Breast Cancer and Bone

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Ohio State University Medical Center and
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Topics

– BMD and breast cancer risk
– Treatment-related bone loss
– Bisphosphonates as anti-cancer drugs
– Vit D and breast cancer prognosis
# BMD and Breast Cancer Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Relative Risk (95% CI)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen (WHI) 2008</td>
<td>prospective cohort</td>
<td>1.3 (1.1-1.4)</td>
<td></td>
</tr>
<tr>
<td>Cauley 2007</td>
<td>randomized trial</td>
<td>BMD is weak predictor</td>
<td></td>
</tr>
<tr>
<td>Kerlikowski 2006</td>
<td>case control</td>
<td>BMD not a risk factor</td>
<td></td>
</tr>
<tr>
<td>Van der Kift 2003</td>
<td>prospective cohort</td>
<td>2.1 (1.1-3.7)</td>
<td></td>
</tr>
<tr>
<td>Nelson (NHANES) 2002</td>
<td>prospective cohort</td>
<td>No effect</td>
<td></td>
</tr>
<tr>
<td>Zmuda 2001</td>
<td>prospective cohort</td>
<td>2.7 (1.4-5.3)</td>
<td></td>
</tr>
</tbody>
</table>

Estrogen Molecule

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Causes of Bone Loss

- Bilateral oophorectomy
- Bilateral orchietomy
- Chemo-induced ovarian failure
- Aromatase inhibitors
- Glucocorticoids
- GnRH agonists

Hypogonadism → Elevated bone turnover → Bone loss → Fracture

Sources of Estrogen in Post vs. Pre

**Premenopausal**
- Adipose tissue
- Ovary
- Brain

**Postmenopausal**
- Adrenal gland
- Aromatase (CYP19)
- Estrogens

**Androgens**
Ovarian failure after chemotherapy

Fig 1. Probability of menopause during the first year after diagnosis (from model shown in Table 3)


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Bone loss at 12 mos in Lumbar Spine

Chemotherapy-Induced Ovarian Failure causes Bone Loss at 1 Year

Women with ovarian failure

Shapiro Fuleilhan Saarto Hershman

% Δ BMD

24 month data

Lumbar spine  Hip

# Randomized Bisphosphonate Trials

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Bisphosphonate</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delmas</td>
<td>53</td>
<td>Risedronate vs. placebo</td>
<td>+</td>
</tr>
<tr>
<td>Saarto</td>
<td>43</td>
<td>Clodronate vs. control</td>
<td>+</td>
</tr>
<tr>
<td>Powles</td>
<td>311</td>
<td>Clodronate vs. placebo</td>
<td>+</td>
</tr>
<tr>
<td>Fuleihan</td>
<td>66</td>
<td>Pamidronate vs. placebo</td>
<td>+</td>
</tr>
<tr>
<td>Hershman</td>
<td>101</td>
<td>Zoledronic acid vs. placebo</td>
<td>+</td>
</tr>
<tr>
<td>Shapiro</td>
<td>439</td>
<td>Zoledronic acid vs. control</td>
<td>+</td>
</tr>
<tr>
<td>Gnant</td>
<td>401</td>
<td>Zoledronic acid vs. placebo</td>
<td>+</td>
</tr>
</tbody>
</table>
Trial Design: 79809

Stratifications
Stage
Tamoxifen

ZA q3 mo
Calcium/ Vit D

Adj Chemo +/- tamoxifen

0 12mo 24mo 36 mo

Calcium/ Vit D

ZA q3 mo
Calcium/ Vit D

Calcium/ Vit D

N=439

Shapiro et al Eur J Cancer 2011
CALGB 79809 Results

% Δ

ZA

2.2 (5.3)

