Management of Bone Metastasis in Breast Cancer: Drugs, Dosing and Duration

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Disclosures

• In the last three years, I have participated in an advisory board for and received a travel grant from Amgen
Learning Objectives

• Explore pathophysiology of bone metastasis
• Review osteoclast inhibitors
  – Bisphosphonates and denosumab
  – Indications and side effects
• Examine the data on dosing interval
• Discuss treatment duration and alternating treatment at progression
Bone Metabolism

- Osteoclasts: bone resorption
- Osteoblasts: bone formation
- Usually balanced and coupled
- Estrogen is important for bone homeostasis
The Role of RANKL in Healthy Bone

- In healthy adult bone, the body regulates the activity of a protein called RANKL to balance bone formation and bone resorption.

RANKL is an Essential Mediator of the Vicious Cycle of Bone Destruction

Osteoblasts and other bone cells increase production of RANKL

Overproduction of RANKL drives increased formation, function, and survival of osteoclasts, leading to excessive bone resorption

Tumor cells produce factors that stimulate osteoblasts to secrete RANKL

Bone resorption releases growth factors from the bone matrix that may perpetuate tumor activity

Cancer Cell Metastasis – New View
Bone Health and Breast Cancer

• Important in all stages of breast cancer

• Prevention of bone loss

• Prevention of cancer recurrence

• Treatment of metastatic disease
Bone Metastasis in Breast Cancer

- Bone is a common site of metastasis
  - Occurs in 65% to 75% patients
- Pain is major issue
- Skeletal-related events (SREs)
  - Pathologic fracture 53%
  - Radiotherapy to bone 43%
  - Hypercalcemia of malignancy 13%
  - Surgical intervention to bone 11%
  - Spinal cord compression 3%

Lipton et al. Cancer 2000;88:1082-90
High Prevalence of SREs in Patients with Advanced Breast Cancer and Bone Metastases

• About 73% of women with advanced breast cancer will develop bone metastases*¹

• About 64% of women with bone metastases will develop SREs²

*At post mortem examination

SREs Are Extremely Common: Some Patients Experience Multiple SREs

Median follow-up of 107 months after diagnosis of metastatic breast cancer (n = 369)

Skeletal complications were defined as hypercalcemia (any calcium level either ≥ 11 mg/dL or requiring treatment), spinal cord compression, surgical intervention to bone, radiation therapy to bone, or pathologic fracture.

Bone Metastases Are Often a Mixture of Osteoblastic and Osteolytic Lesions


At http://www.meddean.luc.edu/lumen/MedEd/Radio/curriculum/Surgery/Met_bone_list1.htm. Permission obtained from LUMEN.
The Vicious Cycle of Bone Destruction and the Prevention of SREs*

Denosumab binds to RANK ligand

Osteoclast function, formation and maturation are inhibited

Bisphosphonates (BPs) inhibit osteoclast function (amino BPs by mevalonate pathway inhibition, while non-amino BPs by ATP inhibition)

Inhibition of osteoclast maturation leads to reduced bone resorption

*Denosumab, ZA, and alendronate are not indicated for the clinical management of cancer treatment-induced bone loss in Canada.

Bisphosphonates

- Inhibit osteoclast-mediated bone resorption
- Bind to mineralized bone surfaces
- Ingested by osteoclasts, block activation signals and lead to apoptosis
- Simple bisphosphononates:
  - Clodronate
- Nitrogen-containing bisphosphonates:
  - Pamidronate, zolendronic acid, alendronate
  - Also inhibit farnesyl pyrophosphate (FFP) synthase
## Selected Trials of Bone-targeted Therapy to Prevent SREs in Advanced Breast Cancer (Clodronate vs. Placebo)

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Trial/Admin</th>
<th>Assessment(s)</th>
<th>Result(s)</th>
</tr>
</thead>
</table>
| Paterson AHG J Clin Oncol 1993 | • Breast cancer  
• Bone metastases | Randomized, double-blind, placebo-controlled  
• Clodronate  
• Placebo | Cumulative morbid skeletal events | Clodronate is superior to placebo in reducing morbid skeletal events (p < 0.001) |

