Recent Progress in Our Understanding of Bone Metastases

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Elderly men with prostate cancer + ADT
Background and Rationale
ADT and Osteoporosis
Proportion of Patients With Fractures 1-5 Yrs After Cancer Diagnosis

Bone metastases
Bone metastases

• > 90% of patients with metastatic CRPC have radiologic evidence of bone metastases\(^1\)
• Skeletal-related events (SREs) include spinal cord compression, pathological fracture, and need for surgery or EBRT\(^2\)
• Bone metastases are a major cause of death, disability, decreased quality of life, and increased treatment cost\(^3\)

Lumbar spine MRI
Bone Metastases: The Clinical Problems

- Replacement of hematopoietic tissues in the bone marrow by the prostate cancer cells may lead to
  - Anemia
  - Increased susceptibility to infection
- Damage caused by bone metastases overgrowth may lead to
  - Pain
  - Fractures
  - Spinal cord compression that may lead to hemiparesis or paresis

### Incidence of bone complications

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo Arms</th>
<th>Pamidronate Trials</th>
<th>ZA Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation time, mos</td>
<td>24</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>Total SREs, %</td>
<td>64</td>
<td>51</td>
<td>49</td>
</tr>
<tr>
<td>Radiation to bone, %</td>
<td>43</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>Pathologic fractures, %</td>
<td>52</td>
<td>37</td>
<td>25</td>
</tr>
<tr>
<td>Hypercalcemia of malignancy, %</td>
<td>13</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Surgery to bone, %</td>
<td>11</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Spinal cord compression, %</td>
<td>3</td>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>

Skeletal-related events in metastatic prostate cancer

24-month data of the placebo arm of a randomized trial; n=208
Bone lesions are associated with worse survival


MDT approach

Urologist

Radiotherapist

Medical oncologist

Surgeon

Nuclear medicine physician
Normal bone remodeling relies on the balance between the activities of osteoblasts and osteoclasts. Normal bone remodeling

- **Reversal**
- **Resorption**
- **Formation**
- **Resting**

**Osteoclasts** and **Mononuclear cells**

**Osteoblasts**

**Mineralized bone matrix**

- **New bone**

The “Vicious Cycle” of Bone Metastases in CRPC

CRPC bone metastases are predominantly osteoblastic

Osteoclasts → Prostate cancer cells → Osteoblasts

Osteolytic factors (PTHrP/IL-6)

Osteoblastic factors (ET-1, BMP, IGFs, FGF, uPA, TGF-β)

Growth factors (ALP, PINP, Unknown GFs)

Formation

Mineralized bone matrix

New bone

CTXI, ICTP, Bone-derived growth factors (TGF-β)

ET, endothelin; ICTP, C-terminal telopeptides of type I collagen; PTHrP, parathyroid hormone–related protein; uPA, urokinase-type plasminogen activator.

The Ability of CRPC Cells to Induce Bone Formation is Essential for Metastatic Growth

Osteoblastic factors secreted from tumor cells

- Promote osteoblast proliferation
- Stimulate osteoblasts to produce factors that trigger proliferation of prostate cancer cells
- Promote the secretion of growth factors that trigger deposition of new bone matrix

Bone Metastasis—Targeted Therapies: Capitalizing on the Altered Microenvironment

Existing therapies for bone metastasis

- Bisphosphonates
- Denosumab

Interfere with deregulated signaling pathways to/from the bone

- γ-Rays: EBRT
- β-Emitters: Strontium-89, samarium-153
- α-Emitter: Radium 223

Target the bone and actively kill the tumor cells

Radium-223 Has a Targeted Mechanism of Action

Targets new bone, e.g. bone metastases

Irradiates adjacent tumor cells leading to highly localized tumor cell killing

Images obtained after 2 injections of Ra-223 showed a significant decrease (≥ 25% decrease of SUV$_{\text{max}}$ from baseline) in [F$^{18}$] FDG uptake intensity in multiple bone mets located in the thoracic and lumbar spine, indicating a partial metabolic treatment response at the level of the tumor cells early during Ra-223 therapy.
Therapies That Interfere With Deregulated Signaling Pathways to/From the Bone

Denosumab

Binds to RANKL and prevents it from binding to RANK on the surface of cells

- Loss of osteoclast formation, function, and survival

- Provides palliative effect

- No survival benefit has been demonstrated

Bisphosphonates

Bind to bone mineral and are taken up by mature osteoclasts at sites of bone resorption

- Loss of resorptive function

Elderly men with prostate cancer
## Pamidronate vs Placebo in Metastatic Prostate Cancer