-6.6 (6.9)

control
Endocrine Therapy plus Zoledronic Acid in Premenopausal Breast Cancer

Michael Gnant, M.D., Brigitte Mlineritsch, M.D., Walter Schippinger, M.D., Gero Luschin-Ebengreuth, M.D., Sabine Pöstlberger, M.D., Christian Menzel, M.D., Raimund Jakesz, M.D., Michael Seifert, M.D., Michael Hubalek, M.D., Vesna Bjelic-Radisic, M.D., Hellmut Samonigg, M.D., Christoph Tausch, M.D., Holger Eidtmann, M.D., Günther Steger, M.D., Werner Kwasny, M.D., Peter Dubsky, M.D., Michael Fridrik, M.D., Florian Fitzal, M.D., Michael Stierer, M.D., Ernst Rücklinger, Ph.D., Richard Greil, M.D., for the ABCSG-12 Trial Investigators
ABCSG Trial 12

Premenopausal, ER+
GnRH agonist + TAM or
Anastrozole
Baseline T-score ≥ -2.0

Zoledronic acid 4 mg
Q6 mo x 3 years

No Zoledronic acid Control

Gnant et al J Clin Oncol
ABCSG-12: BMD

T scores: w/ ZA

T scores: no ZA

Sources of Estrogen in Post

Adipose tissue, ovary; brain

postmenopausal

Adrenal gland

Aromatase (CYP19)

Androgens

Estrogens

Aromatase Inhibitor
# Fractures with Aromatase Inhibitors

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>F/U (mo)</th>
<th>Treatment</th>
<th>Fracture Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AI vs. TAM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAC</td>
<td>9366</td>
<td>100</td>
<td>ANA vs. TAM</td>
<td>11.0 vs. 7.7 [p&lt;0.001]</td>
</tr>
<tr>
<td>BIG 1-98</td>
<td>4922</td>
<td>51</td>
<td>LET vs. TAM</td>
<td>8.6 vs. 5.8 [p&lt;0.01]</td>
</tr>
<tr>
<td><strong>AI after 2-3 years of TAM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>4724</td>
<td>58</td>
<td>EXE vs. TAM</td>
<td>7.0 vs. 5.0 [p=0.003]</td>
</tr>
<tr>
<td>ABCSG8/ ARNO</td>
<td>3224</td>
<td>28</td>
<td>ANA vs. TAM</td>
<td>2.0 vs. 1.0 [p=0.015]</td>
</tr>
<tr>
<td><strong>AI after 5 years of TAM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA-17</td>
<td>5187</td>
<td>30</td>
<td>LET vs. Placebo</td>
<td>5.3 vs. 4.6 [p=0.25]</td>
</tr>
</tbody>
</table>
Bisphosphonates

- Osteoclast inhibitors
  - Inhibit Activation
  - Differentiation
  - Binding to bone matrix
  - Secretion H+
  - FDA-approved

- Side Effects of zoledronic acid
  - Renal toxicity, fevers, pain
  - Osteonecrosis
Z-Fast /ZO-Fast Trial

Postmenopausal
Age 60 years
Letrozole 2.5
Baseline T-score ≥ -2.0

Zoledronic acid 4 mg Q6 mo

Zoledronic acid only if T-score < -2
Results

A

B

Percentage Change in Bone Mineral Density (g/cm²)

Upfront Group
Delayed Group

Month 6
Month 12

P < .0001

P < .0001

Lumbar Spine
Total Hip
## Results of Delayed Group

<table>
<thead>
<tr>
<th>Baseline BMD</th>
<th>36-month BMD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Normal</td>
<td>100</td>
</tr>
<tr>
<td>Osteopenic</td>
<td>100</td>
</tr>
</tbody>
</table>

T-scores did not change for most patients after 3 years; only 15% of Delayed Group received zoledronic acid. Not all patients need bisphosphonate treatment for bone loss.
Sabre Trial: Risk Stratification