**IV** = intravenous
## Selected Trials of Bone-targeted Therapy to Prevent SREs in Advanced Breast Cancer (Pamidronate vs. Placebo)

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Trial/Admin</th>
<th>Assessment(s)</th>
<th>Result(s)</th>
</tr>
</thead>
</table>
| Hortobagyi GN   | • Advanced breast cancer  
• Receiving chemotherapy  
• Bone metastases (at least one lytic lesion) | Multinational, randomized, double-blind, placebo-controlled  
• Pamidronate  
• Placebo | • Time to occurrence of skeletal complications  
• Incidence of skeletal complications | • Pamidronate is superior in increasing median time to first skeletal complication  
(p = 0.005)  
• Pamidronate reduced incidence of skeletal complications at 6, 9, and 12 cycles of therapy  
(p = 0.02; p = 0.002 and p = 0.008, respectively) |
| N Engl J Med    |                                                                             |                                                                            |                                                                              |                                                                                                 |
| 1996            |                                                                             |                                                                            |                                                                              |                                                                                                 |
| Hortobagyi GN   | • Breast cancer  
• Bone metastases (with lytic bone lesions) | Randomly assigned, double-blind, placebo-controlled  
• Pamidronate  
• Placebo | • Skeletal complications | • Pamidronate is superior in reducing skeletal complications  
(p < 0.001) |
| J Clin Oncol    |                                                                             |                                                                            |                                                                              |                                                                                                 |
| 1998            |                                                                             |                                                                            |                                                                              |                                                                                                 |
| Theriault RL    | • Breast cancer  
• Bone metastases [with lytic bone lesion(s)]  
• Receiving HT | Randomized, double-blind, placebo-controlled, multicentre  
• Pamidronate  
• Placebo | • Time to first skeletal complication  
• Skeletal complications per year  
• Occurrence of skeletal complication by end of treatment | • Pamidronate is superior in delaying time to first skeletal complications  
(p = 0.049)  
• Pamidronate is superior in reducing skeletal complication/year at 12th, 18th and 24th cycle of treatment  
(p = 0.028; p = 0.023 and p = 0.008, respectively)  
• Pamidronate is superior in reducing occurrence of skeletal complications by the end of 24 cycles  
(p = 0.027) |
| J Clin Oncol    |                                                                             |                                                                            |                                                                              |                                                                                                 |
| 1999            |                                                                             |                                                                            |                                                                              |                                                                                                 |
Selected Trials of Bone-targeted Therapy to Prevent SREs in Advanced Breast Cancer (Zoledronic Acid vs. Placebo)

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Trial/Admin</th>
<th>Assessment(s)</th>
<th>Result(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kohno N</td>
<td>• Breast cancer</td>
<td>Multicentre, randomized, double-blind, placebo-controlled</td>
<td>SRE rate and between-group ratio</td>
<td>ZA is superior at reducing SREs (HR = 0.61; p = 0.016)</td>
</tr>
<tr>
<td><em>J Clin Oncol</em> 2005</td>
<td>• Bone metastases (with osteolytic lesions)</td>
<td>• Japanese population</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Japanese population</td>
<td>• ZA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IV = intravenous
## Selected Trials of Bone-targeted Therapy to Prevent SREs in Advanced Breast Cancer (4) (Zoledronic Acid vs. Pamidronate)

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Trial/Admin</th>
<th>Assessment(s)</th>
<th>Result(s)</th>
</tr>
</thead>
</table>
| Rosen LS *Cancer* 2003 (breast cancer subset analysis) | • Breast cancer  
• At least one bone metastasis (lytic or mixed)  
• Receiving HT or CT | Randomized, double-blind, double-dummy trial  
• ZA  
• Pamidronate | • Proportion of patients experiencing ≥ 1 SRE over 25 months  
• Relative risk ratios for SREs (including HCM) | • Results are comparable between ZA 4 mg, ZA 8/4 mg and pamidronate 90 mg for the % of patients with ≥ 1 SRE (HT or CT)  
• Risk of developing skeletal complications was significantly more effective in the ZA 4 mg compared group to the pamidronate group (HR = 0.799; p = 0.025) |

