane 80

Exemestane (n=248)

137 continued AI (63.1%)

31 discontinued for other reasons

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Baseline Symptoms and Discontinuation

Symptoms BEFORE AI Initiation

- Depression
- Anxiety
- Poor sleep
- Feeling tired
- Forgetfulness
- Difficulty conc.
- Joint pain
- Vaginal dryness

Discontinued AI
- OR 1.76
- p < 0.001
- OR 1.91
- p = 0.002
- OR 1.66
- p = 0.015

Continued AI
Baseline Symptom Burden and AI Discontinuation in 1 Year

<table>
<thead>
<tr>
<th>% patients who discontinued AI therapy</th>
<th>% with symptoms at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 symptoms</td>
</tr>
<tr>
<td></td>
<td>26%</td>
</tr>
</tbody>
</table>

OR 1.6
OR 2.5

Symptoms:
- Depression
- Anxiety
- Poor sleep quality
- Tired feeling
- Difficulty concentrating

p=0.007
Summary

- Non-persistence with AI therapy is associated with patient-reported symptoms BEFORE initiation of AI therapy.
- Risk of early discontinuation increases with increasing symptom burden.
- Upfront management of constellation of symptoms may be beneficial.
Clinical Relevance

- Possible interventions:
  - Select alternate therapy (tamoxifen, other AI)
  - Pharmacologic therapy (SSRI, SNRI)
    - SWOG S1202: duloxetine vs. placebo
  - Non-pharmacologic therapy (behavioral intervention, exercise)
Randomized Trial of Exercise vs. Usual Care on Aromatase Inhibitor-Associated Arthralgias in Women with Breast Cancer

Melinda Irwin, Brenda Cartmel, Cary Gross, Elizabeth Ercolano, Martha Fiellin, Scott Capozza, Marianna Rothbard, Yang Zhou, Maura Harrigan, Tara Sanft, Kathryn Schmitz, Tuhina Neogi, Dawn Hershman, Jennifer Ligibel
Aromatase Inhibitors and Arthralgia

- Arthralgia, defined as pain or stiffness in the joints, is reported in up to 50% of patients within 6 months of initiating therapy\(^1,2\)
- Arthralgia is the most common reason for drug discontinuation and poor adherence to AI-s\(^2\)

\(^1\)Sestak et al. Lancet Oncol 2008; \(^2\)Hershman DL et al JCO 2010
Benefits of Exercise

- Exercise may be an especially attractive strategy to improve:
  - AI side effects
  - Quality of life
  - Adherence to AI therapy
  - Overall survival
Primary Aims: To examine, in 121 women who have been taking an AI for at least 6 months and are experiencing at least mild arthralgia, the yearlong effect of exercise vs. usual care on side effects of AI use:

- Severity of arthralgia
- Endocrine-related quality of life (QOL)
- Mechanisms influencing the effect of exercise on arthralgia severity
  - Pro-inflammatory biomarkers
  - Bone mass, Lean body mass, Body weight and Body fat
  - Cardiorespiratory fitness
  - Muscular strength
  - Psychological outcomes
Patient Characteristics

- 60 yrs old
- Mostly stage I and II
- Physically Inactive and Overweight
- Two years post-diagnosis
- Taking AI for 1.5 years
- No baseline differences in characteristics between women randomized to exercise vs. usual care
Study Groups

• Yearlong Exercise Program
  – Twice weekly supervised strength training sessions
  – Six common strength-training exercises, 8-12 reps, 3 sets
  – 2.5 hrs/wk of moderate-intensity aerobic exercise (e.g., treadmill)
  – Heart rate monitors to determine intensity

• Usual Care
  – Provided written information (e.g., DHHS physical activity recommendations)
  – Monthly phone calls to assess AI adherence
  – End of study visit with exercise trainer
Brief Pain Inventory (BPI)

- Arthralgia is commonly assessed via the Brief Pain Inventory (BPI) score, with
  - Worst pain
  - Pain severity
  - Pain interference
  reported on a 0-10 scale.
- Developed for use in cancer patients.
- Mild pain is 3-4
- Moderate pain is 5-7
- Severe pain is 8-10
- Reliability: Cronbach alpha 0.77-0.91


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## Change in Exercise and Body Weight

