Bone Health Management in Cancer Patients

A Presentation for HealthTrust Members

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Speaker Disclosures

Neither the presenter nor her preceptor have conflicts of interests related to this presentation.

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Educational Objectives

1. Recall the etiology and pathophysiology of bone health complications in oncology patients
2. Identify patients and cancer therapy related risk factors, diagnosis and clinical presentation for bone complications
3. Recognize various pharmacologic and non-pharmacologic options to manage bone complications in oncology patients

Bone Metastases

Incidence of Bone Metastases

Bone is one of the most common sites of metastases for many cancers - frequently affects the axial skeleton

1. **Multiple Myeloma** – 95%
2. **Prostate Cancer** – 85%
3. **Breast Cancer** – 70%
4. **Lung Cancer** – 40%
5. **Renal Cancer** – 40%

Source: Coleman, R et al. *Ann Oncol*. 2020;31(12):1650-1663

Incidence of Bone Metastases

569,000 patients across 52 US cancer centers from January 2004 – December 2013 were evaluated by Hernandez R, et al:

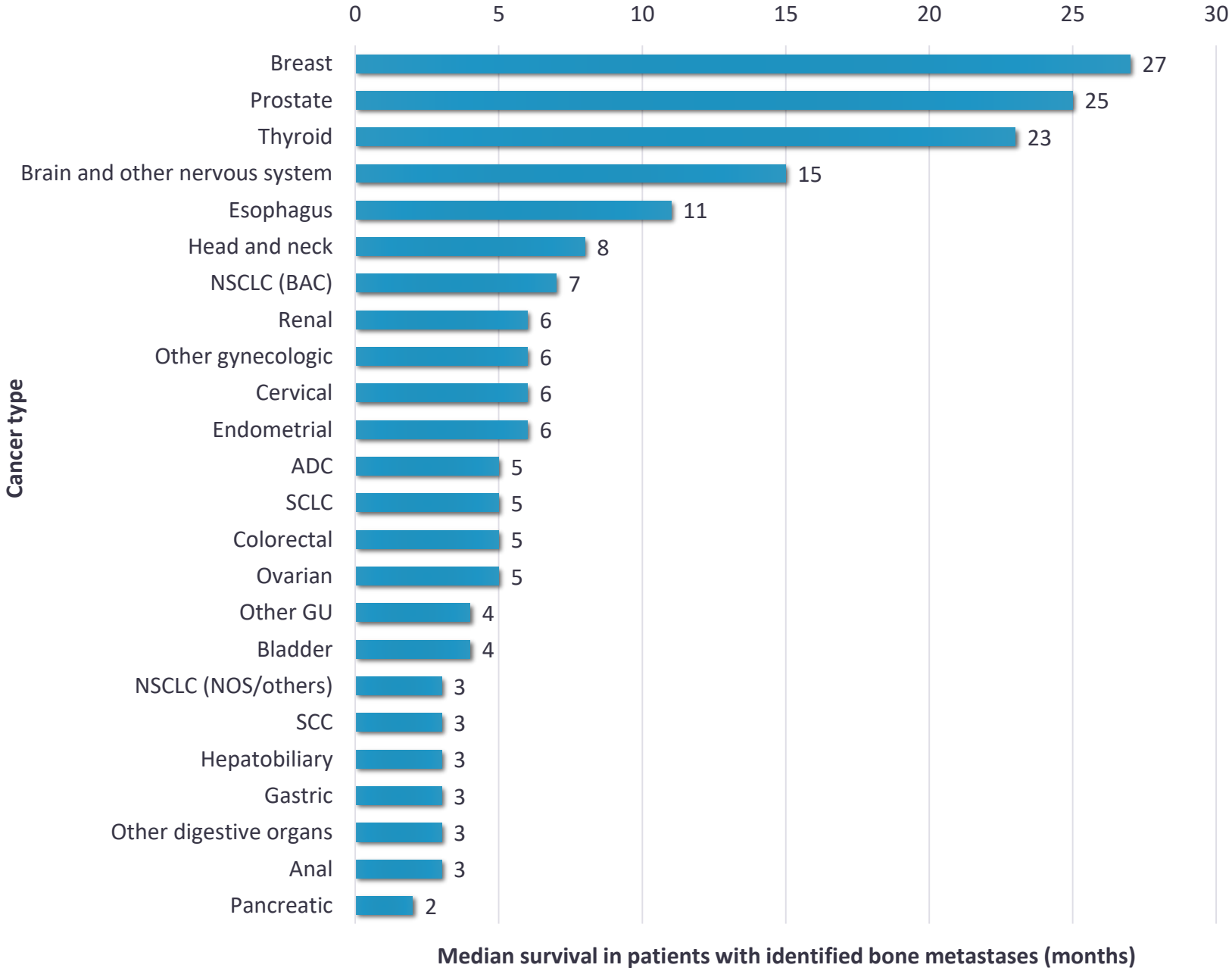
Tumor type and stage at diagnosis	1–year (95% CI)	5–year (95% CI)	10-year (95% CI)
Breast (N = 137,720)*	3.3 (3.2 – 3.4)	5.8 (5.7 – 6.0)	7.9 (7.7 – 8.1)
Stage IV (N = 5,985)	35.7 (34.5 – 36.9)	49.9 (48.6 – 51.3)	60.8 (58.9 – 62.6)
Prostate (N = 22,801)*	17.5 (17.0 – 18.0)	24.0 (23.4 – 24.6)	28.3 (27.5 – 29.2)
Stage IV (N = 3,908)	44.5 (43.0 – 46.1)	60.4 (58.7 – 62.1)	71.1 (68.2 – 73.9)
Lung (N = 59,344)	10.0 (9.8 – 10.3)	12.0 (11.7 – 12.3)	12.7 (12.3 – 13.2)
Stage IV (N = 12,487)	22.1 (21.4 – 22.8)	25.0 (24.3 – 25.8)	N/A
Other tumors (N = 162,868)	1.9 (1.9 – 2.0)	3.1 (3.1 – 3.2)	3.8 (3.6 – 3.9)
Stage IV (N = 22,147)	5.1 (4.8 – 5.4)	7.8 (7.4 – 8.2)	N/A

