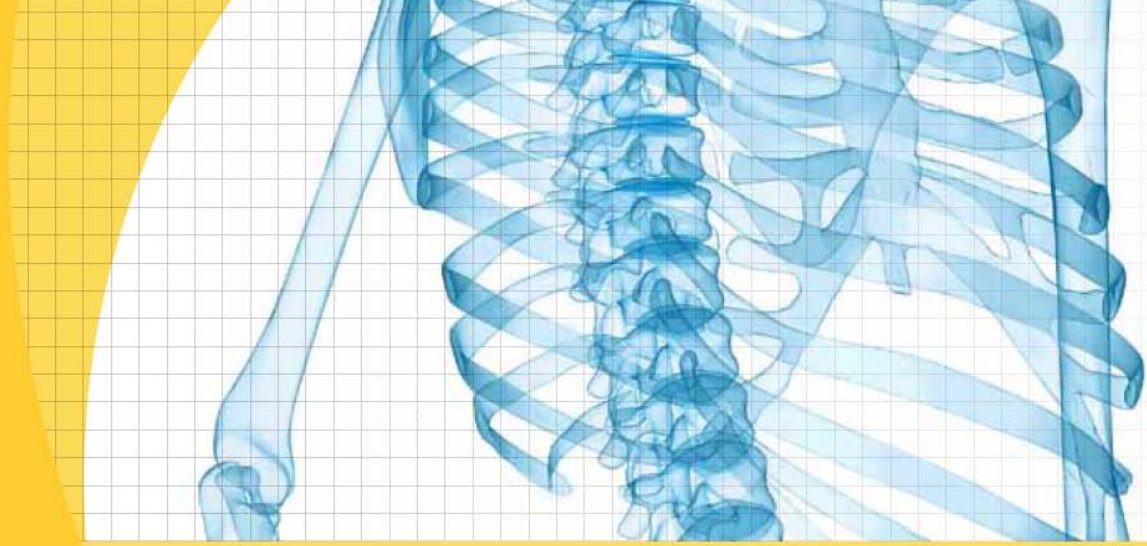

Optimizing Bone Health in Cancer Patients

A knowledge-based CPE activity presented during the
2011 ICHP/MSHP Spring Meeting

Friday, April 15, 2011
St. Charles Convention Center
St. Charles, Missouri
12:00 pm – 1:30 pm

Planned and conducted by ASHP Advantage.
Supported by an educational grant from Novartis Oncology.

ASHP ADVANTAGE

NOVARTIS ONCOLOGY

Optimizing Bone Health in Cancer Patients

ACTIVITY FACULTY

Rowena N. Schwartz, Pharm.D., BCOP
Director of Oncology Pharmacy
The Johns Hopkins Hospital
Baltimore, Maryland

Rowena N. Schwartz, Pharm.D., BCOP is Director of Oncology Pharmacy at The Johns Hopkins Hospital in Baltimore, Maryland. She also maintains an active clinical practice in the Johns Hopkins Hospital Oncology Anticoagulation Service. Dr. Schwartz practice and research interest is in drug therapy for the prevention and/or management of cancer and cancer related complications with a focused interest in geriatric oncology.

Dr. Schwartz has authored numerous chapter, journal articles and abstracts in various topics related to pharmacy practice in oncology. She is a an active member of the American Society of Health-System Pharmacists (ASHP), American College of Clinical Pharmacy (ACCP), Hematology and Oncology Pharmacy Association (HOPA), Geriatric Oncology Consortium, and the International Society of Oncology Pharmacy. She is currently the President of HOPA.

Dr. Schwartz received her Bachelor of Science in Pharmacy at the College of Pharmacy, University of Illinois at the Medical Center in Chicago and Doctor of Pharmacy at the University of Texas Health Science Center at San Antonio. She completed a two-year fellowship in oncology drug development at the University of Texas. Dr. Schwartz is a Board Certified Oncology Pharmacist (BCOP).

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DISCLOSURE STATEMENTS

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Chad M. Barnett, Pharm.D., BCOP, Initiative Co-Chair

Dr. Barnett declares that he has no relationships pertinent to this activity.

Jane Pruemer, Pharm.D., BCOP, FASHP, Initiative Co-Chair

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

Rowena N. Schwartz, Pharm.D., BCOP

Dr. Schwartz declares that she has consulted for Amgen.

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

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

This presentation may include unapproved or off label indications that are currently not approved by the FDA for labeling or advertising.

Visit http://www.optimizingbonehealth.com for e-Newsletters and updates on Bone Health.

ACTIVITY OVERVIEW

Improvements in cancer treatment have increased survival and the need for effective interventions to reduce the risk for skeletal-related events including pathologic bone fractures, spinal cord compression, need for surgery or radiation therapy to bone, and hypercalcemia of malignancy. Many cancer therapies cause bone loss, which increases the risk for fractures. Bisphosphonates are useful for treating bone metastases and slowing or preventing cancer treatment-induced bone loss (CTIBL). These drugs also may reduce the risk of recurrence and improve survival in patients with early breast cancer or other solid tumors. RANK-ligand Inhibitors have also been shown to decrease skeletal-related events in patients with bone metastases from solid tumors. Other agents for the treatment of bone metastases are under investigation. Knowledge of the role of bisphosphonates and new and emerging bone-targeted therapies in treating patients with bone metastases or CTIBL will enable pharmacists to take an active role in the management of these patients.

LEARNING OBJECTIVES

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

- Describe the prevalence, morbidity, mortality, and impact on quality of life of skeletal-related events in patients with cancer.
- Explain normal bone remodeling and the pathogenesis of skeletal-related events in patients with cancer.
- Discuss the mechanism of action, efficacy, and safety of agents used for treating bone metastases and slowing or preventing cancer treatment-induced bone loss (CTIBL).
- Recommend a pharmacologic regimen for a patient with bone metastases or CTIBL.
- Identify new or emerging bone-targeted therapies for patients with bone metastases and describe mechanisms of action and potential roles in improving bone health in 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 hour (0.1 CEU) of continuing pharmacy education credit (ACPE activity # 204-000-11-409-L01P).

