Management of Bone Metastases

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Bone Metastases: Scope of the Problem

Bone metastases affect more than 500,000 patients in the United States

Myeloma: > 90% of patients

Breast: 2/3 of patients

Prostate: 2/3 of patients

Lung: 1/3 of patients
Bone Metastases Can Lead to SREs

Patients who will likely develop an SRE without treatment

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Patients (%)</th>
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<tbody>
<tr>
<td>Renal Cell Carcinoma (n = 74)</td>
<td>74</td>
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<tr>
<td>Multiple Myeloma (n = 179)</td>
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<tr>
<td>Breast (n = 114)</td>
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<tr>
<td>Prostate (n = 208)</td>
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<tr>
<td>NSCLC (n = 250)</td>
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</table>

> Up to 74% of patients with bone metastases may experience an SRE despite standard anticancer treatments

Data are from placebo-controlled arms of bisphosphonate trials.

Distribution of Metastases in Bone

- Skull: 46%
- Cervical spine: 40%
- Scapula and clavicle: 20%
- Proximal humerus: 17%
- Ribs: 53%
- Thoracic spine: 68%
- Lumbar spine: 65%
- Pelvis: 70%
- Proximal femur: 52%

Weight bearing bones at risk for fracture
Normal Bone Biology

Bone is always in an active state of remodeling (build up/break down)

- **Resorption**: stimulated osteoclasts erode bone, creating a cavity
- **Reversal**: bone surface is prepared for osteoblasts to begin forming bone
- **Formation**: osteoblasts replace resorbed bone and fill the cavity with new bone
- **Resting**: bone surface rests until a new remodeling cycle begins

Adapted from Novert's Pharmaceuticals
Bone Metastases: General Mechanism

“seed and soil”

Primary cancer → Angiogenesis → Invasion → Embolism

Response to microenvironment → Extravasation → Adherence → Arrest in distant capillary bed in bone

Transport

Tumor cell proliferation → Bone metastases

-Osteolytic
-Osteoblastic
-Mixt

The Vicious Cycle of Bone Destruction

- Growth factors and cytokines released by tumor cells

- Osteoclastic resorption stimulated
  - Peptides (e.g., TGF-β) released by bone resorption
  - Tumor cell production of factors increased
  - More bone resorption
  - Tumor cell proliferation

Effect of Bisphosphonates on Vicious Cycle of Bone Destruction

- Decrease activity of osteoclasts
  - Reduction in release of peptides
  - Slowed tumor-cell growth
  - Reduced production of PTHrP and other factors
  - Decrease in bone resorption

Bisphosphonates: Mechanism of Action

- Bisphosphonates have a strong affinity for calcium phosphate
  - **Bind to resorption sites**

- Bisphosphonates **inhibit bone resorption**
  - Direct effects on osteoclasts
  - Indirect effects via other cells

- Bisphosphonates **decrease 4 parameters of osteoclast function**
  - ↓ Recruitment of cells
  - ↓ Adhesion to bone
  - ↓ Lifespan of cells (increasing rates of apoptosis)
  - ↓ Cellular activity
Osteolytic metastases

- Tumor cells produce growth factors that stimulate bone destruction
  - i.e. RANK ligand
- Osteoclasts are activated and break down bone
- Osteoblasts cannot build bone back fast enough
- Decreased bone density and strength; high risk for fracture
- Most common in multiple myeloma and breast cancer
- Osteolytic bone metastasis is due to an imbalance in the RANKL/OPG ratio.

Osteoblastic Metastasis

- Osteoblasts are stimulated by tumors to lay down new bone
- Bone becomes abnormally dense and stiff,
- Paradoxically bones are also at risk of breaking
- Most common in prostatic carcinoma
Radiology: How to Evaluate

- Imaging tests
  - X-ray
  - Bone scan
    - Sensitive, not specific.
    - False positives: trauma, arthritis, infection
  - CT (“CAT” scan)
  - PET scan
  - MRI scan

- Bone biopsy – for confirmation

- Blood tests
  - Calcium, alkaline phosphatase
MRI imaging

Sensitive for detection of fluid signal (e.g. edema)
FDG PET/CT imaging

(before and after the cancer treatment)

49 years old, female patient; breast cancer, after 18 months chemo-hormonal-BP therapy.

Sclerotic changes of the bone metastases and hepatic response.

