Role of Pharmacists in Maintaining Bone Health in Patients with Cancer

An application-based CPE activity presented during the OSHP 74th Annual Meeting

Thursday, May 2, 2013
Columbus, Ohio

Planned and conducted by ASHP Advantage and supported by an educational donation provided by Amgen.
Role of Pharmacists in Maintaining Bone Health in Patients with Cancer
Role of Pharmacists in Maintaining Bone Health in Patients with Cancer

Activity Faculty

Kamakshi V. Rao, Pharm.D., BCOP, CPP
Oncology and Bone Marrow Transplant Clinical Pharmacist
University of North Carolina Hospitals and Clinics
Chapel Hill, North Carolina

Kamakshi V. Rao, Pharm.D., BCOP, is Oncology and Bone Marrow Transplant Clinical Pharmacist at the University of North Carolina (UNC) Hospitals and Clinics located in Chapel Hill, North Carolina. At UNC, Dr. Rao’s clinical practice focuses in the area of adult bone marrow and stem cell transplantation. Additionally, Dr. Rao serves is the director of the UNC PGY1 pharmacy residency program and is a preceptor for UNC pharmacy students, PGY1, and PGY2 residents. At UNC, Dr. Rao serves on numerous patient care and oncology-focused subcommittees.

Dr. Rao earned her Doctor of Pharmacy degree from Rutgers University Ernest Mario School of Pharmacy in Piscataway, New Jersey. She then completed a pharmacy practice residency at the Medical College of Virginia followed by an oncology pharmacy fellowship at The Cancer Institute of New Jersey in New Brunswick. She became a board-certified oncology pharmacist in 2003.

She is an active member of the American Society of Health-System Pharmacists (ASHP), Hematology/Oncology Pharmacy Association (HOPA), and American Society for Blood and Marrow Transplantation (ASBMT). Dr. Rao has participated in and presented at a number of meetings, including ASHP, HOPA, ASBMT, American Society of Hematology (ASH), and American Society of Clinical Oncology (ASCO), and has published in numerous journals.
Role of Pharmacists in Maintaining Bone Health in Patients with Cancer

DISCLOSURE STATEMENT

In accordance with the Accreditation Council for Continuing Medical Education’s Standards for Commercial Support and the Accreditation Council for Pharmacy Education’s Guidelines for Standards for Commercial Support, ASHP Advantage requires that all individuals involved in the development of activity content disclose their relevant financial relationships. A person has a relevant financial relationship if the individual or his or her spouse/partner has a financial relationship (e.g., employee, consultant, research grant recipient, speakers bureau, or stockholder) in any amount occurring in the last 12 months with a commercial interest whose products or services may be discussed in the activity content over which the individual has control. The existence of these relationships is provided for the information of participants and should not be assumed to have an adverse impact on presentations.

All faculty and planners for ASHP Advantage education activities are qualified and selected by ASHP Advantage and required to disclose any relevant financial relationships with commercial interests. ASHP Advantage identifies and resolves conflicts of interest prior to an individual’s participation in development of content for an educational activity.

The faculty and planners report the following relationships:

Kamakshi V. Rao, Pharm.D., BCOP, CPP

Dr. Rao declares that she has no relationships pertinent to this activity.

Susan R. Dombrowski, M.S., B.S.Pharm.

Ms. Dombrowski declares that she has no relationships pertinent to this activity.

Erika L. Thomas, M.B.A., B.S.Pharm.

Ms. Thomas declares that she has no relationships pertinent to this activity.

ASHP staff has no relevant financial relationships to disclose.
Role of Pharmacists in Maintaining Bone Health in Patients with Cancer

ACTIVITY OVERVIEW
This activity will focus on the role of pharmacists in maintaining bone health in patients with cancer. The two primary groups of patients to be discussed include patients at different levels of risk for bone loss due to cancer or cancer therapies and patients at risk for skeletal-related events (SREs) due to bone involvement or metastases. For each of these, the safety and efficacy of available treatment options to decrease the risk will be described. New and emerging information related to the use of bone-modifying agents for preventing bone metastases, as well as the essentials for evaluating the pharmacoeconomics of bone-modifying therapies, will be presented.

