Survivorship is on the radar screen

Survivorship in Breast Cancer

DFS (%)

years

T1N0

T1N1-3
How well are we doing?

Breast cancer deaths are decreasing
WHY?

Screening and Better Treatments

Berry et al NEJM 2005
Consequences of treatment

Dynamic Balance in Normal Bone

Gravity

Ratio of OPG/RANKL

- Normal Bone
  - OPG/RANKL = 1
  - Bone resorption = bone formation
- Estrogen Deficiency
  - OPG/RANKL < 1
  - Bone resorption > bone formation

The Osteoporosis Equation

Peak bone mass

Genetics

Exposures

Bone Loss

Aging, family history, race, menopause, diet, exercise, smoking, alcohol, meds

Ramaswamy and Shapiro Semin Oncol 30:763, 2003
Zoledronic Acid (ZA) preserves bone mineral density (BMD) in premenopausal women who develop ovarian failure due to adjuvant chemotherapy: First results from CALGB trial 79809

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The Ohio State University Medical Center and James Cancer Hospital, Columbus, OH; Duke University, Durham, NC; New Hampshire Oncology-Hematology PA, Hookset, NH; Hematology Oncology Associates of Central New York, Syracuse, NY; Miriam Hospital, Providence, RI; Dana Farber Cancer Institute, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; Georgetown University, Washington, DC; University of Chicago, Chicago, IL

Background

- Chemotherapy-induced ovarian failure
  - 50-70% of women
    - Increasing age
    - No standard definition
    - Distinct from amenorrhea that reverses
- Bone loss due to estrogen deficiency

Goodwin, P J Clin Oncol 1999
Bone loss at 12 mos in Lumbar Spine

% Δ


Hypotheses and Outcomes

• Primary Hypothesis:
  – ZA will prevent bone loss in chemo-induced ovarian failure

• Primary Endpoint:
  – Bone loss in lumbar spine at 12 mos (from baseline)

• Secondary Hypothesis:
  – “Early” ZA is more effective than “late” ZA

• Secondary Endpoint:
  – Bone loss in lumbar spine at 36 mos (from baseline)
Trial Design: 79809

“Early”
- ZA q3 mo
- Calcium/ Vit D
- Calcium/ Vit D
- Adj Chemo +/- tamoxifen

“Late”
- ZA q3 mo
- Calcium/ Vit D
- Calcium/ Vit D

Eligibility

- Histologic evidence of invasive breast cancer
- Stages I-III
- Age ≥ 40 years
- Actively menstruating or LMP ≤ 6 months
- Not pregnant
- Decision to use adjuvant or chemotherapy +/- tamoxifen
Treatment and Study Evaluations

- Zoledronic Acid 4 mg IV every 3 mos
- Calcium 1000 mg + Vitamin D 400 IU/daily
- DEXA, FSH, estradiol, pregnancy test at baseline and 12 mos
- Toxicity and Compliance (self-report) every 3 mos
- OF defined at 12 mo with > 3 mos amenorrhea, FSH > 30 miu/ml, non-pregnant

Statistics

- Primary Endpoint: % change in BMD at 12 mos
- Sample Size: 80 women per arm (n=160 total)
- Power: 80% to detect 0.09 g/cm² (10%) difference in lumbar spine BMD assuming a sd=0.2 g/cm² at a two-sided type I error rate=0.05
- Assumptions:
  - 50% women develop OF by 12 mos
  - 20% will not complete 12 mo evaluation
- Total Sample Size Required: N=400
Trial Summary

• Accrual period: 12/2001 to 12/2006
• 439 patients randomized
• DSMB released data when a pre-specified boundary for superiority was crossed at the first interim analysis in Nov 2007
• 166 (38%) women met the definition of OF at 12 mos
• Self-reported compliance with calcium and vitamin D was nearly 100%

Baseline Demographics and Labs

<table>
<thead>
<tr>
<th></th>
<th>ZA (n=81)</th>
<th>Control (n=85)</th>
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<tbody>
<tr>
<td>Age*</td>
<td>46 (3.6)</td>
<td>48 (3.8)</td>
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<tr>
<td>White (%)</td>
<td>95</td>
<td>88</td>
</tr>
<tr>
<td>Stage I/II (%)</td>
<td>77</td>
<td>84</td>
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<tr>
<td>Tam planned (%)</td>
<td>75</td>
<td>62</td>
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<tr>
<td>FSH (miu/ml)*</td>
<td>32 (31)</td>
<td>37 (30)</td>
</tr>
<tr>
<td>Estradiol (pg/ml)*</td>
<td>55 (47)</td>
<td>53 (55)</td>
</tr>
<tr>
<td>BMD LS (g/cm²)*</td>
<td>1.13 (0.18)</td>
<td>1.15 (0.20)</td>
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*mean (sd)
Mean (sd) FSH and Estradiol

| mos | 35 (30) | 36 (57) | 60 (26) | 53 (52) |

ZA toxicity (n=81)

<table>
<thead>
<tr>
<th></th>
<th>Fever</th>
<th>Fatigue</th>
<th>Arthralgia</th>
<th>Pain</th>
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<tr>
<td>Grade 1</td>
<td>9</td>
<td>26</td>
<td>10</td>
<td>19</td>
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<tr>
<td>Grade 2</td>
<td>0</td>
<td>7</td>
<td>7</td>
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<td>Grade 3</td>
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<td>0</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Grade 4</td>
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</tbody>
</table>
Mean % change in BMD in Spine from baseline to 12 mos

Mean % change in BMD with and without Tamoxifen

Mean % change in BMD in Spine from baseline to 12 mos

% Δ

Mean % change in BMD with and without Tamoxifen

% Δ
Conclusions

• ZA prevents bone loss in women with chemo-induced ovarian failure.
• ZA added minimal toxicity to adjuvant chemotherapy.
• “Early” versus “late” results are pending; therefore the optimal timing of ZA remains undefined and follow-up continues for this secondary endpoint.
• ZA was administered every 3 mos in this trial. ZA every 6 mos prevents bone loss in premenopausal women receiving GnRH agonist (Gnant J Clin Oncol 25:820-8, 2007) and is likely to be effective in chemo-induced ovarian failure.

Zoledronic Acid ready for prime time?

• Bone Health:
  – enough trials to conclude preserves BMD; FDA approved for postmenopausal osteoporosis
  – questions remaining: optimal schedule? ZA versus Denosumab?
• Prevention of Metastases?
  – Biologic rationale and preclinical data
  – ABCSG trial not placebo-controlled; < 10% had events; only included ER+ treated with anti-estrogen therapy
  – Ongoing larger trials AZURE, SWOG-Intergroup
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Disclosures

• I have no relevant relationships to disclose.