Attendees must complete a Continuing Pharmacy Education Request online and may print their official ASHP statements of continuing pharmacy education credit at the ASHP Learning Center (http://ce.ashp.org) immediately following this activity.

Complete instructions for receiving your CPE statement of credit online are on the next page.
Be sure to record the five-digit session code announced during this activity.

Optimizing Bone Health in Cancer Patients

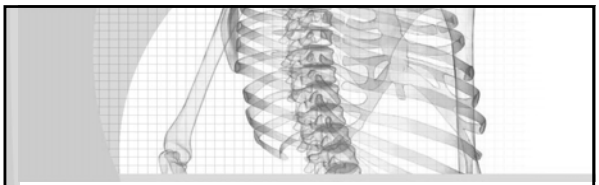
Instructions for Processing Continuing Education (CE)

To obtain CE statements for live symposia, webinars, or webcasts, please visit the ASHP Learning Center at **http://ce.ashp.org**.

1. Select **Process Meeting CE** from bottom left. Log in to the ASHP Learning Center using your e-mail address and password.
2. **If you have not logged in to the new ASHP Learning Center (launched August 2008) and are not a member of ASHP,** you will need to create a free account by clicking on **Register** at the bottom of the **Register as a New User** panel.
3. Once logged in to the site, click on **Process Meeting CE.**
4. If this activity title does not appear in your meeting list, enter the 5-digit activity code in the box above the list and click submit. The **Activity and Session Codes** are announced at the end of the activity. Click **Submit** when prompted and then click on the **Start** link to the right of the activity title.
5. Enter the session code, which starts with the letter "A" and was announced during the activity, and select the number of hours equal to your participation in the activity. Participants should only claim credit for the amount of time they participate in an activity.
6. Click **Submit** to receive the attestation page.
7. Confirm your participation and click **Submit**.
8. Print and/or save your CE statement as appropriate.
9. Complete activity evaluation by selecting the **My Account** tab and continue to **My Transcript.**
10. Select the applicable year from the drop down menu and locate the activity.
11. Click **Complete Evaluation** under the **Status** column to be taken to the evaluation page.
12. Complete **all** evaluation questions and click **Finish.**

Date of Activity	Activity Code	Session Code (announced during the live activity)	CE credit hours
Friday April 15, 2011	11578		1.0

NEED HELP? Contact ASHP Advantage at **support@ashpadvantage.com**.



Optimizing Bone Health in Cancer Patients

Rowena N. Schwartz, Pharm.D., BCOP
Director of Oncology Pharmacy
The Johns Hopkins Hospital
Baltimore, Maryland

Planned and conducted by ASHP Advantage.
Supported by an educational grant from Novartis Oncology.

NOVARTIS ONCOLOGY

Disclosures for Faculty and Planners

- Chad Barnett, Pharm.D., BCOP, Initiative Co-chair
  – No pertinent relationships to report
- Jane Pruemer, Pharm.D., BCOP, FASHP, Initiative Co-chair
  – No pertinent relationships to report
- Rowena N. Schwartz, Pharm.D., BCOP
  – Reports she has a consulted for Amgen
- Erika Thomas, M.B.A., B.S.Pharm.
  – No pertinent relationships to report

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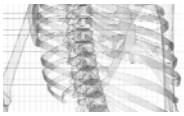
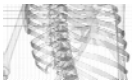
- Recommend a pharmacologic regimen for a patient with bone metastases or CTIBL.
- Identify new or emerging bone-targeted therapies for patients with bone metastases and describe mechanisms of action and potential roles in improving bone health in cancer patients.

Bone Health in Cancer Patients

- Background
- *Cancer Treatment-Induced Bone Loss*
- *Bone metastases*
- *Adjuvant bisphosphonates*
- *New and emerging bone-targeted therapies*



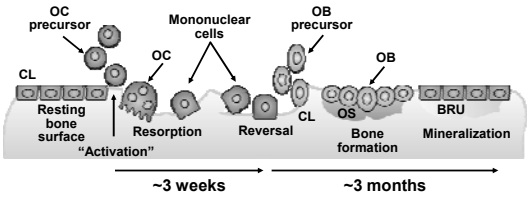
Bone Disease



- Osteoporosis
  - Postmenopausal
  - Aging
  - Hypogonadal states
  - Drug-induced
- Cancer-related bone loss
- Cancer therapy–related bone loss
- Bone metastases
  - Estimated 350,000 deaths per year from bone metastases

Mundy GR. Nature Rev 2002;2:584-93.

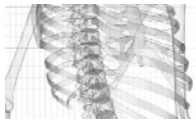
Bone Remodeling in Healthy Individuals



Deal C. Nat Clin Pract Rheumatol. 2009;5:20. Nature clinical practice rheumatology by NATURE PUBLISHING GROUP. Reproduced with permission of NATURE PUBLISHING GROUP in the format Journal via Copyright Clearance Center.

Bone Health in Cancer Patients

- *Background*
- Cancer Treatment-Induced Bone Loss
- *Bone metastases*
- *Adjuvant bisphosphonates*
- *New and emerging bone-targeted therapies*



Patient case #1 - JK

- 64 y.o. postmenopausal white female
- Newly diagnosed right breast cancer
  - T = 0.5 x 0.4 cm; N0 (US), ER/PR+, HER2 negative by IHC
- Underwent segmental mastectomy and sentinel LN biopsy
- Completed radiation and started anastrozole 1 mg PO daily
- Baseline BMD by DEXA scan:

Region	BMD (g/cm2)	T-score	Classification
AP spine	0.830	-2.0	Osteopenic
Femoral neck (left)	0.631	-2.0	Osteopenic
Total hip (left)	0.775	-1.4	Osteopenic
Femoral neck (right)	0.673	-1.6	Osteopenic
Total hip (right)	0.819	-0.6	Normal

BMD, bone mineral density; DEXA, duel –energy x-ray absorptiometry.