LEARNING OBJECTIVES
After attending this application-based educational activity, attendees should be able to

- Identify patients at risk for bone loss due to cancer therapies or bone metastases.
- Describe available treatment options for patients at risk for bone loss due to cancer therapies and for patients at risk for skeletal-related events due to bone involvement or metastases.
- Discuss ongoing research regarding the use of bone-modifying agents in patients with cancer.
- Outline a plan for minimizing the toxicity of bone-modifying agents in patients with cancer.

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) of continuing pharmacy education credit (ACPE activity #0204-0000-13-417-L01-P).

Attendees must complete a Continuing Pharmacy Education Request online and may print their official ASHP statements of continuing pharmacy education credit at the ASHP eLearning site (http://elearning.ashp.org) immediately following this activity.
Role of Pharmacists in Maintaining Bone Health in Patients with Cancer

Instructions for Processing CE Credit with Enrollment Code

**Pharmacists and Technicians:** All ACPE accredited activities which are processed on the eLearning site will be reported directly to CPE Monitor. To claim pharmacy credit, you must have your NABP e-Profile ID, birth month, and birth day. If you do not have an NABP e-Profile ID, go to www.MyCPEMonitor.net for information and application. Please follow the instructions below to process your CPE credit for this activity.

1. The ASHP eLearning site allows participants to obtain statements of continuing education credit conveniently and immediately using any computer with an internet connection. Type the following link into your web browser to access the e-Learning site: http://elearning.ashp.org/my-activities
2. If you already have an account registered with ASHP, log in using your username and password. If you have not logged in to any of the ASHP sites before and/or are not a member of ASHP, you will need to set up an account. Click on the Register link and follow the registration instructions.
3. Once logged in to the site, enter the enrollment code for this activity in the field provided and click Redeem.

   **Note:** The Enrollment Code was announced at the end of the live activity. Please record the Enrollment Code in the grid below for your records.

4. The title of this activity should now appear in a pop-up box on your screen. Click on the Go button or the activity title.
5. Complete all required elements. A green ✔ should appear as each required element is completed. You can now claim your credit.
6. Look for your profession on the right side of the screen (under Achievements) and click the appropriate Claim button.

   **CPE Credit for Pharmacists and Technicians:** To claim continuing pharmacy education (CPE) credit, you will need to enter your NABP e-Profile ID, birth month, and birth day. Once you have entered this information the first time, it will auto fill in the future. Please note: All CPE credit processed on the eLearning site will be reported directly to CPE Monitor.
7. Review the information for the credit you are claiming. If all information appears to be correct, check the box at the bottom and click Claim. You will see a message if there are any problems claiming your credit.
8. After successfully claiming credit, you may print your statement of credit by clicking on Print. If you require a reprint of a statement of credit, you can return here at any time to print a duplicate. Please note that for CPE credit, printed statements may not be necessary because your credit will be reported directly to CPE Monitor.

<table>
<thead>
<tr>
<th>Date of Activity</th>
<th>Activity Title</th>
<th>Enrollment Code</th>
<th>Credit Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>05-02-2013</td>
<td>Role of Pharmacists in Maintaining Bone Health in Patients with Cancer</td>
<td>_ _ _ _ _</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**NEED HELP?** Contact eLearning@ashp.org.
**Learning Objectives**

- Identify patients at risk for bone loss due to cancer therapies or bone metastases.
- Describe available treatment options for patients at risk for bone loss due to cancer therapies and for patients at risk for skeletal-related events due to bone involvement or metastases.
- Discuss ongoing research regarding the use of bone-modifying agents in patients with cancer.
- Outline a plan for minimizing the toxicity of bone-modifying agents in patients with cancer.