HT=hormone therapy; CT=chemotherapy; SRE=skeletal-related event; HCM=hypercalcemia of malignancy
# Selected Trials of Bone-targeted Therapy to Prevent SREs in Advanced Breast Cancer (Zoledronic Acid vs. Pamidronate)

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Trial/Admin</th>
<th>Assessment(s)</th>
<th>Result(s)</th>
</tr>
</thead>
</table>
| Rosen LS Cancer 2004 | • Breast carcinoma  
• At least one bone metastasis | Randomized, double-blind  
• ZA  
• Pamidronate | • Proportion of patients experiencing ≥ 1 osteolytic or nonlytic lesion | • Proportion of patients with ≥1 SRE was comparable in all treatment groups  
• Proportion with SRE was comparable between treatment groups  
• Among patients with breast carcinoma and ≥1 osteolytic lesion, SREs lower in ZA group |

SRE=skeletal-related event
Denosumab

- Fully human monoclonal antibody
- High affinity and specificity for RANKL
- Indicated for reducing the risk of skeletal-related events in patients with bone metastasis from breast, prostate, lung and other solid tumors
- Not indicated for patients with multiple myeloma
Study Schema

Primary endpoint
- Time to first on-study SRE (non-inferiority test)

Patients aged ≥18 years with:
- Histologically or cytologically confirmed breast adenocarcinoma
- Evidence of 1 or more bone metastases
- Adequate organ function
- ECOG performance status of 0, 1, or 2

RANDOMIZATION

120 mg denosumab SC and IV placebo every 4 weeks

ZA 4 mg IV and SC placebo every 4 weeks

BSAP = bone-specific alkaline phosphatase; ECOG = Eastern Cooperative Oncology Group; SC = subcutaneous.
Primary End Point: 
Time to First On-Study SRE

HR = 0.82 (95% CI, 0.71-0.95)*
p < .001 (non-inferiority)
p = 0.01 (superiority)

*Adjusted for multiplicity

No. at risk
IV ZA 4 mg every 4 weeks (n = 1020)
1020 829 676 584 498 427 296 191 94 29
SC denosumab 120 mg every 4 weeks (n = 1026)
1026 839 697 602 514 437 306 189 99 26

CI = confidence interval; HR = hazard ratio.

Breast Cancer Patients with Confirmed Bone Metastases
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>Month 18**</td>
<td>32.3%</td>
<td>28.6%</td>
</tr>
<tr>
<td>At Time of Analysis***</td>
<td>36.5%</td>
<td>30.7%</td>
</tr>
</tbody>
</table>

5.6% relative reduction
11.5% relative reduction
15.9% relative reduction

*49 Weeks, **73 Weeks, ***Study duration = 34 months; Median time on study = 17 months.

Breast Cancer Patients with Confirmed Bone Metastases

Skeletal Morbidity Rate (SMR)

\[ \text{SMR} = \frac{\text{number of SREs for each subject (allowing 1 per 3-week assessment)}}{\text{subject's time at risk}} \]

22% relative reduction

\[ P = 0.004 \]

Mean SMR per subject per year*

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

### Selected Trials of Bone-targeted Therapy to Prevent SREs in Advanced Breast Cancer (ZA vs. Denosumab)

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Trial/Admin</th>
<th>Assessment(s)</th>
<th>Result(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stopeck AT</td>
<td>• Breast cancer</td>
<td>International, randomized, double-blind, double-dummy</td>
<td>• Time to first on-study SRE (non-inferiority and superiority)</td>
<td>• Denosumab is superior to ZA in delaying time to first on-study SRE (p &lt; 0.001 non-inferiority; p = 0.01 superiority)</td>
</tr>
<tr>
<td><em>J Clin Oncol</em> 2010</td>
<td>• Bone metastases (enrolled n = 2049, but 3 excluded)</td>
<td>• Denosumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ZA (Calcium and vitamin D)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Management of Bone Metastases and Prevention of SREs in Breast Cancer: Clinical Practice Guideline Recommendations

**ASCO Clinical Practice Guidelines (Feb 2011)**[1]

- Breast cancer patients with bone metastases should be treated with at least one of the following:
  - Pamidronate, ibadronate, ZA, or denosumab
- For breast cancer patients who have evidence of bone destruction on plain radiograph, denosumab 120 mg SC every 4 weeks, IV pamidronate 90 mg every 2 hours, or ZA 4 mg over 15 minutes every 3 to 4 weeks is recommended.
- There are no prospective clinical data to support the continuation of bone-targeted therapy beyond 1 year.