Question #1

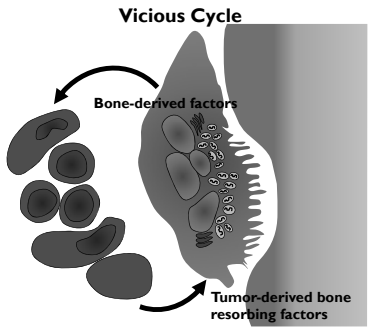
- Which of the following medications is most appropriate for prevention of aromatase inhibitor (AI)-induced bone loss in our patient?
  1. Teriparatide
  2. Raloxifene
  3. Alendronate
  4. Conjugated estrogen

Cancer Treatment–Induced Bone Loss

- Rapid and severe bone loss resulting from cancer therapies that lead to estrogen or androgen deprivation
- Various cancer therapies decrease BMD and increase fracture risk
  - Androgen-deprivation therapy (ADT)
  - Estrogen-deprivation therapy
  - Chemotherapy
  - Surgical (castration)
- CTIBL has significant clinical, social, and economic consequences; treatment-related fractures are associated with decreased quality of life and shorter survival

Coleman RE. *Cancer* 1997;80(8Suppl):1588.
Coleman RE and McCloskey EV. *Bone*. 2011 Feb 18. [Epub ahead of print].

The Vicious Cycle in the Bone Microenvironment



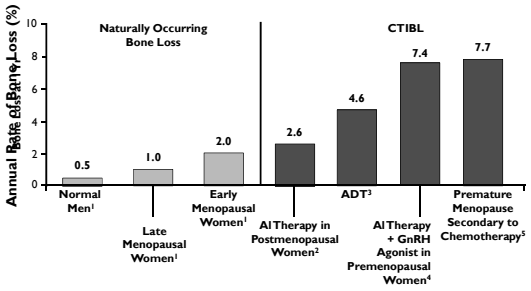
Diagnostic Categories of Bone Mineral Density (T-score)

Diagnostic Category	WHO Criterion-BMD or BMC
Normal	<1.0 SD*
Osteopenia	>1.0 but < 2.5 SD*
Osteoporosis	≥ 2.5 SD*
Severe osteoporosis	≥ 2.5 SD* + ≥ 1 fragility fracture(s)

BMD, bone mineral density; BMC, bone mineral content; SD, standard deviation.
* Compared to reference mean for young adults

Khosla S, Melton LJ 3rd. *N Engl J Med*. 2007; 356(22):2293-300.

Bone Loss With Cancer Therapies



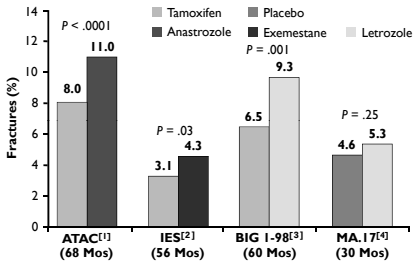
1. Kanis JA. Osteoporosis. 1997:22-55. 2. Eastell R, et al. J Bone Mineral Res. 2002. 3. Maillefert JF, et al. J Urol. 1999;161:1219-1222. 4. Gnant M, et al. Lancet Oncol. 2008;9:840-849. 5. Shapiro CL, et al. J Clin Oncol. 2001;19:3306-3311.

Endocrine Therapies Associated with Bone Loss

- LHRH agonists
  - Goserelin
  - Leuprolide
  - Triptorelin
  - Histrelin
  - Nafarelin
- LHRH antagonists
  - Degarelix
- Aromatase inhibitors
  - Anastrozole
  - Letrozole
  - Exemestane

LHRH = luteinizing hormone-releasing hormone

Aromatase Inhibitors (AI) Increase Fracture Risk Compared With Tamoxifen



1. Buzdar A, et al. Lancet Oncol. 2006;7(8):633-43. 2. Coombes RC, et al. Lancet. 2007; 369(9561):559-70. 3. Rabaglio M, et al. Ann Oncol. 2009; 20(9):1489-98. 4. Goss PE, et al. J Natl Cancer Inst. 2005; 97:1262-1271.

FDA-Approved Agents for Prevention or Treatment of Osteoporosis

Drug	Dose
Alendronate	10 mg/day or 70 mg/week po
Risedronate	5 mg/day or 35 mg/week po
Ibandronate	2.5 mg/day or 150 mg/month po or 3 mg IV every 3 months
Zoledronic acid	5 mg IV every 12 months
Raloxifene	60 mg/day po
Estrogen	Variable doses and routes
Calcitonin	200 international units/day IV
Denosumab	60 mg SQ every 6 months
Teriparatide	20 mcg/day subcutaneously

Khosla S. *N Eng J Med.* 2009; 361:818.

Important Distinctions Between Osteoporosis and SRE Dosing

Medication	Osteoporosis	Prevention of SREs
Zoledronic acid	Reclast® 5 mg IV every 12 months	Zometa® 4 mg IV every 3-4 weeks
Denosumab	Prolia™ 60 mg SC every 6 months	Xgeva™ 120 mg SC every 4 weeks

IV = intravenous, SC = subcutaneous

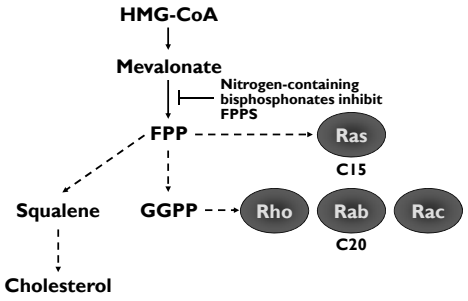
Prolia™ product information. Amgen, Inc, Thousand Oaks, CA;2010;
Reclast® product information. Novartis Pharmaceuticals, East Hanover, NJ; March 2011;
Xgeva™ product information. Amgen, Inc, Thousand Oaks, CA; November 2010;
Zometa® product information. Novartis Pharmaceuticals, East Hanover, NJ; February 2011.

Bisphosphonate: Mechanism of Action

- Diminish bone resorption and subsequently normalize calcium levels
  - Inhibits osteoclastic activity and induces osteoclast apoptosis
  - Prevents development of new osteolytic lesions
  - The newer agents act by inhibiting specific enzymes in the mevalonate pathway of cholesterol biosynthesis in osteoclasts, which in turn leads to impaired prenylation of small GTP-binding proteins

Deal C. *Nat Clin Pract Rheumatol.* 2009; 5:20.