Tateishi U et al. Radiology 2008;247:189-196
Bone metastases and treatment response by PET/CT
False negativity by PET/CT

Progressive Osteoblastic Bone Metastases in Breast Cancer
Negative on FDG-PET

Tatiana Hongo, MD, Camilo Garcia, MD, Ingrid Vandervelde, MD, Ivan Ceroni, MD, Thierry Cal, MD.

FIGURE 4. Bone metastases on SPECT images. A, Tc-99m MDP SPECT shows increased uptake in the third lumbar vertebra body. B, Tc-99m MDP SPECT shows an increased uptake in the spinous process of the fourth lumbar vertebra.
Negative Impact of Bone Complications

**Increased medical costs**[^1]
Treatment of bone complications more than doubles the total treatment costs for patients with bone metastases.

**Impaired mobility**[^6]
Hip fracture associated with a 50% disability rate; 25% of these require nursing home care.

**Skeletal Complications**

**Diminished quality of life**[^2-4]
History of a skeletal complication is associated with lower QOL in breast and prostate cancer.

**Negative impact on survival**[^5]
Men with prostate cancer without skeletal fracture survived 39 months longer than those with a fracture.

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Clinical Consequences of Cancer-Induced Bone Lesions

- Pathological fractures
  - Nonvertebral
  - Vertebral compression
- Spinal cord compression/collapse
- Radiation therapy
- Surgery to bone
- Hypercalcemia

Skeletal-related events

- Bone pain
- Use of analgesics
- Quality-of-life effects
- Survival
Management of Bone Disease in Cancer Requires a Multidisciplinary Approach

- Oncologist
- Surgeons
  - Orthopedist
  - Neurosurgeon
- Radiation therapist
- Nuclear medicine specialist
- Pain specialist
- Rehabilitation/physical medicine
  - Physician
  - Physical therapist
### Structure of Bisphosphonates: Amino Versus Non-aminobisphosphonates

#### Inhibitors of bone loss
- Potency varies greatly depending on R1 & R2 side chains

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<td><strong>Zoledronic acid</strong></td>
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Available IV bisphosphonates

Pamidronate

- In placebo-controlled trials significantly reduced fracture, radiation, pain

Zoledronic Acid

- More potent agent; equally effective in trials
- Shorter infusion time (15 min vs 3 hours)
Newest Bisphosphonate: Ibandronate

- Both oral and IV forms
- Prevents bone events (fractures, radiation, surgery) compared with placebo
- Can relieve bone pain when given with a loading dose (but takes up to 12 weeks)
- May have less kidney toxicity
- Ongoing comparisons to zoledronic acid are underway

Cameron et al, The Oncologist, 2006
Risk of renal impairment after treatment with ibandronate versus zoledronic acid: a retrospective medical records review

Ingo J. Diel · Rudolf Weide · Hubert Köppler ·
Oral versus intravenous ibandronic acid: a comparison of treatment options for metastatic bone disease

Kyriaki Mystakidou · Evangelia Stathopoulou · Efi Parpa · Vassilios Kouloulias · Evangelia Kouskouni · Lambros Vlahos

- 52 pts, 6 months follow up,
- clinical response and safety were tested
- breast, prostate, lung, urogenital or colon cancer pts;
  - received IV ibandronic acid 6 mg infused or oral IB 50 mg/day
- Both formulations improved pain, physical and functioning scores
Meta-analysis: SRE Risk Reduction in MBC With Bone Mets—BPs vs Placebo

- **Zoledronic acid 4 mg** (Kohno 2005) - Risk Reduction: 41% P Value: .001
- **Pamidronate 90 mg** (Aredia study 18 and 19) - Risk Reduction: 23% P Value: < .001
- **Ibandronate iv 6 mg** (Body 2003) - Risk Reduction: 18% P Value: .04
- **Ibandronate oral 50 mg** (Body 2004) - Risk Reduction: 14% P Value: .08
- **Oral clodronate 1600 mg** (Kristensen 1999) - Risk Reduction: 31% P Value: .03 (pooled)
  - (Paterson 1993) - Risk Reduction: 17%
  - (Tubiana-Hulin 2001) - Risk Reduction: 8%

