New Developments in Oncology
Bone Health

Kamakshi V. Rao, Pharm.D., BCPOP, CPP, FASHP
Clinical Manager, Pharmacy Residency Programs
Oncology and Bone Marrow Transplant Clinical Pharmacist
University of North Carolina Hospitals and Clinics
Chapel Hill, North Carolina

Learning Objectives

• Describe the types of bone loss and bone-related events that affect cancer patients and the influence of these events on morbidity, mortality, and quality of life.
• Compare and contrast the mechanism of action, efficacy, and safety of available therapies for use to prevent skeletal complications in cancer patients.
• Explain the mechanism of action, data, and potential role of available bone-targeted therapies in the treatment of cancer.
• Describe the approach to decision making when selecting an appropriate bone-targeted therapy for particular cancer patients.

Disclosures

• The following faculty and planners report no relationships pertinent to this activity:
  – Chad M. Barnett, Pharm.D., BCOP
  – Kamakshi V. Rao, Pharm.D., BCOP, CPP, FASHP
  – Jill A. Sellers, Pharm.D.
• ASHP staff have no relevant financial relationships to disclose.
Bone Health in Cancer Patients

- **Background and risk factors**
- **Screening and diagnosis**
- **Prevention and treatment strategies**
  - Cancer treatment induced bone loss
  - Metastatic disease induced bone loss/skeletal related events (SRE)
- **Novel agents and emerging science**

Normal Bone Physiology

- Normal bone homeostasis is a balance between
  - Osteoblasts: new bone formation
  - Osteoclasts: bone resorption
- Process is regulated by the RANKL pathway
  - Receptor activatory factor-kappa B ligand (RANKL)
  - Osteoprotegerin (OPG)

Balance between RANKL and OPG

- RANKL and OPG are both produced by osteoblasts
  - RANKL binds to RANK receptor on osteoclasts, to stimulate bone resorption
  - OPG is a “decoy receptor” for RANKL. Binding of RANKL to OPG therefore inhibits osteoclast induced bone resorption, allowing bone formation to predominate
- The ratio/balance between RANKL and OPG is the foundation of normal bone remodeling

Incidence of Bone Disorders in the General Population

- **Osteoporosis** - bone mineral density >2.5 standard deviations below the mean for normal young white women
  - Affects 10 million individuals over age 50 in the US
- **Osteopenia** - bone mineral density 1-2.5 standard deviations below the mean for normal young white women
  - Affects 33.6 million people over age 50 in the US
- **Fracture** - Occurs in 1.5 million individuals annually due to bone disease

<table>
<thead>
<tr>
<th>Type of Fracture</th>
<th>White Women (%)</th>
<th>White Men (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>17.5</td>
<td>6.0</td>
</tr>
<tr>
<td>Vertebra</td>
<td>15.6</td>
<td>5.0</td>
</tr>
<tr>
<td>Forearm</td>
<td>16.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Any of the 3</td>
<td>39.7</td>
<td>13.1</td>
</tr>
</tbody>
</table>


**Question #1**

Which of the following diseases is NOT associated with an increased risk of bone disease?

- a. Prostate cancer
- b. Breast cancer
- c. Non-Hodgkins lymphoma
- d. Multiple myeloma

Risk Factors for Bone Disease in Cancer Patients – Treatment Related Factors

- Endocrine
  - Menopause
  - Oophorectomy
  - GnRH agonists
  - Hypoestrogenic states
  - Androgen deprivation
  - Early menopause
- Genetic
  - Family history
  - Race
  - Sex
  - Low body weight
- Lifestyle
  - Smoking
  - Alcohol
  - Sedentary lifestyle
  - Chronic corticosteroid use
  - Prolonged immobilization
- Nutritional
  - Low calcium
  - Low vitamin D
- Diseases
  - Breast cancer
  - Prostate cancer
  - Lung cancer
  - Multiple myeloma
  - Stem cell transplant
  - Pediatric ALL