**NCCN Clinical Practice Guidelines in Oncology: Breast Cancer (Mar 2011)**[2]

- To prevent SREs in metastatic breast cancer, the following agents can be used:
  - IV BP (eg, pamidronate or ZA in the US and clodronate or ibidronate in the EU) and denosumab in combination with oral calcium citrate and vitamin D supplements.
- Data indicates that ZA and pamidronate may be given on 3-5 week schedule in conjunction with antineoplastic therapy.
- The guidelines also urge that before initiating bone-targeted therapy, bone metastases must be confirmed by X-ray, CT scan, or MRI.

BP=Bisphosphonates

Pharmacological Considerations of Pamidronate, Zoledronic Acid (ZA) and Denosumab

<table>
<thead>
<tr>
<th></th>
<th>Pamidronate</th>
<th>ZA</th>
<th>Denosumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route of administration</strong></td>
<td>IV, chair time and nursing support required</td>
<td>IV, chair time and nursing support required</td>
<td>SC injection with 27-gauge needle</td>
</tr>
<tr>
<td><strong>Dose/Frequency</strong></td>
<td>90 mg over 2 hours, Q3-Q4 wks (dose adjusted for patients with renal impairment)</td>
<td>4 mg over 15 minutes, Q3-Q4 wks (dose adjusted for patients with renal impairment) After 12 cycles can give Q 12 wks</td>
<td>120 mg Q4 wks 500 mg calcium and 400 IU vitaminD daily unless hypercalcemic</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Serum calcium</td>
<td>Serum calcium</td>
<td>Serum calcium</td>
</tr>
<tr>
<td></td>
<td>Renal function</td>
<td>Renal function can progress to renal failure</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events of interest</strong></td>
<td>ONJ Deterioration in renal function Acute phase reactions Musculoskeletal pain</td>
<td>ONJ Deterioration in renal function Acute phase reactions</td>
<td>ONJ Hypocalcemia</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td>Renal toxicity</td>
<td>Renal toxicity</td>
<td>Not tested</td>
</tr>
<tr>
<td></td>
<td>Reproductive</td>
<td>Reproductive</td>
<td></td>
</tr>
</tbody>
</table>

1. Novartis Pharmaceuticals Canada Inc. October 25, 2011; Product Monograph: Aredia®
2. Novartis Pharmaceuticals Canada Inc.October 25, 2011; Product Monograph: Zometa®
3. Amgen Canada Inc. October 17, 2011; Product Monograph: XGEVA®
Pharmacological Considerations of Pamidronate, Zoledronic Acid (ZA) and Denosumab

<table>
<thead>
<tr>
<th></th>
<th>Pamidronate</th>
<th>ZA</th>
<th>Denosumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug-drug interactions</strong></td>
<td>Not Tested</td>
<td>Extreme caution when used with all agents effecting renal function: aminoglycosides, antineoplastic agents, ASA, NSAIDS, diuretics, ACE inhibitors, dehydrating agents Thalidomide Calcium-containing IV infusions Do not use with other bisphosphonates</td>
<td>Not Tested</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Hypersensitivity Pregnant or nursing patients</td>
<td>Hypersensitivity Pregnant or nursing patients</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td><strong>Special population considerations</strong></td>
<td>Not recommended in patients with severe renal impaired CrCl &lt;30 mL/min Not recommended for pregnant, nursing or pediatric patients</td>
<td>Not recommended in patients with severe renal impaired CrCl &lt;30 mL/min Not recommended for pregnant, nursing or pediatric patients Precautions in Japanese women leads to higher systemic levels</td>
<td>Not recommended for pregnant or pediatric patients Nursing women should consult physician Renal impaired patient CrCl &lt;30 mL/min or on dialysis at greater risk of hypocalcemia</td>
</tr>
</tbody>
</table>

1. Novartis Pharmaceuticals Canada Inc. October 25, 2011; Product Monograph: Aredia®.
**Select Adverse Events (AEs) with bone-targeted therapy + (ZA vs Denosumab)**