Mechanism of Action of Bisphosphonates



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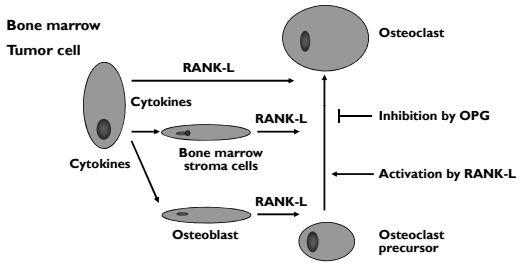
Bisphosphonate Toxicities

- Common
  - Nausea
  - Fatigue
  - Anemia
  - Bone pain
  - Constipation
  - Fever
  - Vomiting
  - Dyspnea
- Less common, but serious
  - Renal toxcity
  - Osteonecrosis of the jaw
- Rare
  - Femoral stress fractures

www.us.zometa.com/health-care-professional/someta-prescribint-information.jsp?site=PC000898Birmasrc=ZOMWB0147&source=01030. Accessed February 20, 2011 Banffy MG, et al. Clin Orthop Relat Res. 2011 Feb 25. [Epub ahead of print].

RANK/RANK-L/Osteoprotegerin Pathway



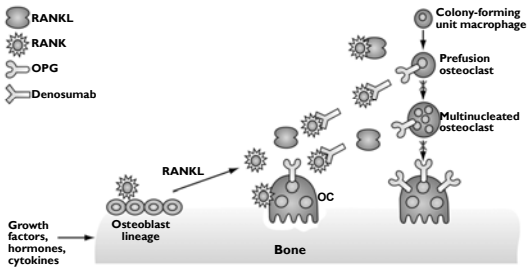
Adapted from Bartsch R, Steger GG. *Expert Opin Biol Ther.* 2009; 9:1225.

Denosumab

- First monoclonal antibody to RANKL
- Fully human monoclonal immunoglobulin G (IgG2) antibody
- 60 mg subcutaneously every 6 months, with calcium and Vitamin D
- Rapid onset of inhibition of bone turnover

Miller PD. *Best Pract Res Clin Endocrin Metab.* 2008; 22:849.
Burkiewicz JS et al. *Ann Pharmacother.* 2009; 43:1445.

Mechanism of Action of Denosumab



Deal C. Nat Clin Pract Rheumatol. 2009;5:20. Nature clinical practice rheumatology by NATURE PUBLISHING GROUP. Reproduced with permission of NATURE PUBLISHING GROUP in the format Journal via Copyright Clearance Center.

Denosumab: Adverse Events

- Common
  - Arthralgias
  - Back pain
  - Bone pain
  - Dermatitis, rash
  - Fatigue
  - Headache
  - Nasopharyngitis
- Less Common, but serious
  - Skin infections
  - Hypocalcemia
  - Hypophosphatemia
  - Hyperphosphatemia
  - Osteonecrosis of the jaw

Burkiewicz JS et al. *Ann Pharmacother.* 2008; 43:1445.

Estrogens

- Antiresorptive agents that inhibit bone resorption, increase bone mineral density, and reduce the risk for both vertebral and hip fractures
- Works through the RANK pathway
- The best prospective fracture data come from the Women's Health Initiative (WHI) study
  - Reduces the risk of fractures by 24%
- Safety issues
  - Increased risk of breast cancer, stroke, or DVT/VTEs

Cauley JA, et al. *JAMA* 2003; 290:1729-38.

Selective Estrogen Receptor Modulators (SERMs): Raloxifene

- Share agonist and antagonistic mechanisms of action with the estrogen receptor
- Agonistic to the bone; antagonistic to the ER on breast and uterine tissue
- MORE trial demonstrated that 60 mg/day of oral raloxifene reduced the incidence of vertebral fractures in women
- Potential negative effect when combined with endocrine therapy for breast cancer
- Concerns for VTE

Ettinger B et al. *JAMA.* 1999; 282:637.

Calcitonin

- A peptide derived from the parafollicular cells of the thyroid (salmon or human synthetic)
- An inhibitor of osteoclast activity
- 100 international units/day injectable or 200 international units/day nasal spray
- Nausea with the injectable formula
- Rhinitis with nasal spray
- Allergic reactions with salmon derivative
- ASCO Guideline on Bone Health Issues in Women with Breast Cancer indicates no issues with calcitonin, but not highly recommended

Hillner BE, et al. *J Clin Oncol* 2003; 21:4042-57.

Teriparatide

- Recombinant human parathyroid hormone
- FDA-approved for use in men and postmenopausal women with osteoporosis who are at high risk for fractures
- Directly stimulates bone formation by increasing the production of bone matrix by osteoblasts and reversing microarchitectural deterioration
- ASCO guidelines do not recommend it for use in women with breast cancer due to increased risk of osteosarcomas in animals

Thomas T. *Joint Bone Spine.* 2006; 73:262.
Hillner BE, et al. *J Clin Oncol* 2003; 21:4042.

Question #1

- Which of the following medications is most appropriate for prevention of AI-induced bone loss in our patient?
  1. Teriparatide
  2. Raloxifene
  3. Alendronate
  4. Conjugated estrogen

Oral Bisphosphonates for Prevention of AI-Associated Bone Loss in Breast Cancer Patients with an Intermediate Risk of Fracture

Bisphos	% change in spine BMD		P-value	% change in hip BMD		P-value
	Bisphos	No bisphos		Bisphos	No bisphos	
Risedronate 35 mg[1]	+5.7	-1.5	0.006	+1.6	-3.9	0.037
Risedronate 35 mg[2]	+2.2	-1.8	<0.0001	+1.8	-1.1	<0.0001
Ibandronate 150 mg[3]	+2.98	-3.22	<0.01	+0.6	-3.90	<0.01

[1]Markopoulos C, et al. *Breast Cancer Res.* 2010; 12(2):R24. Epub 2010 Apr 16.
[2]Van Poznak C, et al. *J Clin Oncol.* 2010; 28(6):967-75.
[3]Lester JE, et al. *Clin Cancer Res.* 2008; 14(19):6336-42.