Bone Health in Cancer Patients

- Background and risk factors
- **Screening and diagnosis**
  - Prevention and treatment strategies
    - Cancer treatment induced bone loss
    - Metastatic disease induced bone loss/SRE
- Novel agents and emerging science

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Screening and Diagnosis – DEXA scan

- The gold standard of bone mineral density (BMD) measurement is dual-energy x-ray absorptiometry (DEXA) scanning
  - T-Score - bone density compared with what is normally expected in a healthy young adult of your sex
  - Z-Score - number of standard deviations above or below what’s normally expected for someone of a particular age, sex, weight, and ethnic or racial origin

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Criterion - BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>T score better than -1</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>T score between -1 and -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>T score &lt; -2.5</td>
</tr>
<tr>
<td>Severe Osteoporosis</td>
<td>T score &lt; -2.5 + osteoporotic fracture</td>
</tr>
</tbody>
</table>

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Screening and Diagnosis – Tool

- **FRAX®** - World Health Organization Fracture Risk Assessment Tool
  - Computer based tool
  - Integrates clinical information, with or without measured BMD, to calculate the 10-year probability of major osteoporotic fracture and hip fracture
  - Takes into account modifiable and nonmodifiable risk factors
Algorithm for Management of Bone Health in Cancer Patients

Cancer patients at increased risk for bone loss and fracture due to age

History and physical examination, BMD screening, FRAX analysis

Lifestyle modifications, calcium, and vitamin D

T-score > -1

T-score between -1 and -1.5

T-score between -1.5 and -2.0

T-score < -2.0 OR FRAX 10-yr fracture risk >20% for major fracture or >3% for hip fracture

Consider checking 25(OH) vitamin D level

Consider pharmacologic therapy

Strongly consider treatment with pharmacologic therapy

Repeat DEXA every 2 years


Bone Health in Cancer Patients

• Background and risk factors
• Screening and diagnosis
• Prevention and treatment strategies
  – Cancer treatment induced bone loss
  – Metastatic disease induced bone loss/SRE
• Novel agents and emerging science

Chemotherapy Induced Bone Loss

• Hormonal therapy
  – Aromatase inhibitors in breast cancer
  – Androgen deprivation therapy in prostate cancer

• Chemotherapy induced ovarian failure (CIOF)

• Hematopoietic stem cell transplant
Question #2

Which of the following agents is associated with the highest rate of bone loss in women with breast cancer?

- a. Aromatase inhibitors
- b. Tamoxifen
- c. Corticosteroids
- d. Fulvestrant

Hormonal Therapy in Breast Cancer

- ATAC Trial: randomized 6,241 ER+ postmenopausal women to 5 years of anastrazole or tamoxifen
  - Fractures occurred in 11% of anastrazole patients compared to 7.7% of tamoxifen patients (p<0.001) at 68 months of follow up
  - After treatment ceased, fracture rates equalized between arms


Hormonal Therapy in Prostate Cancer

- Numerous trials have evaluated the effect of ADT on bone mineral density and fracture risk:
  - Prospective study compared patients receiving >1yr of ADT to matched controls
  - Analysis of 15,716 men with fractures and 47,149 controls showed prostate cancer to be a significant factor associated with increased risk of fracture

<table>
<thead>
<tr>
<th>Years of ADT</th>
<th>None</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N=124</td>
<td>N=112</td>
<td>N=61</td>
<td>N=37</td>
<td>N=35</td>
<td>N=21</td>
</tr>
<tr>
<td>% Normal</td>
<td>19.4</td>
<td>17.8</td>
<td>16.4</td>
<td>10.8</td>
<td>5.7</td>
<td>0</td>
</tr>
<tr>
<td>% Osteopenia</td>
<td>45.2</td>
<td>39.3</td>
<td>34.4</td>
<td>29.7</td>
<td>28.5</td>
<td>19.4</td>
</tr>
<tr>
<td>% Osteoporosis</td>
<td>35.4</td>
<td>42.9</td>
<td>49.2</td>
<td>59.5</td>
<td>65.7</td>
<td>80.6</td>
</tr>
</tbody>
</table>