**Bone Health in Cancer Patients**

- **Background**
- **Risk Factors** – patient, disease, and treatment related
- **Screening and Diagnosis**
- **Available agents**
- **Prevention and Treatment Strategies**
  - Cancer treatment-induced bone loss
  - Metastatic disease-induced bone loss / skeletal related events (SREs)

**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)

**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

**Disclosures**

- Kamakshi V. Rao, Pharm.D., BCOP, CPP
  - No relationships pertinent to this activity
- Erika L. Thomas, M.B.A., B.S.Pharm.
  - No relationships pertinent to this activity
- Susan R. Dombrowski, M.S., B.S.Pharm. (reviewer)
  - No relationships pertinent to this activity
- ASHP Advantage Staff
  - No relationships pertinent to this activity
Incidence of Bone Disorders in the General Population

- **Osteoporosis** - bone mineral density (BMD) >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 1.2-2.5 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>Event</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>Femur (%)</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>

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

<table>
<thead>
<tr>
<th>Endocrine</th>
<th>Genetic</th>
<th>Lifestyle</th>
<th>Nutritional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopause</td>
<td>Family history</td>
<td>Smoking</td>
<td>Low calcium</td>
</tr>
<tr>
<td></td>
<td>Race</td>
<td>Alcohol</td>
<td>Low vitamin D</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>Sedentary lifestyle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low body weight</td>
<td>Prolonged immobilization</td>
<td></td>
</tr>
</tbody>
</table>

Audience Response Question #1

Which of the following malignancies is NOT associated with a high rate of skeletal related events?

A. Breast cancer  
B. Multiple myeloma  
C. Colorectal cancer  
D. Prostate cancer

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

- Some diseases preferentially metastasize to bone, resulting in lytic bone disease and skeletal related events (SREs) including fracture
  - Breast Cancer  
  - Prostate Cancer  
  - Lung Cancer  
  - Multiple Myeloma
Androgen Deprivation Therapy (ADT) in prostate cancer

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

- Chemotherapy Induced Bone Loss (CTIBL)
  - Hormonal Therapy
    - Aromatase Inhibitors (AI) in breast cancer
    - Androgen Deprivation Therapy (ADT) in prostate cancer
- Chemotherapy Induced Ovarian Failure (CIOF)
- Glucocorticoid exposure
- Hematopoietic Stem Cell Transplant (SCT)
- Adult Survivors of Childhood Cancers

Hormonal Therapy in Breast Cancer

- Other trials have evaluated risk for bone related events with letrozole and exemestane, and have demonstrated mixed results
  - Studies were largely underpowered to detect differences in bone events
  - Retrospective review showed that women treated with AIs were 2.5 times more likely to suffer a fracture compared to those treated with tamoxifen

Hormonal Therapy in Breast Cancer

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

- 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 (Hodgkin’s, pediatric acute lymphocytic leukemia (ALL))
    - In women who retain menstrual function after chemotherapy, natural menopause may occur at an earlier age than matched controls

Hormonal Effects of Therapy and Bone Loss

- Overall, treatments for cancer that affect hormonal status have a marked effect on bone mineral density, leading to increased risks of osteopenia, osteoporosis, and fracture
Corticosteroids

- Commonly used in a wide variety of malignancies, including ALL, lymphomas, and other malignancies
- Mechanism of bone loss may include
  - Inhibition of OPG production and stimulation of RANKL production
  - Suppression of androgen and estrogen secretion, leading to increased bone resorption

High Dose Chemotherapy / 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. BMD recovery occurs first in the lumbar spine, then in the femoral neck.
- For patients requiring longer-term therapy with steroids and calcineurin inhibitors, BMD may remain low and not return to normal

Adult Survivors of Childhood Cancers

- ALL is one of the most common pediatric malignancies, for which treatment includes
  - Prolonged glucocorticoid therapy
  - Bone-toxic chemotherapy (methotrexate, alkylating agents)
  - Radiation
  - Stem cell transplantation
- 25% of childhood ALL survivors and 42% of adult survivors of pediatric stem cell transplant are diagnosed with osteoporosis.