Cochrane Database Comparing Placebo-Controlled Trials in Breast Cancer Setting

Efficacy of Clodronate, Pamidronate, and Zoledronate in Reducing Morbidity and Mortality in Cancer Patients With Bone Metastasis: A Meta-Analysis of Randomized Clinical Trials

Marcio Machado, PhD; Lorena Souza Cruz, MBA; Gabriela Tarnus, MBA; and

<table>
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**Morbidity**

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# Summary of bisphosphonate trials assessing skeletal-related events (SREs) associated with breast cancer metastatic to bone

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<th>Main author/year</th>
<th>Patients (n)</th>
<th>SREs/year per patient in bisphosphonate group</th>
<th>SREs/year per patient in placebo group</th>
<th>SRE reduction (%)</th>
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<td>Rosen <em>et al.</em> 2004&lt;sup&gt;23&lt;/sup&gt; (zoledronate) (pamidronate)</td>
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The Journal of International Medical Research
Cost-effectiveness of oral clodronate in breast cancer
A Paterson 2008; 36: 400 – 413

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Germany

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<td>€45.28</td>
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</tr>
<tr>
<td>Total cost/patient</td>
<td>€6916.39</td>
<td>€7758.18</td>
<td>€10585.58</td>
<td>€9906.38</td>
</tr>
</tbody>
</table>

UK
### Bisphosphonates: Structure-related Safety Profiles

<table>
<thead>
<tr>
<th>Bisphosphonates</th>
<th>Non-nitrogen</th>
<th>Nitrogen-containing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Oral</td>
<td>IV</td>
</tr>
<tr>
<td>Esophagitis(^1)</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Diarrhea(^2)</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Acute phase response(^3,4)</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Uveitis/scleritis(^5,6)</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Renal impairment(^7)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

---

### Zoledronic Acid–Adjustment of Starting Dose for Renal Insufficiency

<table>
<thead>
<tr>
<th>Baseline CrCl, mL/min</th>
<th>Recommended Zoledronic Acid Dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>4.0</td>
</tr>
<tr>
<td>50-60</td>
<td>3.5</td>
</tr>
<tr>
<td>40-49</td>
<td>3.3</td>
</tr>
<tr>
<td>30-39</td>
<td>3.0</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>
**Indication of the BPs**

- expected survival; more than 6 months
- proven osteolytic metastases,
- bone pain due to metastases,
- hypercalcemia

<table>
<thead>
<tr>
<th></th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease extent</strong></td>
<td></td>
</tr>
<tr>
<td>Bone only</td>
<td>3</td>
</tr>
<tr>
<td>Bone + soft tissue</td>
<td>2</td>
</tr>
<tr>
<td>Bone + visceral</td>
<td>1</td>
</tr>
<tr>
<td><strong>Bone morbidity</strong></td>
<td></td>
</tr>
<tr>
<td>Previous skeletal event*/pain</td>
<td>3</td>
</tr>
<tr>
<td>Bone pain</td>
<td>2</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>1</td>
</tr>
<tr>
<td><strong>Performance status</strong></td>
<td></td>
</tr>
<tr>
<td>1,2</td>
<td>3</td>
</tr>
<tr>
<td>0,3</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><strong>Underlying treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Chemo / hormone resistant</td>
<td>2</td>
</tr>
<tr>
<td>Potentially hormone sens</td>
<td>1</td>
</tr>
<tr>
<td><strong>Good prognostic factors</strong></td>
<td></td>
</tr>
<tr>
<td>Disease free &gt; 3 yrs</td>
<td>1</td>
</tr>
<tr>
<td>Pre-menopausal</td>
<td>1</td>
</tr>
<tr>
<td>Ductal grade 1 / 2 or lobular</td>
<td>1</td>
</tr>
<tr>
<td>Bone mets at presentation</td>
<td>1</td>
</tr>
</tbody>
</table>

- 11 : Highest priority
- 7-11: Moderate priority
- <7 : Low priority
Biochemical Response and Survival

Baseline NTx stratification

Elevated
- **E group**
  - (≥ 64 nmol/mmol creatinine)

Normal
- **N group**
  - (< 64 nmol/mmol creatinine)

**ZA 4 mg/3-4 wks**

3-mo NTx status

Elevated
- **E group**
- **E**

Normal
- **N group**
- **N**

Biochemical Response Correlates With Improved Outcome

Skeletal Complications
- E-E group (n = 36)
- E-N group (n = 160)
- N group (n = 132)