<table>
<thead>
<tr>
<th></th>
<th>ZA (n = 2836)</th>
<th>Denosumab (n = 2841)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient incidence, n (%) AEs</td>
<td>2745 (96.8)</td>
<td>2734 (96.2)</td>
</tr>
<tr>
<td>Most common AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>895 (31.6)</td>
<td>876 (30.8)</td>
</tr>
<tr>
<td>Anemia</td>
<td>859 (30.3)</td>
<td>771 (27.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>766 (27.0)</td>
<td>769 (27.1)</td>
</tr>
<tr>
<td>Back pain</td>
<td>747 (26.3)</td>
<td>718 (25.3)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>694 (24.5)</td>
<td>656 (23.1)</td>
</tr>
<tr>
<td>CTCAE Grade 3, 4, or 5 AEs</td>
<td>2009 (70.8)</td>
<td>2000 (70.4)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>1620 (57.1)</td>
<td>1599 (56.3)</td>
</tr>
<tr>
<td><strong>Acute phase reactions (first 3 days)</strong></td>
<td>572 (20.2)</td>
<td>246 (8.7)</td>
</tr>
<tr>
<td><strong>Renal AEs</strong></td>
<td>335 (11.8)</td>
<td>262 (9.2)</td>
</tr>
<tr>
<td><strong>Cumulative rate of ONJ</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>37 (1.3)</td>
<td>52 (1.8)</td>
</tr>
<tr>
<td>Year 2</td>
<td>15 (0.5)</td>
<td>22 (0.8)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>141 (5.0)</td>
<td>273 (9.6)</td>
</tr>
</tbody>
</table>

ZA = Zoledronic Acid; CTCAE = Common Terminology Criteria for Adverse Events (version 3.0); ONJ = Osteonecrosis of the Jaw

* Data is from an integrated analysis of pivotal trials of denosumab vs. ZA (n = 5679) from 36% breast, 33% prostate, 14% lung and 17% other solid tumors

Lipton A, et al. 2010 ESMO 35: 1249P
Reported Rates of Hypocalcemia

* Frequency of calcium monitoring = Q4 W in clinical trials
‡ All grades (1-4) hypocalcemia

Fizazi K (mCRPC)
- Denosumab: 13.0% **
- ZA: 6.0% **

Stopeck AT (mBCa)
- Denosumab: 5.5% **
- ZA: 3.4% **

Henry DH (NSCLC and other solid tumors)
- Denosumab: 10.8% **
- ZA: 5.8% **

Fizazi K. Lancet 2011;377:813-822;
Recognizing and Preventing Bisphosphonate-induced Hypocalcemia

• Risk Factors\(^1\):
  – Pre-existing hypoparathyroidism
  – Parathyroid dysfunction
  – Vitamin D deficiency
  – Renal failure

• Preventive measures:
  – Administer 400 IU of vitamin D and 500 mg of calcium\(^2\)
  – NOF recommends ≥ 1200 mg calcium for women > 50 yrs\(^*\) and 800 to 1000 IU vitamin D daily for men and women\(^3,\)*
  – Concurrent vitamin D and calcium during and ideally starting two weeks prior to bisphosphonate therapy\(^1\)

*NOF Calcium recommendations are:
≥ 1,200 mg daily for women > 50 yrs;
1,000 mg daily for men 50-70 yrs;
1,200 mg daily for men ≥ 71 yrs.

2. Novartis Pharmaceuticals Canada Inc. October 25, 2011; Product Monograph: Zometa®
Recognizing and Preventing Denosumab-induced Hypocalcemia

• Preventive measures:
  – Pre-existing hypocalcemia must be corrected prior to initiating therapy.¹
  – All patients, except those with hypercalcemia, should receive at least 500 mg calcium daily and at least 400 IU vitamin D daily.¹
  – NOF recommends ≥ 1200 mg calcium for women > 50 yrs* and 800 to 1000 IU vitamin D daily for men and women²
  – Calcium levels should be monitored monthly while receiving denosumab and more frequently when administered with other drugs that deplete calcium.¹
  – Clinicians should be diligent in ensuring patients are adherent with calcium and vitamin D supplementation.
  – Calcium, magnesium and vitamin D should be administered as necessary based on calcium levels.¹

*NOF Calcium recommendations are:
≥ 1,200 mg daily for women > 50 yrs;
1,000 mg daily for men 50-70 yrs;
1,200 mg daily for men ≥ 71 yrs.