*High incidence and long course of cancer

Source: Hernandez R, et al. *J Clin Oncol*. 2016;34(15)

Median Time of Survival

In the United States ~350,000 people die each year from bone metastasis



Source: Huang JF, et al. *Ann Transl Med*. 2020;8(7):482..

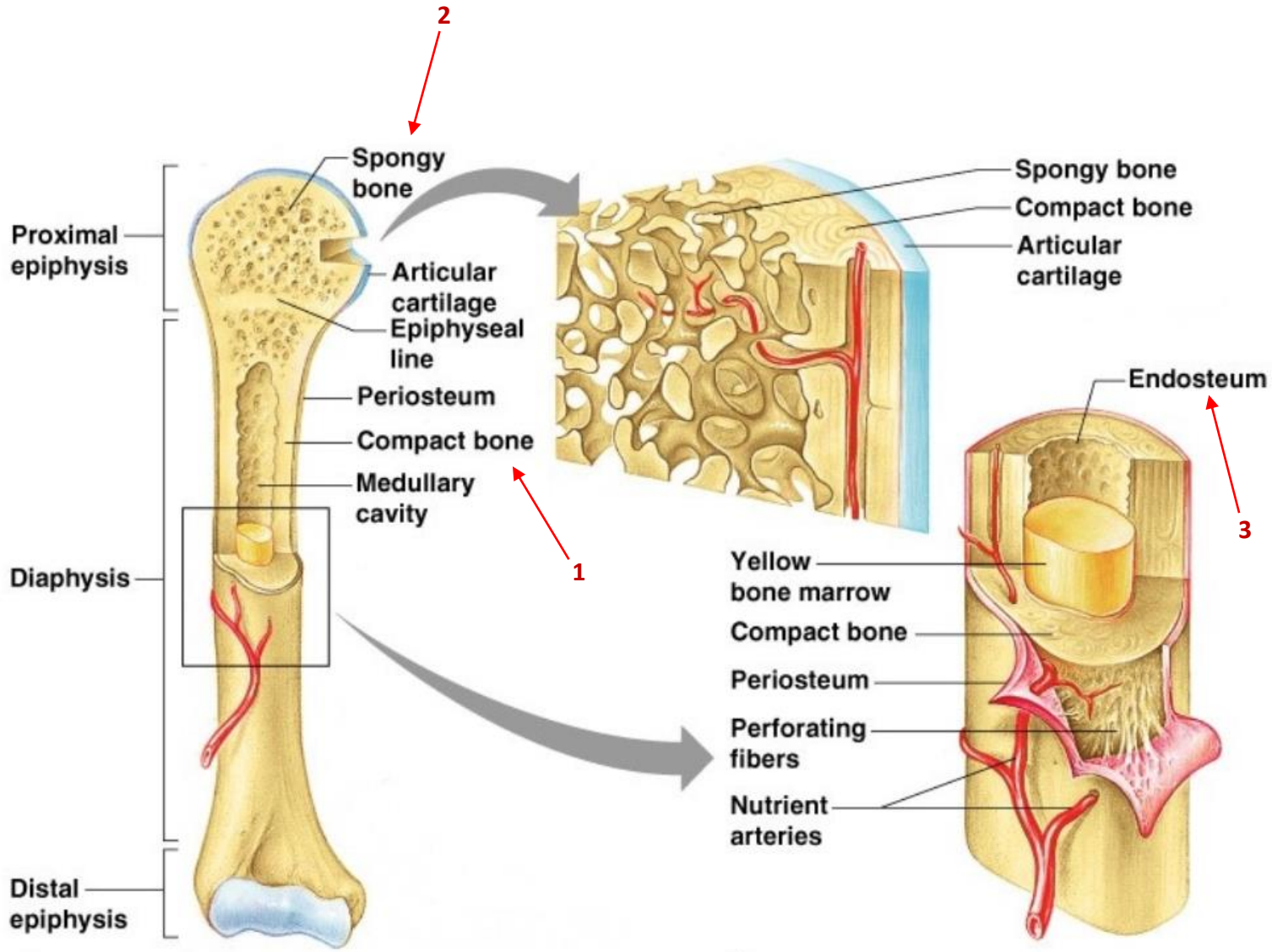
Bone Structure and Function

Bone Cells

- Osteoblasts – bone forming cells
- Osteoclasts – bone resorbing cells

Structural Components

- Cortical (compact) Bone – 80% of total bone mass; high mineral content; mechanical function
  - Covered by periosterum: supply osteoblasts for bone growth and repair
- Trabecular (spongy) Bone – reduces skeletal weight without compromising strength
- Endosteum – contains osteoprogenitor cells that can differentiate into osteoblasts



Source: Berenson JR, et al. *Cancer Biol Ther*. 2006;5(9):1078-1081.; Humagain S. Online Science Note. 11/28/2017.