High Risk
T score ≤ -2.0 (n=38) Risedronate

Moderate Risk (n=154)
T score ≤ -1.0 to ≥ -2.0

Low Risk (n=42)
T score ≥ -1.0 Observation

Van Poznak et al, J Clin Oncol 2010
## SABRE : 24-Month BMD Analysis

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>n</th>
<th>% change BMD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lumbar Spine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Ana</td>
<td>26</td>
<td>−2.1</td>
<td>.0109</td>
</tr>
<tr>
<td>Mod</td>
<td>Ana/Plac</td>
<td>54</td>
<td>−1.8</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Mod</td>
<td>Ana/Rise</td>
<td>60</td>
<td>+2.2</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>Ana/Rise</td>
<td>33</td>
<td>+3.0</td>
<td>.0006</td>
</tr>
<tr>
<td><strong>Total Hip</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Ana</td>
<td>26</td>
<td>−0.4</td>
<td>.5988</td>
</tr>
</tbody>
</table>
| Mod     | Ana/Plac    | 54 | −1.1         | <.0001  *
| Mod     | Ana/Rise    | 60 | +1.8         |         |
| High    | Ana/Rise    | 33 | +2.0         | .0104*  |

131 women
Anastrazole 1 mg
T-score -1 to -2.5

At 2 years LS spine:
I vs. P ~6%, p<0.02

252 women
Aromatase Inhibitor
Mean T score ~1

At 2 years LS spine:
D vs. P ~8%, p<0.0001

ASCO Approach to Bone Loss

Exercise, stop smoking, supplemental calcium/vitamin D

Risk Factors
Ovarian failure
AI treatment

High risk
BMD of L/S spine and Hip by DEXA scan

Low risk
T-score –2.0 to –1
Monitor BMD

T score ≤ –2.5, or < 2.0 w/RF
Monitor BMD
Start bisphosphonate

DEXA Scans

Healthy Lifestyle

Treatments
Bisphosphonates
How well are we doing?

259 ♀ age < 50; 89 (34%) chemo-induced ovarian failure:

<table>
<thead>
<tr>
<th>Recommendations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular exercise</td>
<td>72%</td>
</tr>
<tr>
<td>Calcium/vitamin D</td>
<td>57%</td>
</tr>
<tr>
<td>DEXA scan</td>
<td>40%</td>
</tr>
</tbody>
</table>
Conclusions I

• Estrogen deprivation either through chemotherapy-induced ovarian failure, AI causes bone loss

• Health professionals should be:
  – Familiar with recommendations to maintain bone health
  – DEXA scans to screen for osteoporosis, and criteria for bisphosphonate treatment
  – Generate appropriate referrals

• Recommendations for bone health (calcium, vitamin D, exercise, reduce smoking and alcohol) promote overall health

• Many unanswered questions:
  – who needs a bisphosphonate?; what is the optimal timing, dose, and duration?
Bisphosphonates and Denosumab as anti-cancer drugs
Bone microenvironment is a “rich soil” that is supports metastasis
Stopping the Vicious Cycle

Adjuvant Bisphosphonate
Bone Metastases

Prevalence
~100,000 women living in the USA with metastatic breast cancer (MBC) (Hillner 2000)

Bone metastases & SREs
65-75% of pts w/ MBC have bone lesions (Coleman 1987)
50-70% of pts experience SREs metastatic bone disease (Domcheck 2000, Coleman 2004)
Mean number of SREs/year in MBC 3.7 (Lipton 2000)
SREs account for 63% of UK hospital costs in metastatic breast cancer (Coleman, Cancer 1997)

Median Survival MBC with Metastatic Bone Disease:
2-4 years, with 20% having 5 y survival (Coleman 1997, Giordano 2004, Van Poznak 2005)
Kaplan-Meier estimates of (A) time to first skeletal-related event (SRE) and (B) time to first and subsequent SREs (multiple event analysis), which is represented as the cumulative mean number of SREs over time.

Stopeck A T et al. JCO 2010;28:5132-5139

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Kaplan-Meier estimates of (A) overall survival and (B) time to disease progression by treatment group.