Persistently elevated NTx
- Normalized NTx
- Normalized baseline NTx

E-N vs E-E
- Risk reduction: 49%
- \( P = .0020 \)

Survival
- E-E group (n = 36)
- E-N group (n = 160)
- N group (n = 132)

Persistently elevated NTx
- Normalized NTx
- Normalized baseline NTx

E-N vs E-E
- Risk reduction: 48%
- \( P = .0017 \)

Phase II Trial Evaluating the Palliative Benefit of Second-Line Zoledronic Acid in Breast Cancer Patients With Either a Skeletal-Related Event or Progressive Bone Metastases Despite First-Line Bisphosphonate Therapy

Mark J. Clemens, George Dranitsaris, Wei S. Ooi, Geetha Yogendran, Tatjana Sukovic, Betty Y.L. Wong, Sunil Verma, Kathleen L. Pritchard, Maureen Trudeau, and David E.C. Cole

Fig 1. The impact of zoledronic acid on the worst pain score.

Fig 2. The impact of zoledronic acid on number of pain sites.

Fig 3. Percent change in urinary N-telopeptide (NTX) over time.
## Bisphosphonate-associated osteonecrosis of the Jaws

### Table 3. Cumulative Hazard of Developing Osteonecrosis of the Jaw v Duration of Treatment

**Bamias et al. JCO 2005**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>12 Months</th>
<th>24 Months</th>
<th>36 Months</th>
<th>48 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>All (N = 252)</td>
<td>0</td>
<td>0 to 5</td>
<td>1</td>
<td>1 to 13</td>
</tr>
<tr>
<td>Zoledronic acid (n = 105)</td>
<td>1</td>
<td>0 to 3</td>
<td>7</td>
<td>1 to 13</td>
</tr>
<tr>
<td>Pamidronate/pamidronate and zoledronic acid (n = 127)</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0 to 6</td>
</tr>
</tbody>
</table>
### Possible Mecanism of Bisphosphonate-associated Osteonecrosis of the Jaws

**Table 1. Effects of Bisphosphonates (↑ Increased; ↓ Decreased)**

<table>
<thead>
<tr>
<th>Sphere of Activity</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoblast</td>
<td>Proapoptotic effect on keratinocytes</td>
<td></td>
</tr>
<tr>
<td>Osteocyte</td>
<td>Metabolic activity ↓, Apoptosis ↓ (etidronate, alendronate, pamidronate), Avascular bone necrosis</td>
<td></td>
</tr>
<tr>
<td>Vessels</td>
<td>Angiogenesis ↓, Endothelial growth factor ↓</td>
<td></td>
</tr>
<tr>
<td>Tumor cell</td>
<td>Apoptosis ↑, Proliferation ↓, Invasion ↓, Adhesion ↓</td>
<td></td>
</tr>
<tr>
<td>γδ T-Lymphocytes</td>
<td>Function ↑ (risedronate)</td>
<td></td>
</tr>
</tbody>
</table>

Reduced bone remodeling, proapoptotic effect on keratinocytes, avascular bone necrosis.
### Bisphosphonate-associated osteonecrosis of the Jaws

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients, n (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>171 (46.5)</td>
</tr>
<tr>
<td>Metastatic breast cancer</td>
<td>143 (38.8)</td>
</tr>
<tr>
<td>Metastatic prostate cancer</td>
<td>23 (6.2)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>15 (4.1)</td>
</tr>
<tr>
<td>Other metastatic disease</td>
<td>13 (3.5)</td>
</tr>
<tr>
<td>Paget disease of bone</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>368 (100)</td>
</tr>
<tr>
<td><strong>Bisphosphonate medication</strong></td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>124 (35)</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>110 (31)</td>
</tr>
<tr>
<td>Pamidronate and zoledronic acid</td>
<td>100 (28)</td>
</tr>
<tr>
<td>Oral alendronate</td>
<td>15 (4.2)</td>
</tr>
<tr>
<td>Alendronate and zoledronic acid</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Oral risedronate</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Oral ibandronate</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Ibandronate and zoledronic acid</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Pamidronate, zoledronic acid, and alendronate</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>355 (100)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data from Kohno et al. Int. J Clin Oncol. 2008
Relative Risk Factors for ONJ