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

- The gold standard of bone mineral density measurement is dual-energy x-ray absorptiometry (DEXA) scanning
  - Recommended every 2 years in the general population of women
  - Recommendations vary for screening in patients with cancer
DEXA Scan Evaluation

- **T-score** – BMD compared with what is normally expected in a healthy young adult of your sex*
  
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>T score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt; -1</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>-1 to -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>&lt; -2.5</td>
</tr>
<tr>
<td>Severe Osteoporosis</td>
<td>&lt; -2.5 + osteoporotic fracture</td>
</tr>
</tbody>
</table>
  
- **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

* World Health Organization definitions; National Osteoporosis Foundation

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

Recommendations for Screening

<table>
<thead>
<tr>
<th>Group</th>
<th>Population</th>
<th>Screening</th>
<th>Treatment Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>USPSTF</td>
<td>Women over 65 years</td>
<td>DEXA every 2 yrs</td>
<td>T score &lt; -2.5</td>
</tr>
<tr>
<td>ASCO</td>
<td>High Risk Women:</td>
<td>Annual DEXA scan</td>
<td>T score &lt; -2.5</td>
</tr>
<tr>
<td></td>
<td>* age &gt;/= 65</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>* age 65-64 at high risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>* initiating AI therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>* Premenopausal women with ovarian suppression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCON</td>
<td>Women initiating AI therapy Men receiving ADT</td>
<td>DEXA every 2 yrs</td>
<td>Any of the following:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T score &lt; -2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+ FRAX 10y hip fracture probability &gt;2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+ FRAX 10y probability of major osteoporotic fracture &gt;20%</td>
</tr>
</tbody>
</table>

**Treatment Options**

- Options for treatment have grown over the past 10 years
  - Bisphosphonates
  - Denosumab
  - Selective Estrogen Receptor Modulators (SERMs)
  - Teriparatide

**Bisphosphonates**

- **Mechanism of Action**
  - Decrease bone resorption and increase bone mineralization by inhibiting osteoclast activity

**Bisphosphonates Available Agents**

- Currently available bisphosphonates

<table>
<thead>
<tr>
<th>Agent</th>
<th>Available Formulations</th>
<th>Dose/Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate (Fosamax) PO</td>
<td>Prevention: 5mg Qday/5mg Qweek Treatment: 10mg Qday/70mg Qweek</td>
<td></td>
</tr>
<tr>
<td>Risedronate (Actonel) PO</td>
<td>5mg Qday / 35mg Qweek / 110mg Qmonth</td>
<td></td>
</tr>
<tr>
<td>Ibandronate (Boniva) PO/IV</td>
<td>150mg PO Qmonth / 3mg IV Q2months</td>
<td></td>
</tr>
<tr>
<td>Pamidronate (Aredia) IV (malignancy only)</td>
<td>60-90mg IV Q3months</td>
<td></td>
</tr>
<tr>
<td>Zoledronic Acid (Zometa, Reclast) IV</td>
<td>Nonmalignant: 5mg Q2 years Malignant: 5mg Qyr; 4mg Q2-6 months</td>
<td></td>
</tr>
</tbody>
</table>

- Majority of trials in cancer patients have used IV bisphosphonates
**Bisphosphonates**

**Toxicities**

- Renal Toxicity
  - Azotemia
  - Azoturia
  - Nephrocalcinosis
  - Nephrotic syndrome
- Hypocalcemia
- Osteonecrosis of the jaw

**Denosumab**

- Monoclonal antibody directed towards RANKL

**Denosumab**

**Dosing and Toxicities**

- **Dosing**
  - 60mg SC Q6 months (Prolia®)
    - Treatment of osteoporosis in patients at risk for fracture
    - Bone loss induced by AIs or ADT
  - 120mg SC Q4 weeks (Xgeva®)
    - Treatment of metastatic disease to prevent skeletal related events
- **Toxicities**
  - Hypocalcemia
  - Infusion reactions
  - Osteonecrosis of the jaw