Chemotherapy Induced Ovarian Failure

- Effect of chemotherapy on ovarian function depends on age, class of chemotherapy, and cumulative exposure
  - Risk of CIOF increases with age due to decreased ovarian reserve
    - In pediatric patients, treatment before puberty reduces likelihood of CIOF (Hodgkins, pediatric ALL)
  - In women who retain menstrual function after chemotherapy, natural menopause may occur at an earlier age than matched controls


Hematopoietic Stem Cell Transplant (HCT)

- Numerous factors increase the risk of bone loss in patients undergoing HCT:
  - High dose chemotherapy/radiation
  - Calcineurin inhibitors (tacrolimus, cyclosporine)
  - Gonadal failure
  - Prolonged corticosteroid use
- Bone loss occurs within 6-12 months after HCT. Recovery occurs first in the lumbar spine, then in the femoral neck
- For patients requiring longer-term therapy with steroids and calcineurin inhibitors, bone marrow transplant may remain low and not return to normal

Treatment Options

- Options for treatment have grown over the past 10 years
  - Bisphosphonates
  - Denosumab
  - Selective estrogen receptor modulators
  - Teriparatide
But never forget the basics….

- **Calcium**
  - Calcium carbonate
  - Calcium gluconate
  - Calcium citrate
- **Vitamin D**
  - Monitoring for deficiency
  - Supplementation
- **Weight bearing exercises**

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**Bisphosphonates**

**Mechanism of Action**

- Decrease bone resorption and increase bone mineralization by inhibiting osteoclast activity

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**Bisphosphonates**

**Available Agents**

<table>
<thead>
<tr>
<th>Agent</th>
<th>FDA approved doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate (Fosamax®)</td>
<td>Prevention: 5 mg Qday/35 mg Qweek Treatment: 10 mg Qday/70 mg Qweek</td>
</tr>
<tr>
<td>Risedronate (Actonel®)</td>
<td>5 mg Qday/35 mg Qweek/150 mg Qmonth</td>
</tr>
<tr>
<td>Ibandronate (Boniva®)</td>
<td>150 mg PO Qmonth/3 mg IV Q3months</td>
</tr>
<tr>
<td>Pamidronate (Aredia®)</td>
<td>60-90 mg IV Q3-4 weeks</td>
</tr>
<tr>
<td>Zoledronic Acid (Zometa®, Reclast®)</td>
<td>Nonmalignant: 5 mg Q2years Malignant: 5 mg Qyr/ 4 mg Q3-6months</td>
</tr>
</tbody>
</table>

- Majority of cancer trials have used IV bisphosphonates
Bisphosphonates

Toxicities

• Hypocalcemia
  – Increased risk in patients with vitamin D deficiency and when not used in the setting of hypercalcemia
• Renal toxicity
  – Acute tubular necrosis with zoledronic acid: Increased incidence with faster infusions
  – Acute tubular necrosis with zoledronic acid: Increased incidence with faster infusions
• Osteonecrosis of the jaw
  – Pain, numbness, exposed bone
  – Incidence reported at 1-10%
  – Increased risk in those with previous jaw trauma or dental surgery/extraction
  – Cumulative dose relation
  – IV bisphosphonates > PO bisphosphonates

Denosumab (Prolia®)

• Monoclonal antibody directed towards RANKL

Denosumab Dosing and Toxicities

Dosing

• 60 mg SC Q6 months (Prolia®)
  – Treatment of osteoporosis in patients at risk for fracture
  – Bone loss induced by AI’s or ADT
• 120 mg SC Q4 weeks (Xgeva®)
  – Treatment of metastatic disease to prevent skeletal related events

Toxicities

• Hypocalcemia
• Infusion reactions
• Osteonecrosis of the jaw
• Hypophosphatemia

Denosumab versus ZA (All Phase III Trials)
Selected Adverse Events of Any Severity

<table>
<thead>
<tr>
<th>Body System</th>
<th>Denosumab (n=2841) %</th>
<th>Zoledronic acid (ZA)(n=2836) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/Asthenia</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>32</td>
<td>20</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Cough</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>