Oral Bisphosphonates for Prevention of ADT-Associated Bone Loss in Prostate Cancer Patients

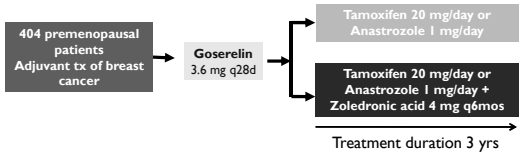
Bisphos	% change in spine BMD		P-value	% change in hip BMD		P-value
	Bisphos	No bisphos		Bisphos	No bisphos	
Alendronate 70 mg wkly[1]	+3.7	-1.4	<0.001	+0.7	-0.7	0.002

Greenspan SL, et al. *Ann Intern Med*. 2007; 146(6):416-24.

Zoledronic Acid for Prevention of AI-Associated Bone Loss in Breast Cancer Patients

- Premenopausal
  - ABCSG-12 bone substudy (n = 404)
- Postmenopausal
  - Z-FAST (N = 602)
  - ZO-FAST (N = 1065)
  - E-ZO-FAST (N = 527)

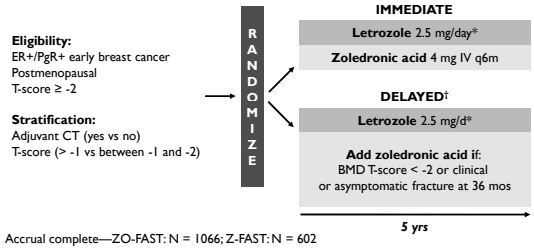
ABCSG-12 Bone Sub-study



Time	% change in spine BMD		P-value	% change in hip BMD		P-value
	ZOL	No ZOL		ZOL	No ZOL	
12 mo	+1.5	-7.4	<0.0001	+0.8	-4.1	0.010
36 mo	+0.4	-11.3	<0.0001	+0.8	-7.3	<0.0001
60 mo	+4.0	-6.3	0.001	+3.9	-4.1	0.058

Gnant M, et al. *Lancet Oncol*. 2008;9(9):840-9.

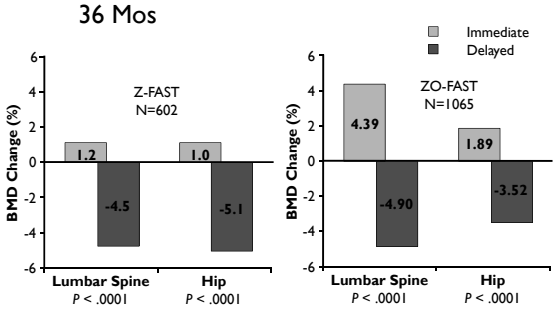
Z/ZO-FAST Trial Design



Accrual complete—ZO-FAST: N = 1066; Z-FAST: N = 602

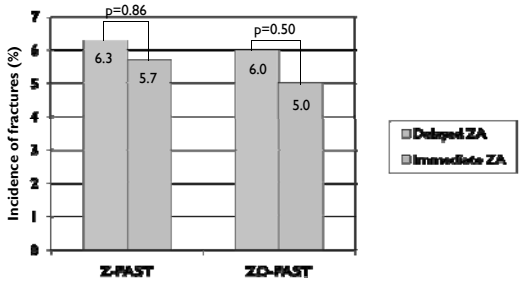
Brufsky AM, et al. *Clin Breast Cancer*. 2009;9(2):77-85.
Eidtmann H, et al. *Ann Oncol*. 2010;21(11):2188-94.

Immediate vs Delayed ZA
Mean % Change in BMD From Baseline to 36 Mos



Brufsky AM, et al. *Clin Breast Cancer*. 2009;9(2):77-85.
Eidtmann H, et al. *Ann Oncol*. 2010;21(11):2188-94.

Immediate vs Delayed ZA
Incidence of Fractures



Brufsky AM, et al. *Clin Breast Cancer*. 2009; 9(2):77-85.
Eidtmann H, et al. *Ann Oncol*. 2010; 21(11):2188-94.

IV Bisphosphonates for Prevention of ADT-Associated Bone Loss in Prostate Cancer Patients

Bisphos	% change in spine BMD		P-value	% change in hip BMD		P-value
	Bisphos	No bisphos		Bisphos	No bisphos	
Pamidronate[1]	+0.5	-3.3	<0.001	+0.2	-1.8	0.005
Zoledronic acid[2]	+5.6	-2.2	<0.001	+1.1	-2.8	<0.001
Zoledronic acid[3]	+4.0	-3.1	<0.001	+0.7	-1.9	0.004
Zoledronic acid[4]	+3.3	-1.5	<0.01	+0.9	-2.0	<0.01

[1]Smith MR, et al. *N Engl J Med*. 2001; 345(13):948-55.
[2]Smith MR, et al. *J Urol*. 2003; 169(6):2008-12.
[3]Michaelson MD, et al. *J Clin Oncol*. 2007; 25(9):1038-42.
[4]Casey R, et al. *Can J Urol*. 2010; 17(3):5170-7.

Denosumab in patients with CTIBL

	Denosumab	Placebo	P-value
Breast cancer patients receiving an AI (n=252)			
% change in LS BMD	+4.8%	-0.7%	<0.0001
Prostate cancer patients receiving ADT (n=1468)			
% change in LS BMD	+5.6%	-1.0%	<0.001

- No difference in fracture incidence in breast cancer study
- Decrease incidence of new vertebral fractures at 36 mo with denosumab vs placebo group (1.5% vs 3.9%, p=0.006) in prostate cancer study

Ellis GK, et al. *J Clin Oncol*. 2008; 26(30):4875-82.
Smith MR, et al. *N Engl J Med*. 2009: 20; 361(8):745-55.

