Hot Topics in Bone Disease in 2017: Building Better Bones – Breaking News in Osteoporosis

Aromatase Inhibitor-Induced Bone Loss in Early Breast Cancer

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Disclosures

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• Off Label Drug Use:
  – None
Objectives

- Estrogen Deficiency in Women and Mechanism of Action of Aromatase Inhibitors
- Effects of Aromatase Inhibitors on Bone Mineral Density
- Potential Treatment Options For Aromatase Inhibitor-Induced Bone Loss
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Scope of the Problem: Breast Cancer is the Most Common Malignancy in Women

- **1.7 million** diagnosed annually worldwide
- **3 million** women living in the U.S. with invasive breast cancer
- Early breast cancer without detectable distant metastasis potentially curable
- **60-75%** women with breast cancer Estrogen Receptor Positive
- Adjuvant endocrine therapy in early breast cancer for 5-10 years considered standard
- Fractures under-reported in oncology trials

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Adjuvant strategies for ER positive breast cancer focus on prevention of activation of ER by estrogens

Postmenopausal **Breast Cancer** Women at Increased Risk For Clinical Fractures

Factors associated with fractures:
- Non-Hispanic White
- Depression
- > 2 falls/12 mos
- Diabetes
- Fracture history
- Osteoporosis

Source: Chen Z et al. *Arch Int Med* 2005; 165: 552-558
How much bone loss is “normal?”
Large Loss of BMD Lumbar Spine During Menopause Transition

Source: Sowers MR et al. JCEM 2010;95:2155-2162
Large Loss of BMD in Femoral Neck During Menopause Transition

Source: Sowers MR et al. JCEM 2010;95:2155-2162
Annual Aromatase Inhibitor-Induced Bone Loss Exceeds Normal Postmenopausal Bone Loss

- Premenopausal Women: <0.4%
- Postmenopausal Women: 1%
- Postmenopausal Women, Breast Cancer + AI: 2.6%

Source: Hadji P. Crit Reviews in Onc/Hem 2009; 69: 73-82
Aromatase Inhibitors Mechanism of Action Vs. Tamoxifen Responsible for Varying Effects On Bone

Estradiol Deficiency:

- Increased osteoblast apoptosis
- Decreased osteoclast and osteocyte cell death
- Increased TNF alpha, IL 1a, cytokines
- Activation RANK ligand

Risk of Bone Fracture Correlates With Estradiol Level: Postmenopausal Women At Risk Prior To Starting AIs

Source: Cummings SR et al. NEJM 1998; 339: 733-8
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- **Effects of Aromatase Inhibitors on Bone Mineral Density**
- Potential Treatment Options For Aromatase Inhibitor-Induced Bone Loss
Third Generation Aromatase Inhibitors Are $\geq 98\%$ Effective Inhibiting Aromatase Enzyme

Androstenedione

Estrone

Exemestane

Letrozole

Anastrozole

Continued BMD Loss On Anastrozole in Healthy Postmenopausal Women Compared With Placebo

<table>
<thead>
<tr>
<th></th>
<th>Lumbar Spine</th>
<th>Total Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BMD Change</td>
<td>Anastrozole -4%</td>
<td>Anastrozole -4%</td>
</tr>
<tr>
<td>Placebo</td>
<td>Placebo -1.2%</td>
<td>Placebo -1.8%</td>
</tr>
</tbody>
</table>

Time (Months)
Fracture Data Limited

Source: Sestak I et al. Lancet Oncol 2014; 15: 1460-68
Tamoxifen Protects Against Bone Loss

![Graph showing the effect of Tamoxifen, Anastrozole, Letrozole, Exemestane, and Placebo on Lumbar Spine BMD over time. The graph indicates that Tamoxifen has a protective effect against bone loss compared to the other treatments.]

Source: Hadji P. BoneKEy Reports 2015; 4 (692)
Fractures Increased On Aromatase Inhibitors Compared With Tamoxifien

Fractures (%)

Absolute Risk of Fracture on AIs for 5 years variable (1-18%)

Higher Prevalence And Severity Of Vertebral Fractures In Aromatase Inhibitor-Treated Patients

Prevalence VFs (%)

Total VFs
- 18.9%
- 31.2%

Mod/Severe VFs

No Aromatase Inhibitor

Aromatase Inhibitor Treated

Source: Pedersini R et al. Bone 2017; 97: 147-152
Shift From Use of Tamoxifen: Aromatase Inhibitors Reduce Recurrence Rates And Breast Cancer Mortality

Recurrence (%)

Tamoxifen

Aromatase Inhibitor

10 years

Time (years)

Source: Early Breast Cancer Trialists' Collaborative Group Lancet 2015; 386: 1341-52
Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years

Extending Aromatase Inhibitor Treatment Lowers Breast Cancer Rates; Increases Disease-Free Survival

Disease-free survival:
95% Letrozole
91% Placebo

Contralateral breast cancer: 34% Letrozole, 5% Placebo

Many Patients Do Not Receive Repeat DXA Evaluation On Aromatase Inhibitors

DXA May Underestimate Risk Of Fracture on Aromatase Inhibitors

- Large Decreases Total Volumetric BMD; Small Decreases Areal BMD
- No prospective validated use of FRAX in AI-Induced Bone Loss