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**AI Induced Bone Loss**

**Z-FAST/ZO-FAST trials**

- Postmenopausal breast cancer patients receiving letrozole 2.5mg PO Qday x 5 years
- Immediate treatment ZA starts immediately
- Delayed treatment: ZA starts when patients experience:
  1. T score < -2.0
  2. Non-traumatic fracture
  3. Asymptomatic fracture at 36 months

- Primary endpoint: % change in spine BMD at 12 months
- Secondary endpoint: % change in total hip BMD


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**AI Induced Bone Loss**

**Z-FAST/ZO-FAST trials**

- Z-FAST results
  - N=602
  - Upfront ZA progressively increased lumbar spine (LS) and total hip (TH) BMD
  - Delayed ZA had significant decreases in LS and TH BMD
  - ZA produced substantial increase in BMD regardless of baseline T score, osteoporosis risk factors, or chemotherapy status.

- ZO-FAST results
  - N= 1065 patients

AI Induced Bone Loss
Denosumab’s role

- Hormone Ablation Bone Loss Trial in Breast Cancer (HALT-BC)
- Phase III trial in 252 women with early stage ER+ Breast cancer, on AI therapy, with evidence of low bone mass (T score of -1 to -2.5)
  - Denosumab 60 mg SC Q6 months x4 vs. placebo
- Primary endpoint: % change in lumbar spine BMD at 12 months


ADT Induced Bone Loss

- 222 patients with M0 prostate CA
  - Within 1 year of starting ADT
  - Within 2 weeks of orchiectomy
- Zoledronic acid 4 mg IV Q3 months x 48 weeks (n= 112)
- Placebo (n= 110)
- Primary Endpoint: % change in lumbar spine BMD
- Secondary Endpoint: % change in total hip BMD

ADT Induced Bone Loss

- Results demonstrate significantly increased BMD in patients treated with ZA vs. placebo

<table>
<thead>
<tr>
<th>% change from baseline BMD</th>
<th>Lumbar Spine</th>
<th>Total Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid</td>
<td>+4.7</td>
<td>+1.6</td>
</tr>
<tr>
<td>Placebo</td>
<td>-2</td>
<td>-2.1</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>


ADT Induced Bone Loss
Denosumab (HALT-PC)

- Randomized, double blind study in patients with prostate cancer on ADT, without metastatic disease
  - Denosumab 60mg SC Q6 months vs. placebo
  - 1468 men (734 denosumab, 734 placebo)
- Primary endpoint: % change from baseline in LS BMD


<table>
<thead>
<tr>
<th>Time point</th>
<th>Cumulative incidence of new vertebral fractures</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>Placebo 1.9, N=13</td>
<td>Denosumab 0.3, N=2</td>
</tr>
<tr>
<td>24 months</td>
<td>Placebo 3.3, N=22</td>
<td>Denosumab 1.0, N=7</td>
</tr>
<tr>
<td>36 months</td>
<td>Placebo 3.9, N=26</td>
<td>Denosumab 1.5, N=10</td>
</tr>
</tbody>
</table>

- At 24 months, 6.7% difference in bone mineral density between denosumab and placebo, favoring denosumab

Chemotherapy Induced Ovarian Failure

• CALGB 79809

Premenopausal women with breast cancer receiving adjuvant therapy

ZA 4 mg Q3 months x 8 starting at 1-3 months
ZA 4 mg Q3 months x 8 starting at 12-14 months

• Primary Endpoint: % change in LS BMD at 1 year
• Secondary Endpoint: % change in LS BMD at 3 years


Chemotherapy Induced Ovarian Failure – CALGB 79809

Total Randomized
N=439

CIOF at 1 year
N=150 (34%)

No CIOF at 1 year
N=289 (66%)

Total BMD at baseline at 1 year
N=302

Total BMD at baseline 3 years
N=177

Median percentage difference in BMD

<table>
<thead>
<tr>
<th></th>
<th>ZA early</th>
<th>ZA late</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIOF @1y</td>
<td>1.2</td>
<td>-6.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All @ 1y</td>
<td>1.4</td>
<td>-5.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All @ 3y</td>
<td>1.0</td>
<td>-0.5</td>
<td>0.019</td>
</tr>
</tbody>
</table>