Patient case #1 - JK

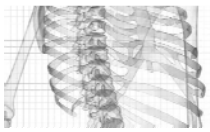
- 64 y.o. postmenopausal white female with newly diagnosed right breast cancer
- Underwent surgery, radiation and started anastrozole
- Baseline BMD by DEXA scan:
  - Osteopenia in spine, left and right femoral neck, left total hip
  - Normal right total hip
- Promote lifestyle changes
- Recommend calcium and vitamin D
  - Assessment of vitamin D levels may be reasonable
- Consider starting an oral bisphosphonate
  - Alendronate, risedronate, or ibandronate
- Monitor BMD by DEXA scan yearly

CTIBL Summary

- Cancer patients may be at increased risk for bone loss and fracture due to specific cancer treatments
- Patients at risk for CTIBL should be assessed for bone loss risk
- Bisphosphonates are the preferred agents for prevention and treatment of CTIBL
- Some data with denosumab for CTIBL
  - May be an option in patients refractory to bisphosphonates?

Bone Health in Cancer Patients

- *Background*
- *Cancer Treatment-Induced Bone Loss*
- Bone metastases
- *Adjuvant bisphosphonates*
- *New and emerging bone-targeted therapies*



Patient case #2

- RR is a 75 year old Caucasian man with newly recurrent prostate cancer which is metastatic to the bones
- Current PSA is 143 and bone scan shows involvement of both femurs and lumbosacral vertebrae
- RR had originally been treated 3 years ago with external beam radiation and brachytherapy with radiation seed implants
- He is now receiving leuprolide 3-month injections

Question #2

- In our patient, which of the following medications would be appropriate for reduction of skeletal-related events (SRE)?
  1. Zoledronic acid or pamidronate
  2. Denosumab and pamidronate
  3. Pamidronate
  4. Zoledronic acid or denosumab

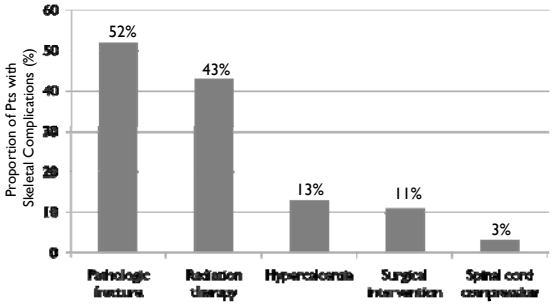
Skeletal-Related Events (SRE) Associated with Bone Metastases

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

SREs

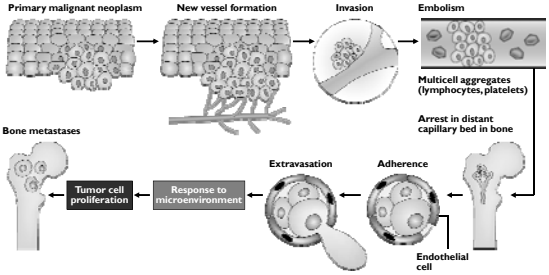
Van Poznak CH, et al. J Clin Oncol. 2011 Feb 22. [Epub ahead of print]

Prevalence of SREs in Patients with Metastatic Breast Cancer



Lipton A, et al. Cancer. 2000; 88(5):1082-90

Development of Bone Metastases



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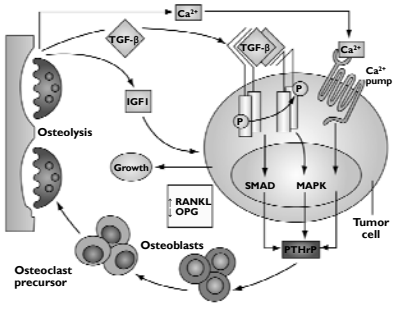
Osteolytic Bone Metastases



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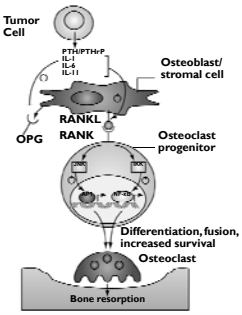
RANK-RANKL System in Osteolytic Bone Metastases



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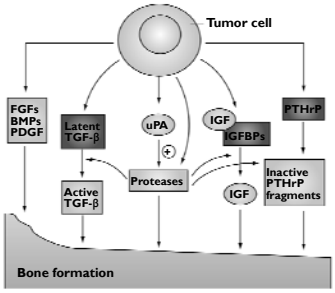
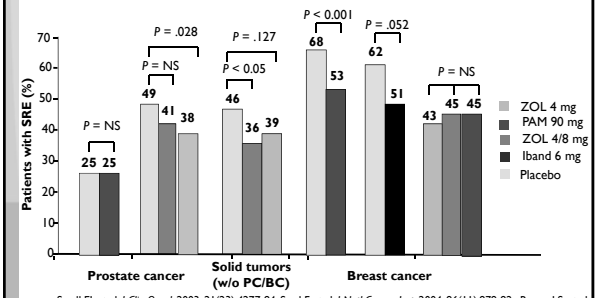
Osteoblastic Bone Metastases



IV Bisphosphonates in Solid Tumors-Selected RCT



Small EJ, et al. *J Clin Oncol.* 2003; 21(23):4277-84. Saad F, et al. *J Natl Cancer Inst.* 2004; 96(11):879-82. Rosen LS, et al. *Cancer.* 2004; 100(12):2613-21. Lipton A, et al. *Cancer.* 2000;88(5):1082-90. Body JJ, et al. *Ann Oncol.* 2003; 14(9): 1399-405. Rosen LS, et al. *Cancer.* 2004; 100(1):36-43.

Denosumab vs Zoledronate in Patients with Bone Metastases

	Denosumab	Zoledronic acid	HR (95% CI)	P-value (noninferiority)
Breast cancer (n=2046)				
Median time to first SRE	Not reached	26.4 mo	0.82 (0.71-0.95)	<0.001[1]
Solid tumors (other than breast and prostate) and multiple myeloma (n=1776)				
Median time to first SRE	20.5 mo	16.3 mo	0.84 (0.71- 0.98)	<0.001[2]
Castrate-resistant prostate cancer (n=1901)				
Median time to first SRE	20.7 mo	17.1 mo	0.82 (0.71- 0.95)	<0.001[3]

[1]p=0.01 (superiority), [2]p=0.06 (superiority), [3]p=0.008 (superiority)

Xgeva™ product information. Amgen, Inc, Thousand Oaks, CA; November 2010.