<table>
<thead>
<tr>
<th>Baseline to 12 Month Changes in Physical Activity (N=121)</th>
<th>Exercisers</th>
<th>Usual Care</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Physical Activity min/wk Mean (SD)</td>
<td>158.9 (136.3)</td>
<td>48.9 (86.1)</td>
<td>.0001</td>
</tr>
<tr>
<td>Attendance to twice-weekly strength training sessions Mean (SD)</td>
<td>70% (28%)</td>
<td>not applicable</td>
<td></td>
</tr>
<tr>
<td>% Change in VO$_2$max Mean (SD)</td>
<td>+6.5% (8.7%)</td>
<td>-1.8% (11.3%)</td>
<td>.0013</td>
</tr>
<tr>
<td>% Change in body weight Mean (SD)</td>
<td>-3.0% (6.9%)</td>
<td>0.0% (4.8%)</td>
<td>.026</td>
</tr>
</tbody>
</table>
Baseline Brief Pain Inventory (BPI) Scores

- Worst Pain
- Pain Severity
- Pain Interference

Controls vs Exercisers
12 Month Change in BPI Scores

Change in Pain Score

Worst Pain | Pain Severity | Pain Interference

* Controls | * Exercisers

*p < .05
12 Month Change in BPI Scores by Dose of Exercise

-2  -1.5  -1  -0.5  0  0.5  1

Worst Pain  Pain Severity  Pain Interference

Usual Care  <80% adherence  80%+ adherence

p < .05 compared to usual care
Potential Mechanisms of Decreased Arthralgia with Exercise

- Increased muscular strength and increased resistance to musculoskeletal injury.
- Improved aerobic conditioning (improved blood flow and maximal oxygen consumption)
- Improved range of motion
- Weight and body fat loss
- Decreased systemic inflammation levels
- Improvement in pain threshold
- In turn, making activities of daily living easier to perform resulting in attenuated pain sensations and decreased arthralgia severity.
Summary

- A yearlong exercise program decreased arthralgia by 30% to mild pain levels

- Improvement in pain has been shown to be better than with glucosamine, vitamin D and acupuncture
Change From Brand To Generic Aromatase Inhibitors And Hormone Therapy Adherence For Early Stage Breast Cancer

Dawn L. Hershman, Jennifer Tsui, Jay Meyer, Sherry Glied, Grace Hillyer, Jason Wright, Alfred I. Neugut

Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center and OptumInsight

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Cost of Oral Drugs

- Cost of oral medications have increased
  - $40 billion in 1999 $234 billion in 2008
- Pharmacy plans have some form of cost-sharing
  - Co-payments
  - Deductibles
  - Dispensing limits
  - Pre-authorization
- 45% of cancer patients report drug costs which result in non-adherence to therapy
- In 2010 generic aromatase inhibitors were introduced

Truffer C et al., *Health Affairs*. 2010
Optum Database

• Members
  – 25 million commercial United Healthcare
  – 6 million Medicare
  – 2 million Medicaid

• Information on each prescription
  – Deductible
  – Out of pocket payment
  – Co-payment

• Aim: how the introduction of generic AI affect discontinuation and adherence
Patient Characteristics

- Women with a diagnosis of early stage breast cancer (2007-2011, n = 13,522)
  - Age >50
  - Filled ≥ 2 prescriptions for hormonal therapy
  - 5990 switched between hormonal meds
    - 72.9% switched from AI-Brand to AI-Generic
30-Day Co-Payment Characteristics

**COPAYMENT (%)**

- >$20: 29.8%
- $10-$20: 28.4%
- <$10: 41.8%

**MEAN CO-PAYMENT COST ($)**

- TAMOXIFEN: 7.74
- AI GENERIC: 9.04
- AI BRAND: 33.3
## Multivariate Analysis – Discontinuation

<table>
<thead>
<tr>
<th>THERAPY</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI-Brand</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AI-Generic</td>
<td>0.62</td>
<td>0.51-0.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>0.93</td>
<td>0.79-1.09</td>
<td>0.40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COPAY</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; $10</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$10-$20</td>
<td>1.21</td>
<td>1.08-1.35</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt; $20</td>
<td>1.59</td>
<td>1.34-1.88</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

adjusted for year*, deductible type, coverage type, provider, surgery, comorbidity*, age*, race, education, income, region*
# Multivariate Analysis – Adherence