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Improved BMD On Combination Risendronate/Anastrozole However No Fracture Data Available

Lumbar Spine

- AI/Risendronate: +1.1%
- AI/placebo: -2.6%

Total Hip

- AI/Risendronate: -0.7%
- AI/placebo: -3.5%

Source: Sestak I et al. Lancet Oncol 2014; 15: 1460-68
Risedronate Counterbalances Aromatase Inhibitor-Induced Bone Loss in Women with Osteoporosis

Limitations: compliance, side effects, efficacy

Source: Sestak I et al. Lancet Oncol 2014; 15: 1460-68
Upfront Zoledronic Acid Prevents Bone Loss Over 12 Months Letrozole; Delay Results in BMD Loss

BMD % Change

Immediate ZA

Immediate ZA

P < .0001

Delayed ZA

Lumbar Spine

Delayed ZA

Hip

Source: Bundred et al. ZO FAST. Cancer 2008; 112: 1001-10
Upfront Zoledronic Acid Significantly, Progressively Increased BMD On Letrozole In Early Breast Cancer

Denosumab prevents interaction of RANKL with RANK

Fracture Data For Denosumab in Early Breast Cancer

Adjuvant denosumab in breast cancer (ABCSD-18): a multicentre, randomised, double-blind, placebo-controlled trial


THE LANCET

Source: Gnant M et al. Lancet 2015; 386: 433-43
Robust Increase in BMD On Denosumab Compared With Placebo

10% Lumbar Spine

7.9% Total Hip

6.5% Femoral Neck

Source: Gnant M et al. Lancet 2015; 386: 433-43
Adjuvant Denosumab Reduces AI-Induced Non-Vertebral Fractures

Time To First Fracture Doubled on Denosumab

Source: Gnant M et al. Lancet 2015; 386: 433-43
Adjuvant Denosumab Benefits Similar Regardless Of T-Score

• Benefits similar if T-score ≥ -1 at baseline or T-score < -1
  
• Similar protective effect regardless of T-score
  
• Similar protective effect seen in younger and older women
  
• Adverse events similar (no AFF or ONJ)

Bisphosphonates have not received regulatory approval for treatment induced bone loss

<table>
<thead>
<tr>
<th>Medication</th>
<th>Regulatory Approval</th>
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<tbody>
<tr>
<td>Denosumab 60 mg sc 6 monthly</td>
<td>Breast cancer</td>
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<tr>
<td>Zoledronic Acid 4 mg IV 6 monthly</td>
<td>None</td>
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<tr>
<td>Alendronate 70 mg po weekly</td>
<td>None</td>
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<tr>
<td>Risedronate 35 mg po weekly</td>
<td>None</td>
</tr>
<tr>
<td>Ibandronate 150 mg po monthly</td>
<td>None</td>
</tr>
<tr>
<td>Pamidronate 90 mg IV every 3 months</td>
<td>None</td>
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</tbody>
</table>

Postmenopausal women treated with aromatase inhibitors are at increased risk of osteoporosis and should have initial and periodic (every 2 years) DEXA scan screening. If major risk factors change, then it is reasonable to consider a repeat DEXA scan at 1 year. All postmenopausal women or premenopausal women receiving ovarian suppression therapy with GnRH agonists are at risk for developing osteoporosis and should be screened according to the US Preventive Services Task Force and the American Association of Clinical Endocrinologists guide for postmenopausal osteoporosis diagnosis and treatment.
European Society Oncology Guidelines Managing Bone Health On AI’s Emphasizes T-Score

T-score > -2.0

- T-score > -2.0 and no additional risk factors
  - Exercise
  - Calcium and vitamin D
- Monitor risk and BMD at 1–2 year intervals

T-score < -2.0

- Exercise
- Calcium and vitamin D
- Bisphosphonate therapy (zoledronic acid, alendronate, risedronate, ibandronate; denosumab may be a potential treatment option in some patients)
- Monitor BMD every 2 years
- Check compliance with oral therapy

“Variable preference on choice of agent in post-menopausal women”- European panel 2016

Personalize Treatment: Assess BMD-Independent Risk Factors

- Shorter course treatment
- Oral bisphosphonates

Any 2 risk factors:

- Age > 65 years
- T-score < -1.5
- Smoking (current/history)
- BMI < 20
- Family history hip fracture
- Personal history fragility fx > 50 yrs
- Oral glucocorticoid > 6 mos

- Prolonged treatment
- Injectable antiresorptive agents

Guidelines vary in thresholds for initiating treatment and risk factors used in fracture risk calculation

Conclusions

• Aromatase Inhibitors standard of care for postmenopausal women with hormone receptor-positive early breast cancer

• Tailor assessment for AI-induced bone loss based on projected bone loss, menopausal status, risk factors for fracture and anticipated treatment duration

• Need follow up of outcomes based on antiresorptive treatment decisions to validate guidelines/algorithms
Special Thanks…

Dr. Daniel Hurley

Dr. Michael McClung

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