Normal Bone Metabolism

Activation

- Osteoclasts migrate to specific skeletal site

Resorption

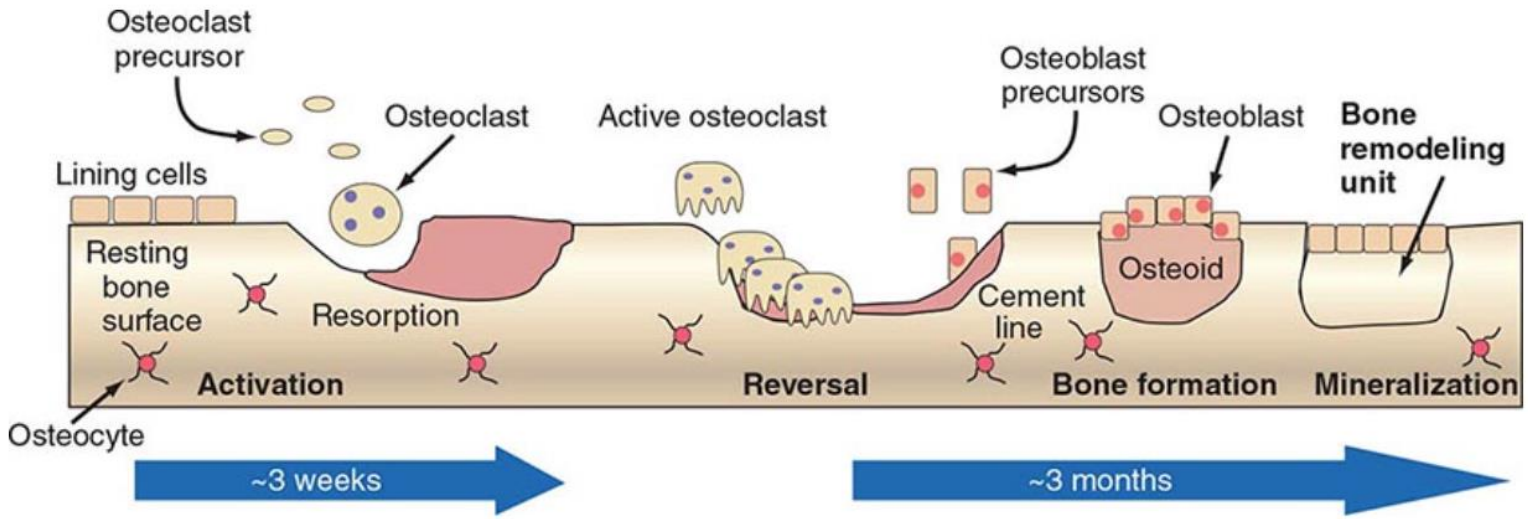
- Skeletal site undergoes osteolysis via osteoclasts

Reversal

- Apoptosis of osteoclasts
- Osteoclasts metabolism:
  - Osteoprotegerin (OPG)
  - Receptor activator of nuclear factor NF-κB ligand (RANKL)
  - Receptor activator of NF-κB (RANK)

Formation

- New bone deposited by osteoblasts



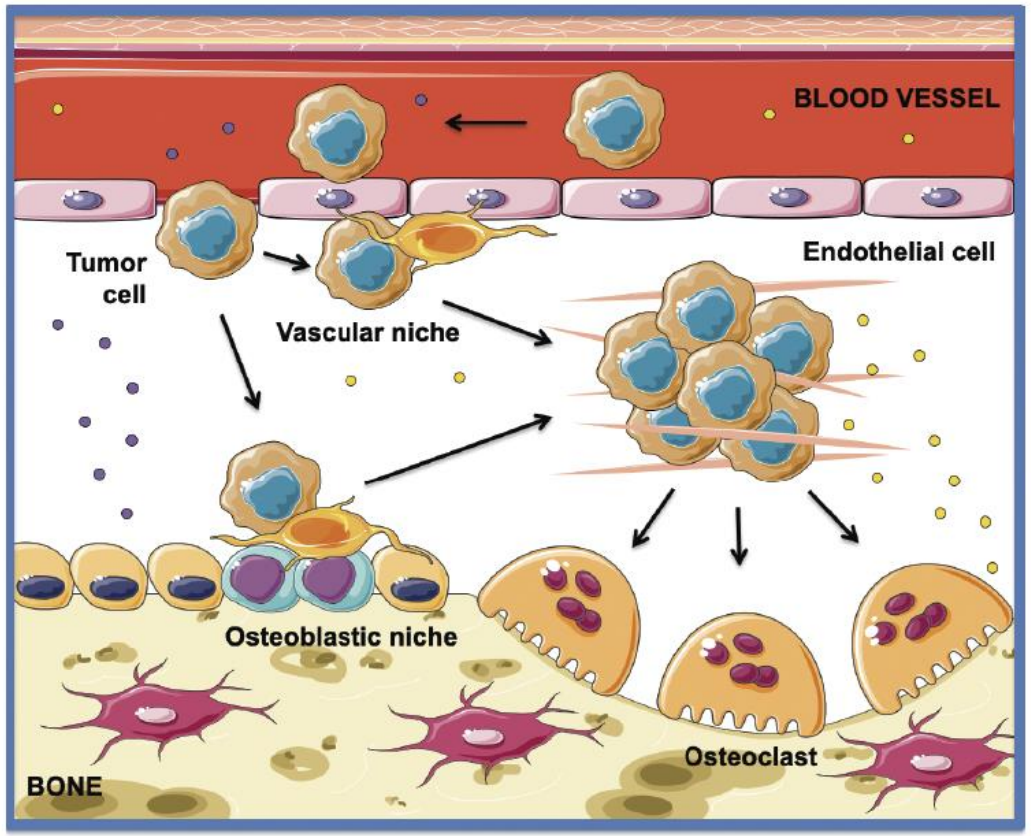
Source: Berenson JR, et al. *Cancer Biol Ther*. 2006;5(9):1078-1081.; Bringhurst, FR, et al. Harrison's. 19th ed. 2015

