Current Management and New Advances for Breast Cancer Bone Metastases

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Bone Metastases in Breast Cancer

- The skeleton is the initial site of recurrence in 35-40% of breast cancer patients
- Ultimate incidence of bone metastases in advanced breast cancer patients approaches > 80%
## Bone Metastases by Cancer Types

<table>
<thead>
<tr>
<th></th>
<th>5-year World Prevalence¹ (thousands)</th>
<th>Incidence of Bone Metastases in Advanced Cancers² (%)</th>
<th>Median Survival¹²-⁵ (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>4406</td>
<td>65-75</td>
<td>19-25</td>
</tr>
<tr>
<td>Prostate</td>
<td>2369</td>
<td>65-75</td>
<td>12-53</td>
</tr>
<tr>
<td>Lung</td>
<td>1369</td>
<td>30-40</td>
<td>6-7</td>
</tr>
<tr>
<td>Bladder</td>
<td>1110</td>
<td>40</td>
<td>6-9</td>
</tr>
<tr>
<td>Melanoma</td>
<td>643</td>
<td>14-45</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Renal</td>
<td>586</td>
<td>20-25</td>
<td>12</td>
</tr>
<tr>
<td>Thyroid</td>
<td>531</td>
<td>60</td>
<td>48</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>183</td>
<td>70-95</td>
<td>48-60</td>
</tr>
</tbody>
</table>

Mechanism and Types of Bone Metastases in Breast Cancer

- **Tumor cell seeding**
  - Circulating cells have affinity for bone

- **Tumor cell dormancy**
  - Bone may serve as reservoir for malignant cells

- **Metastatic growth**
  - Interaction between tumor cells and bone microenvironment contribute to growth

- **Osteoblastic lesions**
  - Build up of weak, lower quality bone

- **Osteolytic lesions**
  - Bone metastases eating away at normal bone, causing “holes”

- **Disruption of normal balance of healthy bone**
Breast Cancer and the Bone Microenvironment

[Diagram showing metastatic cancer cell and interactions with bone-derived growth factors, osteoclasts, osteoblasts, osteolytic bone lesion, and osteoblastic bone lesion.]
Pathogenesis of Bone Metastases

Bone-derived growth factors:
- Tumor-derived osteoclast activating factors:
  - PTH-RP
  - IL-6, -8, -11
  - TNF
  - M-CSF

Osteoblast-derived growth factors:
- ET-1
- TGF-β
- FGF
- BMPs
- IGFs

(+) (+)

Osteoclasts

Osteoblasts

Bone

ET-1 = endothelin-1; PTH-RP = Parathyroid Hormone Related Protein; M-CSF = Macrophage Colony Stimulating Factor

Adapted with permission from Saad F, Schulman CC. Eur Urol. 2004;45:26-34.
Current Treatment of Breast Cancer Bone Metastases

- **Local Therapeutic Strategies**
  - Surgery
  - Radiation

- **Systemic Therapy**
  - Bisphosphonates
  - Pain Medication
Skeletal Complications from Bone Metastases in Breast Cancer Patients

- Spinal Cord Compression
- Pathologic Fracture
- Pain
- Hypercalcemia

Cancer Treatment-Induced Bone Loss
  - Hormonal Effects
  - Chemotherapy Sequela
  - Radiation
Patients With Bone Lesions Are at High Risk for Developing Skeletal Complications

Placebo Arms of Large Randomized Studies

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Patients With SREs (%)</th>
</tr>
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<tbody>
<tr>
<td>Breast¹ 24 mo</td>
<td>52% 11% 3%</td>
</tr>
<tr>
<td>Prostate² 24 mo</td>
<td>43% 25% 4% 8%</td>
</tr>
<tr>
<td>Multiple myeloma³ 21 mo</td>
<td>37% 34% 5% 3%</td>
</tr>
<tr>
<td>NSCLC + other solid tumors⁴ 21 mo</td>
<td>34% 22% 5% 4%</td>
</tr>
</tbody>
</table>

*C21-month data except for surgical intervention and spinal cord compression, for which only 9-month data are available; NSCLC = non-small cell lung carcinoma.