Graph A shows the overall survival rates with Kaplan-Meier estimates. The survival curve for Zoledronic acid 4 mg Q4W (n = 1,020) is represented by the solid blue line, and Denosumab 120 mg Q4W (n = 1,026) by the dashed blue line. The hazard ratio (HR) is 0.96 (95% CI, 0.81 to 1.11) with a p-value of 0.49.

Graph B displays the time to disease progression rates. The solid blue line represents Zoledronic acid 4 mg Q4W (n = 1,020), and the dashed blue line represents Denosumab 120 mg Q4W (n = 1,026). The HR is 1.00 (95% CI, 0.89 to 1.11) with a p-value of 0.93.

Tables showing the number of patients at risk at different study months:

**Graph A**
- Zoledronic acid: 1,020, 962, 897, 834, 757, 699, 615, 532, 484, 411, 336, 277, 218, 179, 44
- Denosumab: 1,026, 984, 916, 849, 771, 690, 511, 336, 177, 57

**Graph B**
- Zoledronic acid: 1,020, 842, 696, 563, 462, 370, 240, 148, 65, 17
- Denosumab: 1,026, 858, 693, 567, 453, 351, 241, 128, 65, 20
CANCER: Breast cancer bone metastases: denosumab or zoledronic acid?
Gabri van der Pluijm

Abstract
Bone metastases cause patient morbidity and mortality. A recent study compared denosumab with zoledronic acid for the treatment of bone metastases in advanced breast cancer. Denosumab seemed to be the front-runner, but is that the whole story?

Nature Reviews Endocrinology 7, 134-135 (March 2011)
ABCSG Trial 12

Premenopausal, ER+
GnRH agonist + TAM or Anastrozole
Baseline T-score ≥ -2.0

Zoledronic acid 4 mg Q6 mo x 3 years

No Zoledronic acid Control

Gnant et al J Clin Oncol
# Events in the Intention-to-Treat Population

**Table 2. Events in the Intention-to-Treat Population.**

<table>
<thead>
<tr>
<th>Event</th>
<th>Tamoxifen (N=900)</th>
<th>Anastrozole (N=903)</th>
<th>No Zoledronic Acid (N=904)</th>
<th>Zoledronic Acid (N=899)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All events</td>
<td>65</td>
<td>72</td>
<td>83</td>
<td>54</td>
</tr>
<tr>
<td>Recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locoregional</td>
<td>16</td>
<td>14</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Distant</td>
<td>29</td>
<td>41</td>
<td>41</td>
<td>29</td>
</tr>
<tr>
<td>Bone metastases</td>
<td>18</td>
<td>21</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>Contralateral breast cancer</td>
<td>10</td>
<td>6</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Secondary malignant condition</td>
<td>9</td>
<td>10</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>15</td>
<td>27</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>Without previous recurrence</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

*Only the first event per patient is included.*

Secondary Endpoints: ZOL vs No ZOL

RFS

HR = 0.64 (0.46-0.91)

OS

HR = 0.63 (0.48 to 0.82)
AZURE UK Trial

Stage II/III
N=3360
Closed 1/2006

Adjuvant Therapy (Neo, Chemo, Endo)

Adjuvant Therapy + ZA

Subset of 205 (<10%) received neoadjuvant
## AZURE Demographics

<table>
<thead>
<tr>
<th></th>
<th>ADJ TX (n=1678)</th>
<th>ADJ TX + ZA (n=1681)</th>
<th>ABCSG-12 (n=1801)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal</td>
<td>45</td>
<td>45</td>
<td>100</td>
</tr>
<tr>
<td>Endocrine Only</td>
<td>4</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>Chemo Only</td>
<td>23</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Endo + Chemo</td>
<td>73</td>
<td>73</td>
<td>0</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>93</td>
<td>93</td>
<td>0</td>
</tr>
<tr>
<td>N+</td>
<td>95</td>
<td>93</td>
<td>~40</td>
</tr>
<tr>
<td>ZA Dosing</td>
<td>Q1 mo x 6; Q3 mo x 8; Q6 mo x 5 = 5 yr</td>
<td>Q6 mo x 3 yr</td>
<td></td>
</tr>
</tbody>
</table>
Disease-free Survival and Invasive-Disease–free Survival in the Intention-to-Treat Population.