Mechanism of Bone Metastasis

Tumor cells detach from primary tumor and enter the systemic vasculature to gain access to new sites

The bone microenvironment provides a fertile setting for the growth and aggressive development of tumor cells

- eg. Breast cancer cells overproduce parathyroid hormone-related peptide (PTHrP) which activates osteoblasts to produce RANKL and downregulate OPG.
- Leads to osteoclast activation and osteolysis which release bone-derived growth factors:
  - Transforming growth factor-β (TGF-β)
  - Insulin-like growth factor 1 (IGF1)
  - Increases extracellular calcium levels
- Create cycle of osteoclastogenesis and osteolytic activity + aggressive growth and behavior of tumor cells



Source: Berenson JR, et al. *Cancer Biol Ther*. 2006;5(9):1078-1081; Clézardin P, et al. *Physiol Rev*. 2021;101(3):797-855; Yin, JJ et al. *Cell Res*. 2005;(15)57-62

Types of Bone Metastasis

Osteolytic

Characterized by increased bone resorption (destruction of normal bone via osteoclasts)

Most commonly seen in all cancer patients

- Multiple Myeloma, Renal Cell Carcinoma, NSCLC[1], Breast Cancer higher incidence

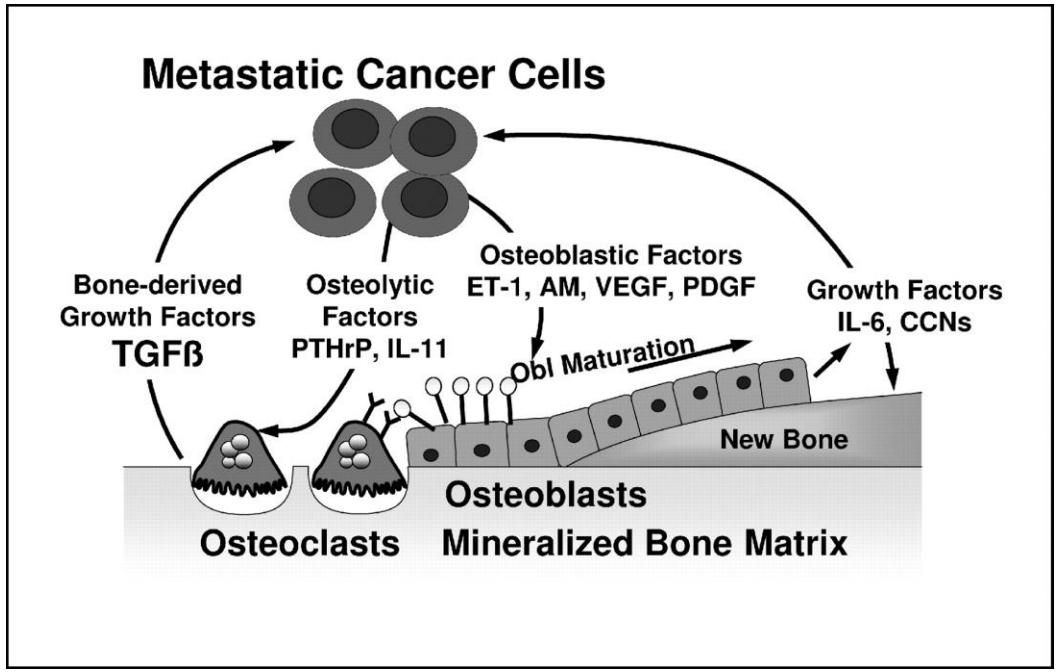
More likely associated with intractable bone pain, pathological fracture, nerve compression syndromes, and hypercalcemia of malignancy