- Cancer
- Radiation therapy
- Corticosteroids
- Poor dental hygiene
- Poor diet
- Dental work
- Trauma
- Ethanol or tobacco use
- Coagulopathy
- Chemotherapy
- Infection
- Bisphosphonates
Longitudinal Cohort Study of Risk Factors in Cancer Patients of Bisphosphonate-Related Osteonecrosis of the Jaw

Konstantinos Valtsevanos, Athanassios Kyrgidis, Evgenia Ververou, Eirini Katodritou, Stefanos Triaridis,

1,621 pts,
29,006 IV BP, monthly administration

The rate of osteonecrosis;
Multpl myeloma 8.5 %,
Breast cancer 3.1 %
Prostatic carcinoma 4.9 %

Multivariate analysis;
Use of dentures,
Dental extraction,
Usage of zolendronat; statistically significant.

Smoking, periodontitis, age, root canal treatment; statistically insignificant
Exposed/necrotic bone;

- **Stage 1**: asymptomatic and have no evidence of infection
  - Antibacterial mouth rinse,
  - Clinical follow-up,
  - Patient education and review of indications for continued bisphosphonate therapy
  - Discontinuation of bisphosphonates therapy until osteonecrosis heals.

- **Stage 2**: associated with infection (pain and erythema with or without purulent drainage)
  - Oral antibacterial mouth rinse and broad-spectrum oral antibiotics
  - Pain control
  - Only superficial debridements to relieve soft-tissue irritation

- **Stage 3**: pain, infection, and 1 of the following: pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border.
  - Antibacterial mouth rinse, antibiotic therapy and pain control
  - Surgical debridement/resection for longer-term palliation of infection and pain

Regardless of the disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone.
Stage III osteonecrosis of the mandible and surgical exposure of the left hemi-mandible after segmental resection

Minimizing the Risk of ONJ

- Excellent oral hygiene is the best prophylaxis
- Limit EtOH and tobacco use
- Patients should have a dental assessment prior to starting IV BPs
  - Dental procedures (extensive) should be done prior to starting IV BPs if possible
- Avoid dental procedures once IV BPs started
Rarely observed side effects

Anterior Uveitis Complicating Zoledronic Acid Infusion

Annalisa Colucci, Giulio Modorati, Elisabetta Miserocchi, Federico Di Matteo, and Paolo Rama
San Raffaele Scientific Institute, Milano, Italy

Ocular inflammation, posterior skleritis, retinal pigment ephelitis were rarely observed.

Zoledronic acid induced osteonecrosis of tibia and femur

Gupta S et al. Ind J Cancer 2009
New Systemic Therapy: Denosumab

- Denosumab: antibody against RANK ligand, the stimulator for osteoclasts
- IgG₂, fully human monoclonal antibody to RANKL
- Once-a-month subcutaneous injection
- Promising results as osteoporosis treatment in clinical trials
- Emerging role in the treatment of bone metastases

*Ellis SABCS 2007; Lipton ASCO breast 2008; McClung et al, NEJM 2006

Blocking RANK ligand in a mouse can fill in a mouse bone metastases

The RANKL/RANK/OPG Axis: Receptor-Ligand Interactions

RANKL; secreted from osteoblasts and other stromal cells, interacts with the RANK receptor on osteoclast precursors and other cells.

Osteoprotegerin; natural decoy receptor that competes for binding with RANK and slows bone turnover.

This important pathway is the basis of a new therapeutic target.
Critical Role for NFκB Ligand (RANKL), RANK, M-CSF in Osteoclastogenesis

Op/op (M-CSF–deficient) mouse also has significant osteopetrosis. However this deficiency can be resolved with:

VEGF[1] or Flt3 ligand[2]

Knocking out osteoprotegrin leads to an inability to inhibit bone resorption and the development of severe osteopenia.

Knocking out RANKL leads to an inability to bone resorption (no osteclast activaty) and the development of significant osteopetrosis.

Denosumab: Potential Mechanism of Action

Cytokines and Growth Factors (IL-6, IL-8, IL-1β, PGE₂, TNF-α, CSF-1, PTHrP)

Growth Factors (TGF-β, IGFs, FGFs, PDGFs, BMPs)

Bone Resorption

Ca²⁺

111 patients enrolled,

Among patients with elevated uNTx despite ongoing IV BP therapy,

Denosumab reduced markers of bone breakdown.