## Completed and Ongoing Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>F/U (mo)</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAPB 34</td>
<td>3223</td>
<td>~ 60</td>
<td>Clod 1660 mg vs. placebo x 3 yr</td>
<td>NA</td>
</tr>
<tr>
<td>AZURE</td>
<td>3160</td>
<td>NA</td>
<td>ZA Q1 mo x 6; Q3 mo x 8; Q6 mo x 5 = 5 yr</td>
<td>Neg</td>
</tr>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INTERGROUP</td>
<td>6000</td>
<td>NA</td>
<td>ZA vs. Clod vs. Ibandronate</td>
<td>NA</td>
</tr>
<tr>
<td>BIG 4-04</td>
<td>1394</td>
<td>NA</td>
<td>Capecitabine +/- Ibandronate</td>
<td>NA</td>
</tr>
<tr>
<td>GAIN</td>
<td>3000</td>
<td>NA</td>
<td>CEP +/- capecitabine +/- Ibandronate</td>
<td>NA</td>
</tr>
</tbody>
</table>
Conclusions II

• For Metastatic disease to bone:
  – Zoledronic acid and Denosumab are FDA-approved
  – Denosumab was superior to zoledronic acid in SRE
  – They both cause osteonecrosis; cost differential:

• For use in early stage breast cancer:
  – Mixed results depending upon menopausal status and treatment
  – Stay tuned
Vit D and Breast Cancer
Vitamin D and Vitamin D Deficiency

• Calcium and Vitamin D reduces fractures
  – WHI randomized placebo-controlled trial and meta-analysis of trials of vitamin D +/- calcium reduces fractures with 800 IU/day

• Vitamin D deficiency
  – Common, caused by decreased sun exposure, intake, absorption
  – Recent study in breast cancer survivors show low or deficient 25-OH in 76% (Healthy Eating, Eating, Activity and Lifestyle or HEAL study)
    • Overall mean (+/- SD) = 25 (10) ng/ml
    • African-American = 18 (9) ng/ml
    • Hispanics = 22 (9) ng/ml

• No consensus on measuring serum vitamin D in breast cancer
  – Correcting D deficiency improves response to bisphosphonate

68,132 WHI CT Participants

31,850 Ineligible or Not Interested

36,282 Randomized

CaD (N = 18,176)
Placebo (N = 18,106)

Close-Out (N=16,936)
Close-Out (N=16,815)

CaD supplement

• 1000 mg elemental calcium as calcium carbonate
• 400 IU vitamin D₃
• Divided dose; with meals
• Mean follow-up 7.0 years
CaD vs Placebo Effect on Breast Cancer

- Invasive breast cancer (HR 0.96; 95% CI 0.85, 1.09)
  - 528 CaD
  - 546 Placebo
- In situ breast cancer (HR 0.94; 95% CI 0.75, 1.18)
  - 145 CaD
  - 152 Placebo
- Total breast cancer (HR 0.96; 95% CI 0.86, 1.07)
  - 668 CaD
  - 693 Placebo

Annualized rates per 10,000 person-years

Chlebowski et al J Natl Cancer Inst. 2008;100(22):1581-91
25-Hydroxyvitamin D and Breast Cancer Recurrence
Vitamin D Deficiency in Breast Cancer

Distant Disease-Free Survival

Proportion distant disease free vs. Years since diagnosis

- Sufficient
- Insufficient
- Deficient

p = 0.02
25-Hydroxyvitamin D and Event Free Survival
Multivariate Effects of Baseline 25-Hydroxyvitamin D on Relapse-Free Survival

- Any type of relapse \( p = 0.57 \)
- Bone only relapse \( p = 0.19 \)
- Bone + other site of relapse \( p = 0.73 \)
- All bone relapse types \( p = 0.66 \)