1. Amgen Canada Inc. October 17, 2011; Product Monograph XGEVA®
Recognizing and Preventing Bisphosphonate-induced Renal Toxicity

- The risk of developing varies with each bisphosphonate
  - ZA requires dose adjustments in patients with renal complications\(^1\)
- Before initiating BP therapy, assessments of renal function by calculating creatinine clearance are recommended for:
  - Older adults\(^2\)
  - Patients with mild to moderate renal impairment\(^3\)
  - Patients with Chronic Kidney Disease\(^3, 4\)
- Serum creatinine should be measured before each dose\(^1, 2, 3\)
- Treatment should be withheld if there is evidence of renal deterioration\(^3\)

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3. Novartis Pharmaceuticals Canada Inc.October 25, 2011;Product Monograph: Zometa®
ONJ in Setting of Bone-targeted therapy

Causally linked to bone-targeted therapy when:

- Current or previous treatment with a bone-targeted therapy
- Exposed bone in the maxillofacial region that has persisted for more than eight weeks
- No history of craniofacial radiation therapy to the jaw

Risk Factors for ONJ in Cancer Patients

- Dentoalveolar surgery: greatest risk factor
- Poor oral health
- History of concomitant oral disease
- Potent bone-targeted therapy
- Longer duration, increased dosing, and frequency of bone-targeted therapy
- Increasing age
- Renal dialysis
- Anemia
- Tobacco use
- Drug therapies: cyclophosphamide, erythropoietin, steroids, antiangiogenics
- Xerostoma (Head/neck RT: Sjogrens)
Etiology of ONJ

• Reduction in osteoclastic activity in an area of bone that is relatively hypocellular
  – Bone-targeted therapy impairs the ability of bone to resorb and replace damaged tissue

• Infection, inflammation, impaired angiogenesis
Cumulative Incidence of ONJ in Phase III Clinical Trials in Advanced Cancers*

*Collected prospectively from 5723 patients with metastatic bone disease and solid tumors or multiple myeloma in three registration trials comparing the efficacy and safety of denosumab with ZA

Prevention of ONJ

• Conduct baseline oral exam and perform all invasive dental procedures before initiating a bone-targeted therapy
  • Do you have oral pain, loose teeth, regular dental care?
  • Look for loose teeth, dental caries, defective restorations, ill-fitting dentures, ulcers, bone growths

• Refer all patients especially those with poor oral hygiene or signs of periodontal disease to a dentist prior to starting therapy

• Counsel patients to adopt healthy dental hygiene including regular dental care

What to Look for During an Oral Examination

Mylohyoid Ridge

The mylohyoid ridge is prone to ONJ because it is covered by a thin mucosa and the bone is very dense and poorly vascularized.

Mandibular Tori (benign bone growths)

Mandibular tori are covered by a thin mucosa. The slightest trauma to these areas may lead to bone exposure and subsequent ONJ.

Dental/Periodontal Examination

Look for:
- Signs of plaque or tartar build-up along the gum line
- The condition of the overall mucosa (i.e., bleeding, inflammation)
- Cavities
- Loose teeth
Manifestations of ONJ

- Oral pain
- Swelling and infection of soft tissue
- Loosening of teeth
- Drainage
- Sensation of heaviness or numbness in the jaw described by patients
Differential diagnosis of ONJ

• Other conditions can be misdiagnosed as ONJ:
  – Periodontal disease
    • Cavities
    • Gingivitis
  – Local malignancies
  – Trauma
  – Sinusitis
  – Temporomandibular joint disorders