**Raloxifene**

- Selective estrogen receptor modulator
  - Bind to estrogen receptor, and act as either an estrogen agonist (in bone) or antagonist (in breast and uterine tissue)
  - Increased BMD
  - Decreased spine fractures
  - No impact on nonspinal fractures
- **Dose:** 60mg PO Qday
- **Toxicities**
  - Hot flashes, increased VTE and stroke risk

**Teriparatide**

- Recombinant parathyroid hormone analog
- **Dose:** 20mcg SC Qday
- Current indications include treatment of
  - Postmenopausal osteoporosis in women
  - Hypogonadal osteoporosis in men
  - Prolonged glucocorticoid induced osteoporosis
- Minimal data in cancer or chemotherapy associated bone loss

**Audience Response Question #2**

What can practitioners do to help minimize the risk of nephrotoxicity associated with zoledronic acid?

A. Avoid use in mild renal insufficiency
B. Dilute in larger renal insufficiency
C. Slow infusion rate
Risk Screening SRE's CTIBL Anticancer Agents Screening SRE's CTIBL

**Background**

- SCT associated bone loss

**Risk Factors**

- CIOF
- ADT induced bone loss
- Breast cancer
- Prostate cancer
- Multiple myeloma

**Treatment and Prevention Strategies**

**Cancer Treatment Induced Bone Loss**
- AI induced bone loss
- ADT induced bone loss
- CIOF

**Metastatic or Bone Involvement**

- Induced Bone Loss
  - Breast cancer
  - Prostate cancer
  - Multiple myeloma

**Zoledronic Acid (ZA) for AI Induced Bone Loss**

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

**Z-FAST results**
- N=602
- Upfront ZA progressively increased lumbar spine and total hip BMD
- Delayed ZA had significant decreases in LS and TH BMD
- ZA produced substantial increase in BMD regardless of baseline Tscore, 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 Ca, on AI therapy, with evidence of low bone mass (T score of -1 to -2.5)
  - Denosumab 60mg SC Q6 months x4 vs. placebo
- Primary endpoint: % change in lumbar spine BMD at 12 months

**Zoledronic Acid (ZA) for ADT Induced Bone Loss**

**Proportion of patients preserving LS BMD at 24 months**

**222 patients with MD prostate CA either:**
- Within 1 year of starting ADT
- Within 2 weeks of orchectomy

**Primary Endpoint:** % change in lumbar spine BMD

**Secondary Endpoint:** % change in total hip BMD
Zoledronic Acid (ZA) for 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

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

Zoledronic Acid (ZA) for Chemotherapy Induced Ovarian Failure

- CALGB Trial 79809

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

Stem Cell Transplant and Bone Loss: Pamidronate for Prevention

- Trial evaluated bisphosphonate use to prevent bone loss after allogeneic SCT

- Included evaluation of potential covariates, including age, aGVHD, cGVHD, average daily steroid dose, duration of cyclosporine use

Image references to support content.
### Stem Cell Transplant and Bone Loss

**Pamidronate for Prevention**

- Group 1: nothing
- Group 2: estradiol 2mg QDay/dihydroprogesterone10mg Qday14d/month
- Group 3: risedronate 35mg PO weekly
- Group 4: zoledronic acid 4mg IV Q month x3 months

### Audience Response Question #3

TP is a 57 year old Asian woman with a diagnosis of locally advanced breast cancer who is on hormonal therapy with tamoxifen, and is receiving adjuvant chemotherapy with cyclophosphamide and doxorubicin. What is the best option for TP for prevention of bone loss?

