New Developments in Oncology Bone Health

Presented as a Live Webinar

Thursday, June 12, 2014
1:00 p.m. – 2:00 p.m. EDT

Wednesday, July 16, 2014
12:00 p.m. – 1:00 p.m.

Tuesday, July 29, 2014
2:00 p.m. – 3:00 p.m.

www.ashpadvantage.com/bonehealth

Planned and conducted by ASHP Advantage and supported by an educational donation provided by Amgen.
New Developments in Oncology Bone Health

Activity Overview

This activity will provide an overview of the types of bone loss and bone-related events that affect cancer patients. The risk factors, incidence, and prevalence of these events, as well as their impact on morbidity, mortality, and quality of life will be discussed. Currently available agents targeting bone health will be described, as well as the approach to using these agents in both the preventative and treatment settings for patients with cancer. Finally, the role of the pharmacist in assessing patients’ risk factors and recommending therapies for bone-directed treatment will be presented. Clinical patient vignettes will be used to illustrate the decision-making process throughout the presentation.

Learning Objectives

At the conclusion of this knowledge-based educational activity, participants should be able to

- 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.

Continuing Education Accreditation

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1.0 hour (0.1 CEU – no partial credit) of continuing pharmacy education credit (ACPE activity #0204-0000-14-477-L01-P for the live activity and ACPE activity #0204-0000-14-477-H01-P for the on-demand activity).

Participants will process CPE credit online at http://elearning.ashp.org/my-activities. CPE credit will be reported directly to CPE Monitor. Per ACPE, CPE credit must be claimed no later than 60 days from the date of the live activity or completion of a home study activity.

Webinar Information

Visit www.ashpadvantage.com/bonehealth to find:

- Webinar registration link
- Group viewing information and technical requirements
- CPE webinar processing information

Additional Educational Activities in this Initiative

This live activity will be archived and offered as web-based on-demand learning at www.ashpadvantage.com/bonehealth.
New Developments in Oncology Bone Health

Activity Faculty

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Clinical Pharmacy Specialist – Breast Oncology
Division of Pharmacy
University of Texas MD Anderson Cancer Center
Houston, Texas

Chad M. Barnett, Pharm.D., BCOP, is Clinical Pharmacy Specialist in the Division of Pharmacy at The University of Texas MD Anderson Cancer Center in Houston, Texas. In addition to his patient care responsibilities, Dr. Barnett is involved in precepting oncology pharmacy practice residents on the Breast Medical Oncology rotation. Dr. Barnett also serves as clinical faculty for the ASHP Oncology Pharmacy Preparatory Review Course. He has authored numerous book chapters and articles and has presented nationally on topics related to breast cancer and bone health in patients with cancer. Dr. Barnett is also actively involved in breast cancer research.

Dr. Barnett received his Doctor of Pharmacy degree from the University of Kansas in Lawrence, Kansas. He completed a pharmacy practice residency at The Methodist Hospital in Houston, Texas and an oncology pharmacy practice residency at the University of Texas M.D. Anderson Cancer Center in Houston, Texas. Dr. Barnett became a Board-Certified Oncology Pharmacist (BCOP) in 2006.

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Clinical Manager, Pharmacy Residency Programs
Oncology and Bone Marrow Transplant Clinical Pharmacist
University of North Carolina Hospitals and Clinics
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Kamakshi V. Rao, Pharm.D., BCOP, CPP, FASHP, is a clinical manager over pharmacy residency programs and an oncology and bone marrow transplant clinical pharmacist practitioner at the University of North Carolina Medical Center in Chapel Hill, North Carolina. She also serves as Associate Professor of Clinical Education at the UNC Eshelman School of Pharmacy.

Dr. Rao earned her Doctor of Pharmacy degree from Rutgers University Ernest Mario School of Pharmacy. She completed a pharmacy practice residency at the Medical College of Virginia and an oncology fellowship at The Cancer Institute of New Jersey.

Dr. Rao is an active member of the American Society of Health-System Pharmacists (ASHP), Hematology/Oncology Pharmacy Association, and American Society for Blood and Marrow Transplantation. She is currently a board-certified oncology pharmacist and a Fellow of the ASHP.
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- Kamakshi V. Rao, Pharm.D., BCOP, CPP, FASHP
- Jill A. Sellers, Pharm.D.

ASHP staff has no relevant financial relationships to disclose.
New Developments in Oncology Bone Health

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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.
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• Describe the approach to decision making when selecting an appropriate bone-targeted therapy for particular cancer patients.