CTIBL Summary

• Cancer patients may be at increased risk for bone loss and fracture due to cancer treatments
• Patients at risk for CTIBL should be assessed for bone loss risk
• Bisphosphonates and denosumab are appropriate options for prevention and treatment of CTIBL
Bone Health in Cancer Patients

- Background and risk factors
- Screening and diagnosis
- Prevention and treatment strategies
  - Cancer treatment induced bone loss
  - Metastatic disease induced bone loss/SRE
- Novel agents and emerging science

Question #3

RJ is a 66 year old man with newly diagnosed multiple myeloma. Which of the following options would be appropriate for reduction of skeletal-related events (SRE)?

1. Zoledronic acid or pamidronate
2. Denosumab
3. Pamidronate
4. Zoledronic acid or denosumab

SRE Associated with Bone Metastases

- Pathological fractures
  - Nonvertebral
  - Vertebral compression
- Spinal cord compression/collapse
- Radiation therapy
- Surgery to bone
- Hypercalcemia
  - Not included in some studies

Prevalence of SRE in Patients with Metastatic Breast Cancer


Development of Bone Metastases


Osteolytic Bone Metastases

Osteoblastic Bone Metastases


Treatment of Bone Metastases

- Antineoplastic therapy
- Bone modifying agents (BMA)
  - Bisphosphonates
  - RANK-L inhibitors
- Localized radiation
- Radiopharmaceuticals
- Surgery

Bisphosphonates for Breast Cancer to Bone

<table>
<thead>
<tr>
<th>Study treatments</th>
<th>Number of patients</th>
<th>Pts with an SRE (%)</th>
<th>Median time to first SRE (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamidronate 90 mg IV q3-4 weeks</td>
<td>380</td>
<td>43</td>
<td>13.1</td>
</tr>
<tr>
<td>Placbo</td>
<td></td>
<td></td>
<td>7.0</td>
</tr>
<tr>
<td>Pamidronate 90 mg IV q4weeks</td>
<td>371</td>
<td>56</td>
<td>10.4</td>
</tr>
<tr>
<td>Placbo</td>
<td></td>
<td></td>
<td>6.9</td>
</tr>
<tr>
<td>ZA 4 mg IV q4weeks</td>
<td>227</td>
<td>30</td>
<td>NR*</td>
</tr>
<tr>
<td>Placbo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pamidronate 90 mg IV q3-4weeks</td>
<td>524 (chemotherapy)</td>
<td>46 vs 49</td>
<td>11.6</td>
</tr>
<tr>
<td>ZA 4 mg IV q3-4weeks</td>
<td>606 (endocrine therapy)</td>
<td>12.2</td>
<td></td>
</tr>
<tr>
<td>Pamidronate 90 mg IV q3-4weeks</td>
<td></td>
<td></td>
<td>13.8</td>
</tr>
<tr>
<td>ZA 4 mg IV q3-4weeks</td>
<td></td>
<td></td>
<td>12.3</td>
</tr>
</tbody>
</table>

*NR, not reached

### Bisphosphonates for Castration-Resistant Prostate Cancer to Bone

<table>
<thead>
<tr>
<th>Study treatments</th>
<th>Number of patients</th>
<th>Pts with an SRE (%)</th>
<th>Median time to first SRE (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamidronate 90 mg IV q3weeks</td>
<td>350</td>
<td>25</td>
<td>N/A*</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZA 4 mg IV q3weeks</td>
<td>122</td>
<td>38</td>
<td>16.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>49</td>
<td>49</td>
<td>10.7</td>
</tr>
</tbody>
</table>

* N/A, not available


### Bisphosphonates in Cancer to Bone (w/o breast and prostate cancers)

<table>
<thead>
<tr>
<th>Study treatments</th>
<th>Number of patients</th>
<th>Pts with an SRE (%)</th>
<th>Median time to first SRE (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid 4 mg IV q3weeks</td>
<td>507</td>
<td>39</td>
<td>7.9</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