Bone Complications Can Negatively Impact Quality of Life (QOL)

- Increased medical costs
- Impaired mobility
- Skeletal Complications
- Diminished QOL
- Negative impact on survival

Bisphosphononates and Bone Metastases

- Role in treatment of hypercalcemia, bone metastases, preservation of bone mineral density, possible role in prevention?
- Several approved for reduction in skeletal related complications in patients with bone metastases, but no improvement in survival in metastatic disease has yet been seen.
- Mechanism of action involves suppression of bone turnover through targeting osteoclasts.
Bisphosphonate Inhibition of Osteoclast Activity: Mechanism of Action

Bisphosphonates inhibit osteoclast activity, and promote osteoclast apoptosis\(^1\)

Bisphosphonates are released locally during bone resorption\(^1\)

Bisphosphonates are concentrated under osteoclasts\(^1\)

Bisphosphonates may modulate signaling from osteoblasts to osteoclasts

Increased OPG production\(^2\)
Decreased RANKL

Zoledronic Acid Reduces the Risk of SREs Across All Tumor Types

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Risk Reduction</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast$^1$</td>
<td>41%</td>
<td>0.019</td>
</tr>
<tr>
<td>Prostate</td>
<td>36%</td>
<td>0.002</td>
</tr>
<tr>
<td>Solid tumors$^3$</td>
<td>31%</td>
<td>0.003</td>
</tr>
<tr>
<td>Lung cancer$^3$</td>
<td>32%</td>
<td>0.016</td>
</tr>
<tr>
<td>RCC$^4$</td>
<td>58%</td>
<td>0.010</td>
</tr>
</tbody>
</table>

RCC = renal cell carcinoma; ZOL = zoledronic acid.
Could Zoledronic Acid prolong Overall Survival?

- **Indirectly**
  - Reduce incidence and delay onset of life-limiting SREs
  - Preserve functional independence and quality of life

- **Directly**
  - Anti-tumor activity may slow progression of disease

- In 2010, no evidence based study shows bisphosphonates prolong Overall Survival
Calcium
NIH Office of Dietary Supplements

• Calcium is the most abundant mineral in the body
  ◦ 99% in bones and teeth (storage site)
  ◦ Necessary for muscles, many enzymes, the heart and nervous system

• Sources of calcium
  ◦ Food sources: milk, yogurt, cheese, some vegetables (chinese cabbage, kale, broccoli)
  ◦ Supplements: (1,000 – 1,500 mg/day)
    • Calcium carbonate (cheap, 40% calcium) vs calcium citrate (21% calcium) – absorption similar except citrate better with low stomach acid
  ◦ Split the doses!
Vitamin D
NIH Office of Dietary Supplements

- Vitamin D is a fat soluble vitamin that sends signals to the gut to absorb calcium and phosphorus
  - Liver and kidney convert vitamin D to active form
  - By promoting calcium absorption, helps maintain strong bones
- Sources of vitamin D:
  - Food: fortified milk, fish, other dairy
  - Sunlight: UV rays from sunlight stimulate vitamin D production in the skin
  - Supplements: calciferol (vitamin D3) 200-800 IU/day (upper limit 2,000 IU/day)
- Measurement of serum 25 hydroxy vitamin D levels
- Vitamin D may be protective against some cancers
Vitamin D is a Natural Brake on Estrogen and Growth Factor Signaling
When to start therapy?

- Treatment of hypercalcemia
- Treatment of bone metastases
  - Reduction in skeletal-related events (fracture, radiation, surgery, cord compression)
  - Improvement in pain, QOL
Choosing a Bisphosphonate

• Several bisphosphonates approved throughout the world for reduction in skeletal-related complications in patients with bone metastases
  ◦ clodronate (po)
  ◦ pamidronate (IV) - US
  ◦ zoledronic acid (IV) - US
  ◦ ibandronate (IV, po)
In Vitro Potency of Bisphosphonates

- **Non-nitrogen containing**
  - etidronate (Didronel) 1
  - clodronate (Bonefos) 10

- **Nitrogen containing**
  - pamidronate (Aredia) 100
  - alendronate (Fosamax) 1,000
  - risedronate (Actonel) 5,000-10,000
  - ibandronate (Bondronat) 10,000
  - zoledronic acid (Zometa) 20,000
Bisphosphonate Side Effects

- Oral administration:
  - Poorly absorbed from the GI tract (0.5-4%)
  - Non-nitrogen-containing: diarrhea
  - Nitrogen-containing: esophagitis, nausea

- IV administration:
  - Fever, flu symptoms, arthralgias/myalgias, hypocalcemia
  - Renal insufficiency (related to dose, volume, rate)

- Potential for interference with mineralization
  - Skeletal ½-life several years
  - Osteonecrosis of the jaw
Bisphosphonate Side Effects: Osteonecrosis of the Jaw (ONJ)