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 activator factor-kappa B ligand (RANKL)
  – Osteoprotegerin (OPG)

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
  Lifetime Risk of Fracture at Age 50

<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 above</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

<table>
<thead>
<tr>
<th>Endocrine</th>
<th>Genetic</th>
<th>Lifestyle</th>
<th>Nutritional</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopause</td>
<td>Family history</td>
<td>Smoking</td>
<td>Low calcium</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>Race</td>
<td>Alcohol</td>
<td>Low vitamin D</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>GnRH agonists</td>
<td>Sex</td>
<td>Sedentary lifestyle</td>
<td></td>
<td>Lung cancer</td>
</tr>
<tr>
<td>Hypoestrogenic states</td>
<td></td>
<td>Chronic corticosteroid use</td>
<td></td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Androgen deprivation</td>
<td></td>
<td>Prolonged immobilization</td>
<td></td>
<td>Stem cell transplant</td>
</tr>
<tr>
<td>Early menoapuse</td>
<td></td>
<td></td>
<td></td>
<td>Pediatric ALL</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


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

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>

Screening and Diagnosis - Tool

- FRAX® - World Health Organization Fracture Risk Assessment Tool
  - Computer based tool which 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 |


See enlargement, p. 15
Bone Health in Cancer Patients

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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

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

Bisphosphonates

Mechanism of Action

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

Roodman GD. Clinical Care Options: treatment of myeloma bone disease. August 9, 2010 (URL in ref list).

See enlargement, p. 16

Bisphosphonates

Available Agents

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


See enlargement, p. 17

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

See enlargement, p. 17

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

<table>
<thead>
<tr>
<th>Body System</th>
<th>Denosumab (%)</th>
<th>Zoledronic acid (%)</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/Asthema</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>


See enlargement, p. 17

Al 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

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


See enlargement, p. 17

Al 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

AI Induced Bone Loss
Denosumab’s role


ADT Induced Bone Loss


ADT Induced Bone Loss

• Primary Endpoint: % change in lumbar spine BMD
• Secondary Endpoint: % change in total hip BMD

See enlargement, p. 18

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


ADT Induced Bone Loss

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

% change from baseline BMD

<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>


 Chemotherapy Induced Ovarian Failure

• CALGB 79809

Chemotherapy Induced Ovarian Failure – CALGB 79809

No CIOF at 1 year N=286 (66%)
CIOF at 1 year N=150 (34%)

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

Tumor cell proliferation
Response to microenvironment
Endothelial cell
Multicell aggregates (lymphocytes, platelets)
Embolism
Invasion
New vessel formation
Primary malignant neoplasm

Bone metastases
Tumor cell proliferation
Response to microenvironment
Endothelial cell
Multicell aggregates (lymphocytes, platelets)
Embolism
Invasion
New vessel formation
Primary malignant neoplasm


Osteolytic Bone Metastases

Osteolysis
TGF-β
Ca2+
TGF-β
Ca2+
Ca2+
pump
IGF1
Growth

↑
RANKL
↓
OPG
PTHrP
SMAD MAPK
Osteoclast
precursor
Osteoblasts
Tumor cell


Osteoblastic Bone Metastases

FGF
BMP
PDGFLatent TGF-β IGFBP
PTHrP
Active TGF-β Proteases uPA IGF
Inactive PTHrP fragments

Bone formation


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>Placebo</td>
<td></td>
<td>56</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>Placebo</td>
<td></td>
<td>67</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>Placebo</td>
<td></td>
<td>50</td>
<td>12.1</td>
</tr>
<tr>
<td>Pamidronate 90 mg IV q3-4 weeks</td>
<td>524</td>
<td>46 vs 49</td>
<td>11.6</td>
</tr>
<tr>
<td>ZA 4 mg IV q3-4weeks (chemotherapy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pamidronate 90 mg IV q3-4weeks</td>
<td>606</td>
<td>46 vs 49 (combined analysis)</td>
<td>13.8</td>
</tr>
<tr>
<td>ZA 4 mg IV q3-4weeks (endocrine therapy)</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>25</td>
<td>N/A</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></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>46</td>
<td>5.2</td>
<td></td>
</tr>
</tbody>
</table>


Denosumab vs. Zoledronate in Patients with Bone Metastases

<table>
<thead>
<tr>
<th>Patients</th>
<th>Denosumab (n=2046)</th>
<th>Zoledronate (n=1901)</th>
<th>Median time to first SRE (mo)</th>
<th>HR (95% CI)</th>
<th>P-value (noninferiority)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>Not reached</td>
<td>26.4 mo</td>
<td>0.82 (0.71-0.95)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Castrate-resistant prostate cancer (n=1901)</td>
<td>20.7 mo</td>
<td>17.1 mo</td>
<td>0.82 (0.71-0.95)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Solid tumors (other than breast and prostate) and multiple myeloma (n=1776)</td>
<td>20.5 mo</td>
<td>16.3 mo</td>
<td>0.84 (0.71-0.98)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