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Antibiotics, analgesics as appropriate</td>
</tr>
</tbody>
</table>
| 1     | Antibacterial mouth rinse  
      | Follow-up q3mo |
| 2     | Antibiotics, analgesics as appropriate  
      | Pain control  
      | Superficial debridement (for soft tissue irritation) |
| 3     | Antibiotics, analgesics  
      | Antibacterial mouth rinse  
      | Surgical debridement/resection (for longer-term palliation of infection and pain) |
| All   | Remove mobile segments of bony sequestrum without exposing uninvolved bone  
      | Consider extracting symptomatic teeth within exposed necrotic bone |
Efficacy and Safety of Continued Zoledronic Acid every 4 Weeks versus every 12 Weeks in Women with Bone Metastases from Breast Cancer: Results of the OPTIMIZE-2 Trial

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The University of Texas MD Anderson Cancer Center, Houston, TX; Penn State Hershey Medical Center, Hershey, PA; University of California-Davis, Sacramento, CA; Northwestern University Feinberg School of Medicine, Chicago, IL; Novartis Pharmaceuticals Corporation, East Hanover, NJ; University of Michigan, Ann Arbor, MI
Final OPTIMIZE-2 study design

**Patients:**
- Patients with breast cancer and bone metastases
- Prior therapy with $\geq 9$ doses of IV BP
- N=412 patients

**Randomization 1:1**
- Zoledronic acid q4wk (n=206)
- Zoledronic acid q12wk (n=206) (placebo for interim infusions)

**Protocol revisions during the course of the clinical trial**
- The placebo arm was dropped early in the study secondary to poor accrual
- The sample size was reduced from n=705 to n=412, based on new data that became available (ZOOM trial)
- The statistical assumption of 10% non-inferiority margin remained unchanged.
# Demographics, Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Zoledronic Acid every 4 weeks (N = 200)</th>
<th>Zoledronic Acid every 12 weeks (N = 203)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>59.2 (11.1)</td>
<td>58.6 (11.2)</td>
</tr>
<tr>
<td><strong>Baseline serum creatinine, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (&lt;1.4 mg/dL)</td>
<td>196 (98.0)</td>
<td>192 (94.6)</td>
</tr>
<tr>
<td>Abnormal (&gt;=1.4 mg/dL)</td>
<td>2 (1.0)</td>
<td>10 (4.9)</td>
</tr>
<tr>
<td><strong>Baseline ECOG status, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>191 (95.5)</td>
<td>195 (96.1)</td>
</tr>
<tr>
<td>≥2</td>
<td>6 (3.0)</td>
<td>6 (3.0)</td>
</tr>
<tr>
<td><strong>Baseline BPI composite pain score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.03 (1.90)</td>
<td>2.22 (2.09)</td>
</tr>
<tr>
<td>Median, Min, Max</td>
<td>1.63, 0.8</td>
<td>175, 0, 8</td>
</tr>
<tr>
<td><strong>Time from initial diagnosis of cancer to randomization (weeks)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>430 (334)</td>
<td>369 (307)</td>
</tr>
<tr>
<td>Median, Min, Max</td>
<td>352, 48.1, 1463.1</td>
<td>284.44.1, 1765.0</td>
</tr>
</tbody>
</table>
SRE Rate (Primary Endpoint)

At a Median of 11.9 months of follow up, the 12 week dosing interval was non-inferior to that of the 4 week zoledronic acid:

The Upper limit of the 95% CI for the rate difference is 9.8, which is lower than the non-inferiority margin of 10%

<table>
<thead>
<tr>
<th></th>
<th>Zoledronic Acid every 4 weeks</th>
<th>Zoledronic Acid every 12 weeks</th>
<th>Proportion difference and 95% C.I.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of subjects</td>
<td>Total number of subjects</td>
<td>Number (%) with at least one SRE</td>
<td>Total number of subjects</td>
<td>Number (%) with at least one SRE</td>
</tr>
<tr>
<td>Overall SRE</td>
<td>200</td>
<td>44 (22.0%)</td>
<td>203</td>
<td>47 (23.2%)</td>
</tr>
</tbody>
</table>
Time-to-First SRE

Times to first on-study SRE were similar in the two arms

HR = 1.06; 95% CI, 0.70 to 1.60

\[ P = 0.792 \]
## Skeletal Morbidity Rate (SMR)

<table>
<thead>
<tr>
<th>SMR (No. of events per year)</th>
<th>Zoledronic Acid every 4 weeks (N = 200)</th>
<th>Zoledronic Acid every 12 weeks (N = 203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>200</td>
<td>203</td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td><strong>0.46 (1.063)</strong></td>
<td><strong>0.50 (1.500)</strong></td>
</tr>
<tr>
<td>Median</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0.0, 6.4</td>
<td>0.0, 15.9</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td><strong>0.854</strong></td>
</tr>
</tbody>
</table>

-An SMR for patient is defined as the ‘number of occurrences’ of any SRE allowing for only one event in any 3 week interval, divided by the ‘time at risk’ in years.