- **Osteonecrosis of the Jaw: DEFINITION**
  - Exposed bone in the maxillofacial region
    - Spontaneous or induced (if induced, no signs of healing)
    - May or may not be associated with infection
    - May or may not be associated with pain or other symptoms
  - In the absence of radiation to the head and neck
S0702 ONJ Prospective Registry Trial

- Rationale: Gathering information about how often osteonecrosis of the jaw occurs in patients receiving zoledronic acid for bone metastases may help doctors learn more about the disease and provide the best follow-up care.
- Multicenter study in which patients undergo dental assessments at baseline and every 3-6 months for 3 years
- Primary outcome: Assess the incidence of ONJ at 3 years in cancer patients
Receptor Activator of Nuclear Factor \( \kappa B \) Ligand (RANKL) and Osteoprotegerin (OPG)

Stromal cell/Osteoblast

Parathyroid hormone/Parathyroid hormone–related protein

1,25D\(_3\)

PGE\(_2\)

RANKL

OPG

Interleukin-11

Osteoclast Precursor

Osteoclast

1,25D\(_3\) = 1,25 dihydroxyvitamin D\(_3\); PGE\(_2\) = prostaglandin E-2.

New Agents: Denosumab

• Fully human monoclonal antibody binds to RANK Ligand (RANKL)
• Administration via subcutaneous (SC) injection
• FDA Approved for the Treatment of Osteoporosis, and an Indication for Bone Metastases is likely in near future
Prevention of SREs in Patients with Breast Cancer and Bone Metastasis: Denosumab vs Zoledronic Acid

Advanced breast cancer and bone metastasis
No prior or current IV bisphosphonates (N = 2046)

1:1

Denosumab 120 mg SC + Placebo IV q4wk (n = 1026)

Zoledronic acid 4 mg IV + Placebo SC q4wk (n = 1020)

Primary end point: time to first on-study SRE

Denosumab vs Zoledronic Acid in Patients With Breast Cancer and Bone Metastasis

**Time to First On-Study SRE**

- **HR 0.82 (95% CI: 0.70, 0.95)**
- **P < 0.0001 (Noninferiority)**
- **P = 0.01 (Superiority)**

**KM Estimate of Median Months**

- Denosumab: Not reached
- Zoledronic Acid: 26.5 mo

**18% Risk Reduction**

<table>
<thead>
<tr>
<th></th>
<th>Time to First On-Study SRE (median)</th>
<th>Time to First Radiation to Bone (median)</th>
<th>Skeletal Morbidity Rate (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denosumab</td>
<td>Not reached</td>
<td>Not reached</td>
<td>0.45/subject/y</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>25.2 mo</td>
<td>Not reached</td>
<td>0.58/subject/y</td>
</tr>
<tr>
<td><em>P</em>-value</td>
<td>0.007</td>
<td>0.01</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Denosumab vs Zoledronic Acid: Adverse Events

<table>
<thead>
<tr>
<th>Events (%)</th>
<th>Denosumab (n = 1020)</th>
<th>Zoledronic acid (n = 1013)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall AEs</td>
<td>96</td>
<td>97</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td>Acute phase reactions*</td>
<td>10.4</td>
<td>27.3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0.9</td>
<td>11.5</td>
</tr>
<tr>
<td>Bone pain</td>
<td>1.3</td>
<td>3.6</td>
</tr>
<tr>
<td>Chills</td>
<td>0.3</td>
<td>3.6</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1.5</td>
<td>3.2</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>0.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Flushing</td>
<td>0.0</td>
<td>0.3</td>
</tr>
<tr>
<td>AEs related to renal toxicity</td>
<td>4.9</td>
<td>8.5</td>
</tr>
<tr>
<td>Serious AEs related to renal toxicity</td>
<td>0.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw†</td>
<td>2.0</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*Within 3 days of drug administration; †P = 0.39.
Why shouldn’t all newly diagnosed breast cancer patients receive bisphosphonates?

- Further data needed to recommend broad use in breast cancer patients
  - Ongoing trials
  - Side Effects and Toxicity (ONJ, bone quality)
  - Quality of Life factors
  - Cost
Take Home Points

- Bone Metastases are a relatively common complication of Metastatic Breast Cancer and SREs affect quality of life
- Bisphosphonates have reduced SREs in metastatic bone disease
- Bisphosphonates should be dosed with Calcium and Vitamin D supplementation
- Inhibition of RANK ligand is a promising new therapy for metastatic
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