Reduction of SREs in Solid Tumors: Remaining Questions

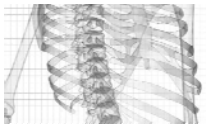
- Optimal length of treatment?
  - Little data available beyond 2 years of tx
- Optimal dosing interval of bisphosphonates?
  - Monthly vs every 3 months
  - Trials ongoing – OPTIMIZE 2, CALGB 70604
- Bisphosphonates or denosumab?
  - Concerns regarding long-term toxicities with denosumab?
  - Cost/economics

Question #2

- In our patient, which of the following medications would be appropriate for reduction of SREs?
  1. Zoledronic acid or pamidronate
  2. Denosumab and pamidronate
  3. Pamidronate
  4. Zoledronic acid or denosumab

Bone Health in Cancer Patients

- *Background*
- *Cancer Treatment-Induced Bone Loss*
- *Bone metastases*
- Adjuvant bisphosphonates
- *New and emerging bone-targeted therapies*



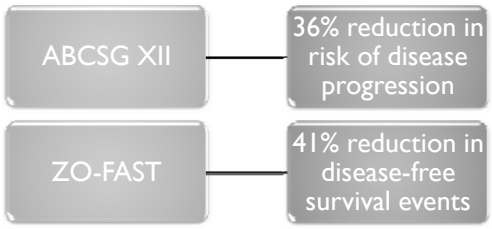
Patient case #3 - JK

- 64 y.o. postmenopausal white female with newly diagnosed right breast cancer
- Currently taking calcium/vitamin D, alendronate, and anastrozole
- Patient calls clinic to inquire about anti-cancer effects of bisphosphonates

Question #3

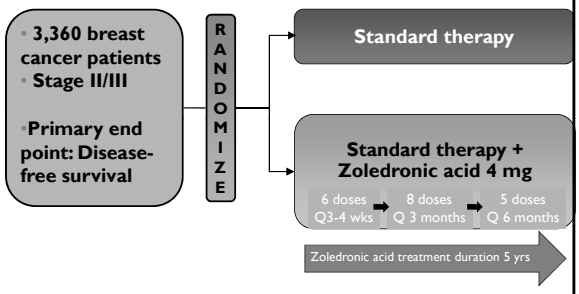
- Based on the results from the AZURE trial, your response is:
  - Adjuvant bisphosphonates resulted in worse disease-free survival
  - Adjuvant bisphosphonates improved disease-free survival
  - Risk of ONJ was increased with adjuvant bisphosphonates
  - Adjuvant bisphosphonates increase the risk of neutropenia compared to placebo

Adjuvant Zoledronic Acid



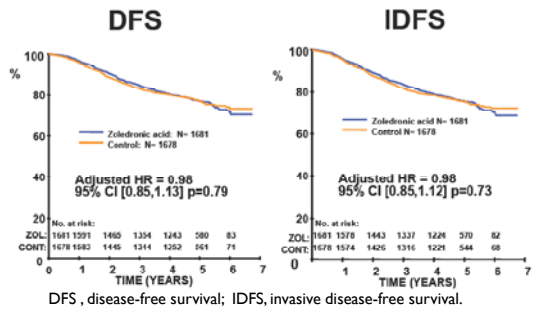
Gnant M, et al. *N Engl J Med*. 2009; 360(7):679-91.
Eidtmann H, et al. *Ann Oncol*. 2010; 21(11):2188-94.

AZURE Study Design



Coleman RE, et al. SABCS 2010; S4-5.

Standard Therapy +/- Zoledronate



DFS , disease-free survival; IDFS, invasive disease-free survival.

Coleman RE, et al. SABCS 2010;S4-5.

Standard Therapy +/- Zoledronate Toxicity

	Control Group	Zoledronic Acid Group
Adverse Event	Number (%)	Number (%)
Neutropenic sepsis	159 (9.5)	159 (9.5)
Neutropenia	49 (2.9)	41 (2.5)
Pyrexia	24 (1.4)	37 (2.2)
Vomiting	23 (1.4)	35 (2.1)
Lower Respiratory Infection	33 (2.0)	24 (1.4)
Central line infection	21 (1.3)	24 (1.4)
Cellulitis	21 (1.3)	21 (1.3)
Pulmonary embolus	13 (0.8)	25 (1.5)
Confirmed ONJ	0	17*
Possible ONJ	0	9

*p<0.0001

Coleman RE, et al. SABCS 2010;S4-5.

Adjuvant Bisphosphonates Conclusions

- Antitumor results preliminary at this time
  - No difference in DFS or OS in AZURE study
  - Awaiting further results of these and other trials
    - NSABP B34
    - SWOG 0307
  - Adjuvant denosumab?
- Must consider adverse events from agents
  - Osteonecrosis of the jaw
  - Acute inflammatory response
  - Musculoskeletal pain

Question #3

- Based on the results from the AZURE trial, your response is:
  1. Adjuvant bisphosphonates resulted in worse disease-free survival
  2. Adjuvant bisphosphonates improved disease-free survival
  3. Risk of ONJ was increased with adjuvant bisphosphonates
  4. Adjuvant bisphosphonates increase the risk of neutropenia compared to placebo

Bone Health in Cancer Patients

- *Background*
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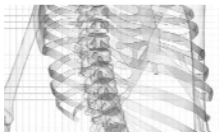
- *Bone metastases*
- *Adjuvant bisphosphonates*
- New and emerging bone-targeted therapies



Cathepsin K Inhibitors

- Cathepsin K is a key enzyme responsible for osteoclastic bone resorption
- Expressed in tumors that commonly metastasize to bone (breast, prostate)
- Odanacatib
  - Phase II trial in women with MBC showed suppression of markers of bone resorption after 4 weeks of treatment
  - Few ongoing trials in patients with cancer to bone

Santini D, et al. *Cancer Treat Rev*. 2010; 36 Suppl 3:S6-S10; http://www.clinicaltrials.gov. Accessed 3/1/11.