<table>
<thead>
<tr>
<th>Skeletal Event by Study Week 27, n (%)</th>
<th>Pamidronate (n = 169)</th>
<th>Placebo (n = 181)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SRE</td>
<td>42 (25)</td>
<td>46 (25)</td>
</tr>
<tr>
<td>Radiation to bone for pain relief</td>
<td>25 (15)</td>
<td>29 (16)</td>
</tr>
<tr>
<td>Radiation to bone to prevent fracture</td>
<td>8 (5)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Nonvertebral fractures</td>
<td>14 (8)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Vertebral fractures</td>
<td>11 (7)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>5 (3)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Surgery to bone</td>
<td>5 (3)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>1 (&lt;1)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>
ZA vs Placebo: Time to First On-Study SRE

Patients at Risk, n

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Patients at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZA 4 mg</td>
<td>214</td>
</tr>
<tr>
<td>ZA 8/4 mg</td>
<td>221</td>
</tr>
<tr>
<td>Placebo</td>
<td>208</td>
</tr>
</tbody>
</table>

Denosumab vs ZA: Time to First On-Study SRE


HR: 0.82 (95% CI: 0.71-0.95; \( P = .0002 \) for noninferiority analysis; \( P = .008 \) for superiority analysis)

Median Mos (95% CI)
- Denosumab: 20.7 (18.8-24.9)
- ZA: 17.1 (15.0-19.4)

Patients at Risk, n
- Denosumab: 950, 758, 582, 472, 361, 259, 168, 115, 70, 39
- ZA: 951, 733, 544, 407, 299, 207, 140, 93, 64, 47
Time to First and Subsequent On-Study SRE (Multiple Event Analysis)*

![Graph showing cumulative mean number of SREs per patient over time, comparing Denosumab (n = 950) and ZA (n = 951).]

Rate ratio: 0.82 (95% CI: 0.71-0.94; \(P = .004\); adjusted \(P = .008\))

*Events occurring at least 21 days apart.

## Comparison of First SRE After Starting Bone-Directed Therapy

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>ZA (n = 951)</th>
<th>Denosumab (n = 950)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total confirmed events</td>
<td>386 (41)</td>
<td>341 (36)</td>
</tr>
<tr>
<td>Radiation to bone</td>
<td>203 (21)</td>
<td>177 (19)</td>
</tr>
<tr>
<td>Pathologic fracture</td>
<td>143 (15)</td>
<td>137 (14)</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>36 (4)</td>
<td>26 (3)</td>
</tr>
<tr>
<td>Surgery to bone</td>
<td>4 (&lt; 1)</td>
<td>1 (&lt; 1)</td>
</tr>
</tbody>
</table>

Comparison of Bone-Directed Therapies

<table>
<thead>
<tr>
<th></th>
<th>Zoledronic Acid</th>
<th>Denosumab</th>
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</thead>
<tbody>
<tr>
<td><strong>Route</strong></td>
<td>Intravenous</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td><strong>Acute phase reactions</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Renal toxicity</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Hypocalcemia</strong></td>
<td>Rare</td>
<td>Not rare</td>
</tr>
<tr>
<td><strong>ONJ</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Survival benefit</strong></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Reimbursement concerns</strong></td>
<td>Usually not</td>
<td>Regional</td>
</tr>
</tbody>
</table>
Abiraterone and SRE

Radiation to bone can require multiple treatments\textsuperscript{5-7}

- The most common reason for radiation is pain palliation; it is also used as prophylaxis for impending fracture or as an adjunct to surgery to reduce risk of bone complications\textsuperscript{6,8}

- A common schedule of radiation is 10 treatments over 2 weeks\textsuperscript{5-7}

Pathologic fractures can be painful and often do not heal, resulting in bone destruction\textsuperscript{9}

- Pathologic fractures occur most commonly in the ribs, vertebrae, pelvis, and femur\textsuperscript{10-12}

- Fractures of weight-bearing bones often require surgical stabilization\textsuperscript{13}

Surgery to bone may be required to treat pain, pathologic fracture, or other complications\textsuperscript{5,13}

- Postsurgical rehabilitation is often necessary\textsuperscript{14}

Spinal cord compression is considered an oncologic emergency\textsuperscript{10}

- The most common tumor types associated with spinal cord compression are: \textsuperscript{15,17}
  - Breast (20\%-30\%)
  - Lung (15\%)
  - Prostate (10\%-15\%)
Beta emitters: long range increases bone marrow exposure

<table>
<thead>
<tr>
<th>Beta</th>
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</thead>
<tbody>
<tr>
<td>Range in tissue (μm)</td>
<td>50–12 000</td>
</tr>
<tr>
<td>Relative particle mass</td>
<td>1</td>
</tr>
<tr>
<td>DNA hits for cell kill</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>

Range of beta particle
(10–1000 cell diameters²)