1p=0.01 (superiority), 2p=0.008 (superiority), 3p=0.08 (superiority)

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

<table>
<thead>
<tr>
<th>Patients</th>
<th>Denosumab 120 mg SC and placebo IV every 4 weeks</th>
<th>ZA 4 mg IV and placebo SC every 4 weeks</th>
<th>Median time to first SRE (mo)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer (n=2046)</td>
<td></td>
<td></td>
<td></td>
<td>1.00 (0.89 to 1.12)</td>
<td>1.0</td>
</tr>
<tr>
<td>Prostate Cancer (n=1901)</td>
<td></td>
<td></td>
<td></td>
<td>0.95 (0.83 to 1.08)</td>
<td>0.43</td>
</tr>
<tr>
<td>Other Solid Tumors or Multiple Myeloma (n=1776)</td>
<td></td>
<td></td>
<td></td>
<td>0.92 (0.75 to 1.13)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Denosumab 120 mg SC and placebo IV every 4 weeks

• Risk of disease progression (HR > 1.0 favors denosumab): 0.95 (0.78 to 1.18)
• Risk of death 0.95 (0.83 to 1.08) 0.43


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

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

Interaction Between Tumor Cells and the Bone Microenvironment


See enlargement, p. 20
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 activator factor-kappa B ligand (RANKL)
  - Osteoprotegerin (OPG)


Screening and Diagnosis - Tool

- FRAX® - World Health Organization Fracture Risk Assessment Tool
  - Computer based tool which 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
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


Bisphosphonates

Mechanism of Action

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

Roodman GD. Clinical Care Options: treatment of myeloma bone disease. August 9, 2010 (URL in ref list).
Denosumab (Prolia®)

- Monoclonal antibody directed towards RANKL

![Mechanism of action of denosumab](image)


### Al 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

Al Induced Bone Loss
Denosumab’s role

% Change in LS BMD from baseline for all patients at 24 months

Proportion of patients preserving LS BMD at 24 months


Development of Bone Metastases

Osteolytic Bone Metastases

Osteoblastic Bone Metastases

Interaction Between Tumor Cells and the Bone Microenvironment

Selected References


New Developments in Oncology Bone Health

Abbreviations

ADT androgen deprivation therapy
AI androgen inhibitor
ASCO American Society of Clinical Oncology
ATAC anastrazole, tamoxifen, alone or in combination
BMA bone modifying agents
BMD bone mineral density
BMP bone morphogenic proteins
CA cancer
CIOF chemotherapy induced ovarian failure
DEXA dual energy x-ray absorptiometry
ER estrogen receptor
ET-1 endothelin-1
ETA endothelin A
FGF fibroblast growth factors
GnRH gonadotropin-releasing hormone
HCT hematopoietic stem cell transplant
HR hazard ratio
IGF insulin-like growth factor
IGFBP insulin-like growth factor-binding protein
LS lumbar spine
MAPK mitogen-activated protein kinase
MM multiple myeloma
NSCLC non-small cell lung cancer
OPG osteoprotegerin
PDGF platelet-derived growth factor
PTH parathyroid hormone
PTHrP parathyroid hormone-related peptide
RANK receptor activator factor-kappa B
RANKL receptor activator factor-kappa B ligand
SRE skeletal related events
TGF transforming growth factor
TH total hip
uPA urokinase
ZA zoledronic acid
Self-assessment Questions

1. Which of the following adverse events was more common with denosumab compared to zoledronic acid for treatment of metastatic cancer to bone?
   a. Osteonecrosis of the jaw.
   b. Cough.
   c. Nausea.
   d. Hypophosphatemia.

2. The bisphosphonates reduce skeletal related events in patients with metastatic cancer to bone by:
   a. Promoting osteoclast apoptosis and decreasing osteoclast bone resorption.
   b. Binding to RANK-ligand and inhibiting the stimulatory effects on osteoclast activity.
   c. Pharmacologically mimicking the effects of osteoprotegerin and stimulating osteoclastic activity.
   d. Simulating osteoblasts and increasing bone formation.

3. AJ is a 56 year-old male with castration-resistant prostate cancer to the bone receiving docetaxel. Which of the following medication(s) would be appropriate to reduce the risk of skeletal-related events?
   a. Denosumab.
   b. Pamidronate or zoledronic acid.
   c. Zoledronic acid or denosumab.
   d. Pamidronate, zoledronic acid, or denosumab.

Answers

1. d
2. a
3. c