Osteoblastic

Characterized by increased bone formation (deposition of new bone)

More commonly seen in Prostate Cancer and SCLC[2]

Patients suffer severe bone pain and pathological fractures



1. Non-small cell lung cancer
2. Small cell lung cancer

Source: Yin, JJ et al. *Cell Res*. 2005;(15)57-62; Guise TA et al. *Clin Cancer Res*. 2006;12(20 Pt 2):6213s-6216s.

Signs and Symptoms

Bone Pain

- Important factor to predict impending fracture
- Poorly localized, worse at night, not necessarily relieved with sleep or lying down
- Origin:
  - Inflammatory – release of cytokines and chemical mediators by tumor cells, periosteal irritation, stimulation of intraosseous nerves
  - Mechanical – related to pressure or mass effect of tumor tissue within bone, with loss of bone strength turning into activity-related pain

Fractures

- Most commonly in proximal parts of the long bones; femur accountings for over half of all cases
- Rib fractures and vertebral collapses common

Spinal Cord Compression

- Back or neck pain, numbness or weakness in the legs, bowel or stool incontinence
- More commonly seen in breast cancer (20%-30%) and lung cancer (15%)

Hypercalcemia

- Nausea, vomiting, constipation, confusion
- Contributors:
  - Focal osteolysis by tumor cells
  - Generalized osteolysis by humoral factors secreted by the tumor
  - Increased renal tubular reabsorption of calcium
  - Impaired renal glomerular function

Source: Coleman, R et al. *Ann Oncol*. 2020;31(12):1650-1663; Macedo F et al. *Oncol Rev*. 2017;11(1):321

Diagnosis: Bone Metastasis

Plain Radiographs	• Insensitive test for metastasis - oldest method • Recognizes alterations in bone density - information on fracture risk
Computed Tomography (CT)	• Improved sensitivity • Assess lesion size and cortical reaction
Magnetic Resonance Imaging (MRI)	• High sensitivity and specificity for bone marrow metastasis, including early lesions
Skeletal Scintigraphy	• Effective for screening the whole body for bone metastasis • Detect metastatic tumors via increased osteoblastic activity
Blood Tests	•alkaline phosphatase, lactate dehydrogenase, blood cell counts, blood chemistry tests, serum calcium, TSH, parathyroid hormone level
F-fluorodeoxyglucose PET-CT	•Most commonly used - differentiate between tumor progression or response to therapy •Increased aerobic glycolysis of lesions = greater FDG uptake
Bone Biopsy	• Useful in bone only disease • Allows reassessment of biomarkers that may direct future therapies
Bone Biomarkers	• Reflect ongoing rates of bone resorption and formation • sensitivity and specificity are low

Source: Coleman, R et al. *Ann Oncol*. 2020;31(12):1650-1663; Macedo F et al. *Oncol Rev*. 2017;11(1):321

Skeletal Related Events

TYPICALLY INCLUDE:

1. Pathologic fracture
2. Radiotherapy to bone
3. Surgery to bone
4. Spinal cord compression – associated with pain and neurologic complications
5. Hypercalcemia of malignancy