Fewer patients receiving denosumab experienced on-study SREs than those receiving IV BPs
A Comparison of Denosumab Versus Zoledronic Acid for the Prevention of Skeletal Related Events in Breast Cancer Patients With Bone Metastases

Alison Stopeck¹, Richard de Boer,² Yasuhiro Fujiwara³, Mikhail Lichinitser⁴, Katia Tonkin⁵, Denise Yardley⁶, Michelle Fan⁷, Qi Jiang⁷, Susie Jun⁷, Roger Dansey,⁷ Ada Braun⁷

¹University of Arizona, Arizona Cancer Center, Tucson, AZ, USA ²Rush and Royal Melbourne Hospitals, Victoria, Australia ³National Cancer Center Hospital, Tokyo, Japan ⁴Sakharov Cancer Research Center, Moscow, Russia ⁵Cross Cancer Institute, Edmonton, AB, Canada ⁶James Cannon Research Institute, Nashville, TN, USA ⁷Amgen Inc, Thousand Oaks, CA, USA

San Antonio Breast Cancer Symposium 2009
Study Design: International, Randomized, Double-Blind, Active-Controlled Study

Key Inclusion
- Adults with advanced breast cancer and confirmed bone metastases

Key Exclusion
- Current or prior intravenous bisphosphonate administration

Denosumab 120 mg SC and Placebo IV* every 4 weeks (N = 1026)
Supplemental Calcium and Vitamin D
Placebo SC every 4 weeks and Zoledronic acid 4 mg IV* (N = 1020)

1. Endpoint: Time to first on-study SRE (non-inferiority)
2. Endpoints:
   - Time to first on-study SRE (superiority)
   - Time to first and subsequent on-study SRE (superiority)

Time to First-and-Subsequent On-Study SRE* (Multiple Event Analysis)

Rate Ratio 0.77 (95% CI: 0.66, 0.89)
Risk Reduction 23%
P = 0.001*  

Proportion of Subjects Experiencing an SRE

<table>
<thead>
<tr>
<th></th>
<th>Zoledronic acid (N = 1020)</th>
<th>Denosumab (N = 1026)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 12</td>
<td>26.6%</td>
<td>25.1%</td>
</tr>
<tr>
<td></td>
<td>5.6% relative reduction</td>
<td></td>
</tr>
<tr>
<td>Month 18</td>
<td>32.3%</td>
<td>28.6%</td>
</tr>
<tr>
<td></td>
<td>11.5% relative reduction</td>
<td></td>
</tr>
<tr>
<td>At Time of Analysis</td>
<td>36.5%</td>
<td>30.7%</td>
</tr>
<tr>
<td></td>
<td>15.9% relative reduction</td>
<td></td>
</tr>
</tbody>
</table>

Skeletal Morbidity Rate (SMR)

<table>
<thead>
<tr>
<th></th>
<th>Zoledronic acid 4 mg Q4W (N = 1020)</th>
<th>Denosumab 120 mg Q4W (N = 1026)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMR per subject per year*</td>
<td>0.58</td>
<td>0.45</td>
</tr>
</tbody>
</table>

*SMR = number of SREs for each subject (allowing 1 per 3-week assessment), divided by the subject’s time at risk.
**Time to Experiencing Moderate or Severe Pain**
(Worst Pain Score > 4 Points per Brief Pain Inventory)