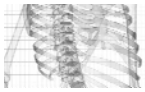
C-Src inhibitors

- Ubiquitously expressed nonreceptor tyrosine kinase
- Involved in signaling cascades important for receptor-mediated osteoclast formation and function
- Preclinical data show Src promotes bone metastases
- Currently being evaluated in clinical trials for patients with metastatic bone disease from solid tumors
  - Dasatinib

Santini D, et al. *Cancer Treat Rev*. 2010;36 Suppl 3:S6-S10; http://www.clinicaltrials.gov. Accessed 3/1/11.

Conclusions

- Bone loss is a significant problem for patients with CTIBL or metastatic cancer to bone
- Bisphosphonates and more recently RANKL inhibitors:
  - Prevent bone loss in pts with CTIBL
  - Reduce SREs in pts with metastatic cancer to bone
- Adjuvant bisphosphonate use is still preliminary in patients with early stage breast cancer
- Ongoing clinical trials with novel agents for patients with metastatic breast and prostate cancers



Questions?

Thank You!

Process your CPE statement online through the ASHP Learning Center.

The Session Code for this activity is A11___.

Refer to your handout for complete instructions.

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45. Xgeva™ product information. Amgen, Inc, Thousand Oaks, CA; November 2010.

SELF–ASSESSMENT QUESTIONS

1. Which of the following cancer therapies has been shown to decrease bone mineral density and increase fracture risk?
    a. Radiation for primary brain tumors
    b. Thalidomide for multiple myeloma
    c. Androgen-deprivation therapy for prostate cancer
    d. Erlotinib for non-small cell lung cancer

2. The process of activation of osteoclasts and resorption of bone in healthy individuals takes about:
    a. 3 days
    b. 3 weeks
    c. 3 months
    d. 3 years

3. The definition of osteoporosis includes having a T-score via bone mineral density of:
    a. Greater than 1.0
    b. Less than or equal to -1.0 to -2.5
    c. Less than or equal to -2.5
    d. Greater than or equal to 2.5

4. Aromatase inhibitors increase fracture risk compared with tamoxifen.
    a. True
    b. False

5. Which of the following drugs is considered to be an anabolic agent to treat osteoporosis?
    a. Zoledronic acid
    b. Raloxifene
    c. Denosumab
    d. Teriparatide

6. Which of the following agents is a RANK-ligand inhibitor as its mechanism of action in the treatment of bone disease?
    a. Pamidtronate
    b. Tamoxifen
    c. Denosumab
    d. Calcitonin

Answers:

1. c
2. b
3. c
4. a
5. d
6. c

Optimizing Bone Health in Cancer Patients

Activity Evaluation Form

April 15, 2011 **Rowena N. Schwartz, Pharm.D., BCOP** *St. Charles, MO*

ASHP Advantage appreciates your participation in this educational activity and values your feedback. Please complete this brief evaluation form to assist us in improving the quality of future educational activities.

1 = strongly disagree 2 = disagree 3 = neither agree nor disagree 4 = agree 5 = strongly agree

Evaluation of Educational Objectives

After attending this knowledge-based CPE activity, I am able to	Strongly Disagree				Strongly Agree
1. Describe the prevalence, morbidity, mortality, and impact on quality of life of skeletal-related events in patients with cancer.	1	2	3	4	5
2. Explain normal bone remodeling and the pathogenesis of skeletal-related events in patients with cancer.	1	2	3	4	5
3. Discuss the mechanism of action, efficacy, and safety of agents used for treating bone metastases and slowing or preventing cancer treatment-induced bone loss (CTIBL).	1	2	3	4	5
4. Recommend a pharmacologic regimen for a patient with bone metastases or CTIBL.	1	2	3	4	5
5. Identify new or emerging bone-targeted therapies for patients with bone metastases and describe mechanisms of action and potential roles in improving bone health in cancer patients.	1	2	3	4	5

Evaluation Content

	Strongly Disagree				Strongly Agree
1. The content presented was relevant to the target audience……..	1	2	3	4	5
2. I will be able to apply the knowledge skills I learned ……..	1	2	3	4	5
3. The activity fulfilled my education needs ……..	1	2	3	4	5
4. The activity enhanced my ability to apply learning objectives to my practice …….	1	2	3	4	5

5. Based on my previous knowledge and experience, the content level of the activity for attending audience was:
☐ Too basic ☐ Appropriate ☐ Too Complex

Faculty/Instructional Materials

	Strongly Disagree				Strongly Agree
6. The teaching methods were effective……	1	2	3	4	5
7. The instructional materials were effective ……	1	2	3	4	5

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Optimizing Bone Health in Cancer Patients

Faculty/Instructional Materials *(continued)*

8. Please indicate the extent to which you agree or disagree with the following statement: "Faculty statements and therapeutic recommendations in this activity were based on supported evidence or professional opinion and did **NOT** evidence commercial bias."

   ☐ Strongly Disagree ☐ Disagree ☐ Agree ☐ Strongly Agree

9. If you answered **strongly disagree or disagree** to question 8, what commercial bias did you perceive in this activity?
   _____

10. What did you find to be the most helpful aspect of this activity?
    _____
    _____

11. What was the least helpful aspect of this activity?
    _____
    _____

12. List ONE (and no more than three) changes that you intend to make in your practice as a result of this activity.
    _____
    _____

13. How confident are you that you will be able to apply these changes in your practice?
    a. Very confident
    b. Somewhat confident
    c. Not confident

14. Please indicate any barriers you perceive to implementing these changes.
    a. Cost
    b. Lack of experience
    c. Lack of resources
    d. Lack of administrative support
    e. Other, please specify:_____
       _____

15. What question(s) do you still have about this topic?
    _____

16. Based on your educational needs, list any topics you would like to see addressed in future educational activities.
    _____

17. Other comments or suggested improvements:
    _____
    _____

18. Using the following scale, in the table below rate presentation skills, content knowledge, degree of balance, objectivity, and scientific rigor of faculty:

1 = very poor 2 = poor 3 = average 4 = above average 5 = excellent

	Presentation Skills	Knowledge of Content	Degree of Balance, Objectivity, & Scientific Rigor
Rowena N. Schwartz, Pharm.D., BCOP	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5