-P-value is from the Cochran-Mantel-Haenszel test with modified ridit score.
Safety Summary

The safety profiles of zoledronic acid every 12 weeks and every 4 week dosing were similar

<table>
<thead>
<tr>
<th>Adverse Events Overall Summary</th>
<th>Adverse Events of Special Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of subjects (%)</strong></td>
<td><strong>Zoledronic Acid every 4 weeks (N=198)</strong></td>
</tr>
<tr>
<td>AEs</td>
<td>189 (95.5%)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>50 (25.3%)</td>
</tr>
<tr>
<td>Grade 3 &amp; 4 AEs</td>
<td>94 (47.5%)</td>
</tr>
<tr>
<td>AEs leading to dose adjustment, interruption</td>
<td>21 (10.6%)</td>
</tr>
<tr>
<td>AEs leading to study medication discontinuation</td>
<td>23 (11.6%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>10 (5.1%)</td>
</tr>
<tr>
<td><strong>Number of subjects (%)</strong></td>
<td><strong>Zoledronic Acid every 4 weeks (N=198)</strong></td>
</tr>
<tr>
<td>Renal AEs</td>
<td>19 (9.6%)</td>
</tr>
<tr>
<td>ONJ (Adjudicated) AEs</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>Cardiac ischemic events</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Atrial fibrillation events</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Atypical subtrochanteric femoral fracture events (Adjudicated)</td>
<td>0</td>
</tr>
</tbody>
</table>
Conclusions

- The efficacy of continuing zoledronic acid for an additional year at the reduced dosing frequency of every 12 weeks was non-inferior to that of every 4 weeks among patients with metastatic breast cancer involving the bone who had previously received zoledronic acid or pamidronate for at least 9 doses, using a non-inferiority margin of 10%

- Safety profiles were similar between the two treatment arms

- Bone marker profiles were similar between the two treatments arms

- Due to study limitations, results should be interpreted with caution
  - Placebo arm dropped because of low accrual
  - Statistical concerns related to the determination of the non-inferiority margin
Duration

- Patients with MBC may live for years
- Start agents in patients with bone destruction
- Bone modifying agents continued indefinitely
  - If no excessive toxicity
  - If consistent with treatment goals
- May continue after anti-cancer therapy
- Minimum duration of six months
- Less frequent dosing after a year
Duration

- Continue calcium and vitamin D
- Continue oral health assessment
- Repeat imaging every 12 to 24 weeks in stable or asymptomatic patients
- Monitor serum calcium and creatinine
- Also electrolytes, magnesium and phosphate
SRE Occurrence During BP Therapy in Patients With Breast Cancer

Progressive Disease

- Worsening of symptoms, new lesions seen on imaging studies or occurrence of a SRE
- Continue osteoclast inhibition
- Usually the same drug
- If on pamidronate consider switch to zolendronic acid or denosumab
- If on ZA consider switch to denosumab
- Depends on patient preference and cost
Switching Studies

Bone metastases
Despite BP therapy:
SRE / progressive bone disease
Elevated NTx

Zoledronic acid

Ibandronate

Denosumab

Phase II Trial of Switch to Denosumab

• 111 patients with bone mets and elevated urinary N-telopeptide on IV bisphosphonates
• Excess bone resorption and risk of SRE
• Randomized to
  – Continue current IV bisphosphonate
  – Switch to denosumab
• More patients in denosumab arm had
  – uNTx < 50 nmol/L at week 13 (71% vs 29%)
  – Fewer on study SRE (8% vs 17%)

Conclusion

• Bone metastasis and their complications are common in patients with MBC
• Management is complex and involves multidisciplinary team
• Ongoing monitoring is essential to toxicity management