A. Calcium + vitamin D  
B. Screening DEXA scan every 2 years  
C. Alendronate 70mg PO every week  
D. Zoledronic acid 4mg IV every 6 months

### Treatment and Prevention Strategies

**Cancer Treatment Induced Bone Loss**
- AI induced bone loss  
- ADT induced bone loss  
- CIOF  
- SCT associated bone loss

**Metastatic or Bone Involvement Induced Bone Loss**
- Breast cancer  
- Prostate cancer  
- Multiple myeloma
Skeletal Related Events (SREs)

- Fracture
  - Pathologic
  - Vertebral
  - Non-vertebral
- Radiation therapy to bone
- Surgery to bone
- Spinal cord compression
- Hypercalcemia of malignancy

Preventing SRE’s – Multiple Myeloma & Breast Cancer

- Randomized, double dummy trial of zoledronic acid vs. pamidronate in multiple myeloma and breast cancer
  - In multiple myeloma, Zoledronic acid and pamidronate found to be not significantly different for occurrence of SREs in MM
  - In Breast Cancer
    - ZA reduced risk of SRE’s by 20% over 2 years compared to pamidronate
    - If administered before the onset of pain, ZA reduced SRE incidence by 41% compared to pamidronate

Preventing SRE’s – Prostate Cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Baseline</th>
<th>Denosumab 20051019*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>642 men with metastatic HRPC</td>
<td>250 men with metastatic HRPC</td>
</tr>
<tr>
<td>Treatment</td>
<td>Zoledronic acid 4mg IV Denosumab and 4mg IV Placebo</td>
<td>Denosumab 120mg SC QH vs. zoledronic acid 4mg IV QH weeks</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Proportion of patients with ≥1 SRE</td>
<td>Change from baseline self-reported pain score</td>
</tr>
<tr>
<td>Result</td>
<td>SRE’s occurred in 33.2% of ZA pts and 44.2% of placebo pts (p=0.021)</td>
<td>No difference between arms</td>
</tr>
</tbody>
</table>

Preventing SRE’s Denosumab vs. Zoledronic Acid

- 3 phase III trials have evaluated denosumab vs. zoledronic acid in patients with metastatic disease, comparing denosumab 120mg SC vs zoledronic acid 4mg IV every 4 weeks
  - N=5723 (2862 denosumab, 2861 zoledronic acid)
  - Breast cancer, prostate cancer, solid tumor, or myeloma with evidence of ≥1 bone lesion
  - Denosumab was superior to ZA in
    - reducing risk of SRE by 17% (HR 0.83, 95%CI 0.76-0.90), p=0.001
    - Reducing median time to first SRE (27.66 months for ZA vs 19.45 months for denosumab)
    - reducing risk of multiple SREs
  - Rates of adverse events were similar between groups
    - Increased rate of hypercalcemia with denosumab
    - Increased rate of renal toxicity and acute phase reactions with zoledronic acid

Bone-targeted agents as Anticancer therapy

- Data exists to support the use of bone modifying agents to prevent bone metastases in patients with
  - Multiple myeloma
  - Breast cancer
  - Prostate cancer

Bone-targeted agents as Anticancer therapy: Myeloma

- MRC IX trial
  - N=1960
  - Comparison between clofodronate 1600mg/day PO and zoledronic acid 4mg IV every 3-4 weeks with induction, then every 4 weeks
  - Zoledronic acid
    - Improved PFS by 12%
    - Decreased risk of death by 16%
    - Increased OS by 5.5 months
  - Long term follow up showed that >2 years of therapy may confer further benefit in those with bony disease at time of randomization
Background

Risk Factors: Screening

Anticancer Agents

CTIBL

Screening SRE's

Anticancer Effects

Bone-targeted agents as Anticancer therapy: Breast Cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>ABCSG-12</th>
<th>ZURUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1803</td>
<td>3360</td>
</tr>
</tbody>
</table>

Treatment arms: tamoxifen + zoledronic acid, tamoxifen alone, goserelin + zoledronic acid, goserelin alone

Primary Endpoint: Disease free survival

Results: 16% relative risk reduction in risk of disease progression

Zoledronic acid did not produce DFS benefit in interim analysis.