**KM Estimate of Median Days**
- **Denosumab**: 86
- **Zoledronic Acid**: 64

HR 0.87 (95% CI: 0.79, 0.97)  
*P* = 0.009

**Between-Group Differences in Adverse Events With Unadjusted *P* < 0.05**

<table>
<thead>
<tr>
<th>Event</th>
<th>Denosumab (N=1020)</th>
<th>Zoledronic Acid (N=1013)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>17 (5.7)</td>
<td>247 (24.4)</td>
</tr>
<tr>
<td>Bone pain</td>
<td>106 (10.2)</td>
<td>238 (23.6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>250 (24.5)</td>
<td>291 (28.7)</td>
</tr>
<tr>
<td>Anemia</td>
<td>192 (18.8)</td>
<td>232 (22.9)</td>
</tr>
<tr>
<td>Chills</td>
<td>20 (2.0)</td>
<td>58 (5.7)</td>
</tr>
<tr>
<td>Pain</td>
<td>72 (7.1)</td>
<td>97 (9.6)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2 (0.2)</td>
<td>25 (2.5)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>52 (5.1)</td>
<td>74 (7.3)</td>
</tr>
<tr>
<td>Lumbar vertebral fracture</td>
<td>35 (3.4)</td>
<td>56 (5.5)</td>
</tr>
<tr>
<td>Alkaline phosphatase increase</td>
<td>28 (3.2)</td>
<td>47 (4.6)</td>
</tr>
<tr>
<td>Edema</td>
<td>22 (2.2)</td>
<td>40 (3.9)</td>
</tr>
<tr>
<td>Hypercalcaemia</td>
<td>17 (1.7)</td>
<td>35 (3.5)</td>
</tr>
<tr>
<td>Metastases to spine</td>
<td>9 (0.9)</td>
<td>21 (2.1)</td>
</tr>
<tr>
<td>Skin hyperpigmentation</td>
<td>7 (0.7)</td>
<td>18 (1.8)</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>4 (0.4)</td>
<td>15 (1.5)</td>
</tr>
<tr>
<td>Breachocaspider</td>
<td>2 (0.2)</td>
<td>10 (1.0)</td>
</tr>
<tr>
<td>Blood urea increased</td>
<td>0 (0.0)</td>
<td>18 (1.8)</td>
</tr>
<tr>
<td>Renal failure acute</td>
<td>1 (0.1)</td>
<td>7 (0.7)</td>
</tr>
<tr>
<td>Toothache</td>
<td>57 (5.6)</td>
<td>37 (3.7)</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>56 (5.5)</td>
<td>34 (3.4)</td>
</tr>
</tbody>
</table>

**Risk Difference**
- **Favors Denosumab**
- **Favors Zoledronic Acid**

**Time to First Radiation to Bone**

HR 0.74 (95% CI: 0.59, 0.94)  
*P* = 0.01

**Overall Survival**

HR 0.78 (95% CI: 0.61, 0.99)  
*P* = 0.05

**Overall Disease Progression**

HR 1.00 (95% CI: 0.98, 1.01)  
*P* = 0.89
Denosumab and prostat cancer

Castrate resistant, bone metastases, no previous BP

(N = ~ 1900)

Primary endpoint: SREs
Accrual complete 2008 Q4
Final analyses 2009

ClinicalTrials.gov identifier: NCT00321620
Systemic Agents in Development

- **Cathepsin K inhibitors**
  - Cathepsin K degrades the bone
  - An oral inhibitor reduced bone turnover from breast cancer bone metastases (ASCO 2009 poster)

- **SRC kinase inhibitors (dasatinib)**
  - SRC necessary for osteoclast bone breakdown
  - Dasatinib is oral, approved for chronic leukemia, may have activity against breast cancer as well

- Ongoing trials are using these drugs after, with, or instead of zoledronic acid
Bone-Seeking Radiopharmaceuticals

• Composition
  – Radioactivity: samarium-153, strontium-89
  – Targets bone — especially areas of increased activity
    • EDTMP with samarium-153
    • Strontium (acts like calcium)

• Radiopharmaceuticals are proven to relieve pain in patients with osteoblastic bone lesions that enhance under radionuclide bone scans.

• Major toxicity is hematologic
  – Proximity to bone marrow
Samarium-153 Lexidronam

Change in AUPC-VAS at Wk 4 Among Primary Tumor Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>Placebo</th>
<th>0.5 mCi/kg</th>
<th>1.0 mCi/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients (n = 118)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate Cancer (n = 78)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast Cancer (n = 21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung and Other Cancers (n = 19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AUPC-VAS, area under the pain curve-visual analogue scale.

Local Therapies

• Local therapies treat a limited number of locations; do not treat the whole body

• Types:
  – Radiotherapy
  – Interventional Radiology
  – Surgery

• Goals:
  – Relieve pain
  – Prevent fracture
  – Enhance mobility and function
  – Preserve quality of life
Radiation Therapy

- Radiation therapy can be used to treat painful bone metastases refractory to systemic therapies.
  - 80-90% of breast cancer patients experience relief of symptoms
  - 40-46% experience full relief
  - 70% never have pain in that region again
  - May take months before full pain relief is realized