### Denosumab versus ZA Study Schema

- Breast Cancer (n=2046)
- Prostate Cancer (n=1901)
- Other Solid Tumors or Multiple Myeloma (n=1776)

Denosumab 120 mg SC and placebo IV every 4 weeks

Denosumab 120 mg SC and placebo SC every 4 weeks

ZA 4 mg IV and placebo SC every 4 weeks

Denosumab vs. Zoledronate in Patients with Bone Metastases

<table>
<thead>
<tr>
<th></th>
<th>Denosumab</th>
<th>Zoledronic acid</th>
<th>HR (95% CI)</th>
<th>P-value (noninferiority)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer (n=2046)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to first SRE</td>
<td>Not reached</td>
<td>26.4 mo</td>
<td>0.82 (0.71-0.95)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Castrate-resistant prostate cancer (n=1901)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to first SRE</td>
<td>20.7 mo</td>
<td>17.1 mo</td>
<td>0.82 (0.71-0.95)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Solid tumors (other than breast and prostate) and multiple myeloma (n=1776)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to first SRE</td>
<td>20.5 mo</td>
<td>16.3 mo</td>
<td>0.84 (0.71-0.96)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

* Denosumab is superior to Zoledronic acid


Denosumab versus ZA in Patients with Cancer to Bone (w/o breast and prostate cancers)

- Risk of disease progression (HR < 1.0 favors denosumab):
  - HR 0.79 for NSCLC (95%CI 0.65-0.95)
  - HR 2.26 for multiple myeloma (MM) (95%CI 1.13-4.50)
  - HR 1.08 for other solid tumors (95%CI 0.90-1.30)

- Risk of death stratification (HR < 1.0 favors denosumab):
  - HR 0.95 (0.83 to 1.08) for death


ASCO Guidelines for the Use of BMA in MM

- Bisphosphonates should be considered in all patients with MM receiving first-line antimyeloma therapy
- Appropriate options include:
  - Pamidronate 90 mg IV over no less than 2 hours every 3-4 weeks
  - Zoledronic acid 4 mg IV over no less than 15 minutes every 3-4 weeks

**ASCO Guidelines for the Use of BMA in Breast Cancer to Bone**

- Appropriate options for breast cancer to bone:
  - Pamidronate 90 mg IV over no less than 2 hours every 3-4 weeks
  - Zoledronic acid 4 mg IV over no less than 15 minutes every 3-4 weeks
  - Denosumab 120 mg SC every 4 weeks
- Insufficient evidence to demonstrate greater efficacy of one agent over another


**Bone Health in Cancer Patients**

- Background and risk factors
- Screening and diagnosis
- Prevention and treatment strategies
  - Cancer treatment induced bone loss
  - Metastatic disease induced bone loss/SRE
- Novel agents and emerging science

**Interaction Between Tumor Cells and the Bone Microenvironment**

SRC inhibitors

- Proto-oncogene non-receptor tyrosine kinase
- Has been shown to be involved in bone remodeling, cancer metastasis, and tumor growth
- Dasatinib is currently being evaluated in clinical trials for patients with metastatic bone disease from solid tumors
  - Ongoing phase II study in patients with stage IV breast cancer that has spread to bone (NCT00410813)


Endothelin A Receptor Antagonists

- Endothelin-1 (ET-1) can stimulate osteoblast activity and promote metastasis of prostate cancer via stimulation of the endothelin A (ETA) receptor
- Atrasentan and zibotentan are ETA receptor antagonists being evaluated in clinical trials
  - Zibotentan no longer being evaluated in patients with prostate cancer to bone due to lack of efficacy
  - Awaiting results with atrasentan and zoledronic acid in patients with prostate cancer to bone (NCT00181558)


Summary

- Malignancy associated bone loss and bone involvement are associated with significant morbidity
- Appropriate screening can help identify patients at high risk, to minimize or avoid consequences
- Pharmacists can play an important role in medication selection and dosing