<table>
<thead>
<tr>
<th>THERAPY</th>
<th>OR</th>
<th>95% C.I.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Brand</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Al-Generic</td>
<td>1.37</td>
<td>1.09-1.74</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>0.68</td>
<td>0.56-0.83</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COPAY</th>
<th>OR</th>
<th>95% C.I.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; $10</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$10-$20</td>
<td>0.84</td>
<td>0.73-0.96</td>
<td>0.01</td>
</tr>
<tr>
<td>&gt; $20</td>
<td>0.55</td>
<td>0.45-0.67</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INCOME</th>
<th>OR</th>
<th>95% C.I.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; $40k</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$40k-100k</td>
<td>1.15</td>
<td>0.98-1.36</td>
<td>0.09</td>
</tr>
<tr>
<td>&gt; $100k</td>
<td>1.38</td>
<td>1.11-1.69</td>
<td>0.003</td>
</tr>
</tbody>
</table>

adjusted for year*, deductible type, coverage type, provider, and other factors.
Summary

• Treatment of baseline symptom burden may improve compliance with AI therapy

• A yearlong exercise program improved arthralgias by 30%

• Generic drugs are associated with better adherence by increasing access

• Cancer Treatment Fairness Act
Compass HEROES Group Visits
Health and Educational Resources for Our Exceptional Survivors

Compass Oncology strives to provide the best care for our cancer survivors. We recognize the complex needs after cancer treatment and the importance of surveillance, prevention and education so you are the strongest advocate for your integrated care. Compass HEROES Group Visits are 90-minute sessions addressing different topics each month. Each visit includes a 45-minute presentation, group discussion and Q&A time.

**Fatigue in Survivorship**
Tuesday, January 21, from 5:30 - 7:00 pm
Compass Oncology Tualatin
19260 SW 65th Avenue, Tualatin OR 97062

**Intimacy and Sexuality after Cancer**
Tuesday, February 25, from 5:30 - 7:00 pm
Compass Oncology West
9555 SW Barnes Rd, Portland OR 97225

**Emotional Distress after Cancer**
Friday, March 14, from 2:00 - 3:30 pm
Compass Oncology Adventist
10101 SE Main St., Ste 1012, Portland OR 97216

**TO REGISTER:**
Fatigue in Survivorship, call 503.692.2032
Intimacy and Sexuality after Cancer, call 503.297.7403
Emotional Distress after Cancer, call 503.256.3627
Ask for the Survivorship scheduler

**INSURANCE:**
Your insurance will be billed and you will be responsible for your regular office visit co-pay at the visit.

---

**Virginia Hill, LCSW, LICSW**
Virginia earned her masters degree in social work from Portland State University and has been a licensed clinical social worker for the past 19 years. She joined Compass Oncology nearly two years ago focusing on counseling and medical social work. Her goal is to ease her patients and their families’ journey through challenging times by providing them with both emotional and practical support.

**Magdolna Solti, MD**
Dr. Solti received her training at the University of Szeged, Hungary, Cleveland Clinic Health System, and Thomas Jefferson University. She joined Compass Oncology as a medical oncologist seven years ago where she focuses on breast cancer and also serves as the medical director of the Compass Survivorship program. She is a strong proponent of survivor education, support programs and survivorship research.

**Joyce Koerber, PA-C**
Joyce completed her Masters of Physician Assistant Studies at the University of Colorado and is a NCCPA board certified Physician Assistant. She joined the Compass Oncology team in April 2013. Joyce is excited to bring her primary care skills of listening to all of her patient’s concerns and caring for the whole body and mind, which will help patients in their transformation and long term He of survivorship.

**Rosemary McDermott, RN**
Rosemary has been practicing in the oncology field since 1975, working with cancer patients during treatment, research and rehabilitation. She has been with Compass Oncology for 12 years and has served in a variety of positions. She now works as the patient and community outreach liaison providing education and resources to patients during their entire course of treatment and beyond.

**Tracy Webb, PA-C**
Tracy completed her Masters of Sciences in Physician Assistant studies at Philadelphia University and is a NCCPA board certified Physician Assistant. She joined Compass Oncology over two years ago and enjoys helping patients address their concerns. She does this by empowering them with strategies to maximize their health potential and to prevent recurrence after treatment.

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Find your path to hope and healing at CompassOncology.com.
Thank you!