Tong et al, Cancer 1982
Radiation Therapy: Specifics

• Can take 1-4 weeks; 2 weeks is most common

• Chemotherapy is usually on hold during RT

• Side effects: nausea, diarrhea, low blood counts, fatigue

• Typically radiation is not used again in the same place
Interventional Radiology

• What is it?
  – Minimally invasive procedures performed by specialized radiologists to treat symptoms from bone metastases

• Indications:
  – To treat bone pain refractory to other conservative pain control measures
  – Specialized technique for metastatic cancer to spine bones
    • Stabilize broken bone
Interventional Radiology: Techniques

• **Vertebroplasty:**
  – Injection of bone cement to support weakened bones
  – Provides immediate and substantial pain relief

• **Kyphoplasty:**
  – Balloon inflation of compressed spine bone is performed before cement injection
  – Used for compression fractures
Positioning in Interventional Radiology
Example: Vertebroplasty
Example: Vertebroplasty
Concept of kyphoplasty
Concept of kyphoplasty
Other Local Techniques

- Radiofrequency Ablation (RFA) and cryoablation
  - Minimally invasive procedures to “burn” or “freeze” a tumor
  - Desensitizes by killing nerve endings near the metastasis

- Most commonly used for cancer in the spine

- Techniques can achieve excellent pain control

- Use may expand with further data
Surgical Joint Stabilization

• Indications for surgery for bone metastases:
  – Prevention of bone fracture ("prophylactic")
    • Risk depends on location of metastasis, type, size, and presence of symptoms
  – Alleviation of pain
  – Maintain ability to walk (for hip metastases)
  – Stabilize broken bone after pathologic fracture

*Beals et al, Cancer 1971*
Surgical Joint Stabilization

• Benefits of surgery
  – Procedures designed for rapid recovery
    • Simple pin placement to full hip replacement
  – Most are walking again soon after hip surgery
  – Most have good to excellent pain relief
  – Can dramatically improve healing after fracture

• Typically performed in combination with radiotherapy

Ongoing Trials
Randomized phase III metastasis-prevention studies of bisphosphonates

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stage</th>
<th>Number of patients</th>
<th>Treatment</th>
<th>Primary Endpoint</th>
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<tr>
<td>NSABP B-34</td>
<td>I-II</td>
<td>3323</td>
<td>Clodronate vs. placebo for 3 years</td>
<td>DFS</td>
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<td>AZURE</td>
<td>II-III</td>
<td>3360</td>
<td>Zoledronic acid vs. control for 5 years</td>
<td>DFS</td>
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<td>SUCCESS</td>
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<td>Zoledronic acid: 2 years vs. 5 years</td>
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<td>NATAN</td>
<td>I-III</td>
<td>654</td>
<td>Patients must have received neoadjuvant chemotherapy with anthracycline + taxane</td>
<td>EFS</td>
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<td>Residual tumour in histopathological surgical resection specimen</td>
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<td>S0307 Intergroup</td>
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<td>ICE</td>
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<td>Ibibandronate for 2 years</td>
<td>EFS</td>
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<td>Further randomization to capecitabine for 2 years vs. control</td>
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<td>Evaluation of ETC vs. EC-TX</td>
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<td>Further randomization to ibandronate vs. control for 2 years</td>
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</tbody>
</table>

Bisphosphonates;
may enhance the antitumour activity of cytotoxic drugs,
increase tumour cell apoptosis,
inhibit tumour cell adhesion, invasion and proliferation and angiogenesis by modifying the bone microenvironment

Potential antitumor effects of nitrogen-containing bisphosphonate in hormone receptor negative breast cancer patients with bone metastases

317 patients with initial bone metastasis;

87 patients (27.4%) had HR negative.

HR negative and ZA received group had better survival (1.7 vs 1.3 years).


The impact of zoledronic acid therapy in survival of lung cancer patients with bone metastasis.

NSCLC patients with bone metastases;

Group A: 87 pts received ZOL, 4 mg i.v. every 21 days
Group B: 57 patients received no ZOL

Docetaxel-Cisplatin-Zolendronat vs DC

PFS and OS (578 vs 384 days)

The antitumoral effectiveness of the BP

Studies from Turkey


Division of Medical Oncology, Tulay Aktas Oncology Hospital, School of Medicine, Ege University, Bornova, Izmir, Turkey.


Akdeniz University, Department of Biochemistry, Antalya, Turkey.
Thanks