Other: 32 month follow-up showed persistent benefit

Preplanned subset analysis revealed significant benefit in postmenopausal women (HR 0.71, p<0.05)


Bone-targeted agents as Anticancer therapy: Breast Cancer

- Taken together, data show that zoledronic acid, when added to adjuvant therapy, may improve DFS and disease related outcome
- Question remaining: which particular subset of patients will benefit most from bone directed therapy?

Bone-targeted agents as Anticancer therapy: Prostate Cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Trial Type</th>
<th>Population</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Randomized controlled trial</td>
<td>Nonmetastatic HRPC with rising PSA</td>
<td>Zoledronic acid 4mg q4 weeks vs. placebo</td>
</tr>
</tbody>
</table>

Primary Endpoint: Time to first metastatic lesion

Results: Poor accrual, no differences seen

Denosumab prolonged metastasis free survival by 4.2 months & delayed time to metastasis


Background

Risk Factors: Screening

Anticancer Agents

CTIBL

Screening SRE's

Anticancer Effects

Cost of Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid 4mg</td>
<td>$844/dose</td>
</tr>
<tr>
<td>Denosumab 60mcg</td>
<td>$990/dose</td>
</tr>
<tr>
<td>Denosumab 120mcg</td>
<td>$1980/dose</td>
</tr>
<tr>
<td>Calcium 1200mg/Vitamin D</td>
<td>$120/month</td>
</tr>
</tbody>
</table>

Source: RedBook Online (www.redbook.com/redbook/online)

But, NEVER FORGET!

- REMEMBER, modifiable risk factors should be addressed with all patients
  - Weight bearing exercise
  - Physical activity
  - Supplemental calcium and vitamin D
In Summary

- Bone loss related to cancer and cancer therapy is an important and widespread issue
- Pharmacists should screen for cancer-associated and treatment-associated bone loss and encourage patients with cancer to adhere to recommendations for screening, prevention, and treatment of bone loss
- Proper selection of agents to treat and prevent osteoporosis, bone metastases, and skeletal related events can lead to significant improvements in patient outcomes
Role of Pharmacists in Maintaining Bone Health in Patients with Cancer

SELECTED REFERENCES


Role of Pharmacists in Maintaining Bone Health in Patients with Cancer


Wirth M, Tammela T, DeBruyne F et al. Effectiveness of zoledronic acid for the prevention of bone metastases in high-risk prostate cancer patients. A randomized, open-label, multicenter study of the European Association of Urology (EAU) in cooperation with the Scandinavian Prostate Cancer Group (SPCG) and the AUO. A report
Role of Pharmacists in Maintaining Bone Health in Patients with Cancer


SELF-ASSESSMENT QUESTIONS

1. Compared to tamoxifen, aromatase inhibitors are associated with which of the following?
   a. Similar rates of bone loss.
   b. Higher rates of bone loss.
   c. Lower rates of bone loss.
   d. No difference.

2. Results of the Z-FAST and ZO-FAST demonstrated that
   a. Early initiation of zoledronic acid was equal to delayed initiation in reducing bone loss.
   b. Delayed initiation of zoledronic acid was associated with better efficacy against bone loss with less toxicity.
   c. Early initiation of zoledronic acid was associated with better efficacy against bone loss with similar toxicity.

3. RF is a 58 year old woman with a diagnosis of locally advanced breast cancer that is ER+. She is started on adjuvant chemotherapy and anastrazole. Based on the results of the AZURE trial, what patient specific characteristic might help you decide if RF should receive a bisphosphonate?
   a. Age.
   b. Metastatic disease.
   c. Menopausal status.
   d. Type of adjuvant treatment.

4. The incidence of chemotherapy Induced Ovarian Failure depends on which of the following factors?
   a. Age.
   b. Class of chemotherapy.
   c. Cumulative exposure.
   d. All of the above.

Answers
1. b
2. c
3. c
4. d