ASSOCIATED WITH:

1. Loss of mobility and social functioning
2. Reduced quality of life
3. Increased healthcare expenditure
4. Worse survival

Source: Coleman, R et al. *Ann Oncol*. 2020;31(12):1650-1663

Skeletal Related Events (SRE)

BREAST CANCER

Incidence of SREs in women ≥ 65-years with breast cancer from July 1, 1999 to Dec 31, 2005 in the Epidemiology and End Results (SEER)-Medicare database (n = 7,189)

SREs occurred in 46% of women (3,319)

Hazard Ratio for death:

- Bone metastasis/-SRE: 4.9 (95% CI 4.7 to 5.1)
- Bone metastasis/+SRE: 6.2 (95% CI: 5.9 to 6.5)

PROSTATE CANCER

Incidence of SREs in men ≥ 65-years with prostate cancer from July 1, 1999 to Dec 31, 2005 in the Epidemiology and End Results (SEER)-Medicare database (n = 9,746)

SREs occurred in 44% of men (4,296)

Hazard Ratio for death:

- Bone metastasis/-SRE: 6.6 (95% CI 6.4 to 6.9)
- Bone metastasis/+SRE: 10.2 (95% CI: 9.8 to 10.7)

Source: Sathiakumar N, et al. *Prostate Cancer Prostatic Dis*. 2011;14:177-183; Sathiakumar N, et al. *Breast Cancer Res Treat*. 2012;131:231-238

Treatment

Therapy Options

AIM - Preventing disease progression and symptom palliation

Treatments vary depending on -

- Underlying malignancy
- Localized or widespread bone disease
- Presence or absence of extraskeletal metastases

Resistance may develop, necessitating periodic changes of therapy to control disease

Available Treatment Options:

- Palliative Radiation Therapy
- Radionuclide Therapy
- Orthopedic Surgery
- Bone-Targeted Agents

Source: Coleman, R et al. *Ann Oncol*. 2020;31(12):1650-1663

Treatment

Palliative Radiation Therapy

- Local: effective for relieving bone pain with reported ORRs of 70-80%; 40% of responders see relief in within 10 days
- Side effects depend on the body area that is treated
- An initial flare in bone pain is common and can be reduced by prophylactic treatment with dexamethasone + analgesics

Radionuclide Therapy

- Aim: effective for relieving bone pain and prevention of morbidity and disease progression; 60% – 70% show response; 20% - 30% see complete pain relief
- Bone-seeking beta emitters in breast cancer: $^{89}SrCl_2$ & ^{135}Sm-EDTMP – palliation of bone but bone marrow toxicity and lack of survival benefit
- Bone-seeking beta emitters in prostate cancer: ^{223}Ra – improved OS by 3.6 months and delayed new symptomatic skeletal events by 5.8 months; greater benefit seen in patients treated with bisphosphonates (prior/concomitant use)

Orthopedic surgery

- Aim: maintain patient functionality and mobility by relieving pain preventing impending fractures and neural compression or stabilizing pathological fractures
- Lesions at high risk for fractures: lytic lesions ≥ 2.5 cm in diameter, encompassing > 50% of the bone diameter, or the presence of lesser trochanter avulsion

Source: Coleman, R et al. *Ann Oncol*. 2020;31(12):1650-1663; Gralow, Julie R et al. *J Natl Compr Canc Netw*. 2013;11 Suppl 3:S1-S51

Treatment: Bone-Targeted Agents (BTA)

BISPHOSPHONATES

Ibandronate

Zoledronic acid

MONOCLONAL ANTIBODY

Denosumab

GENERAL RECOMMENDATIONS

No approved tool to predict which patients will develop a SRE or when BTA should be initiated

SRE occurs early in course of disease

- Trial comparing densoumab to zoledronic acid, 37% of patients already experienced an SRE at study inclusion at 2 months from initial diagnosis

Recommend starting BTA as soon as diagnosis is made and continuing therapy indefinitely

Consider interrupting if

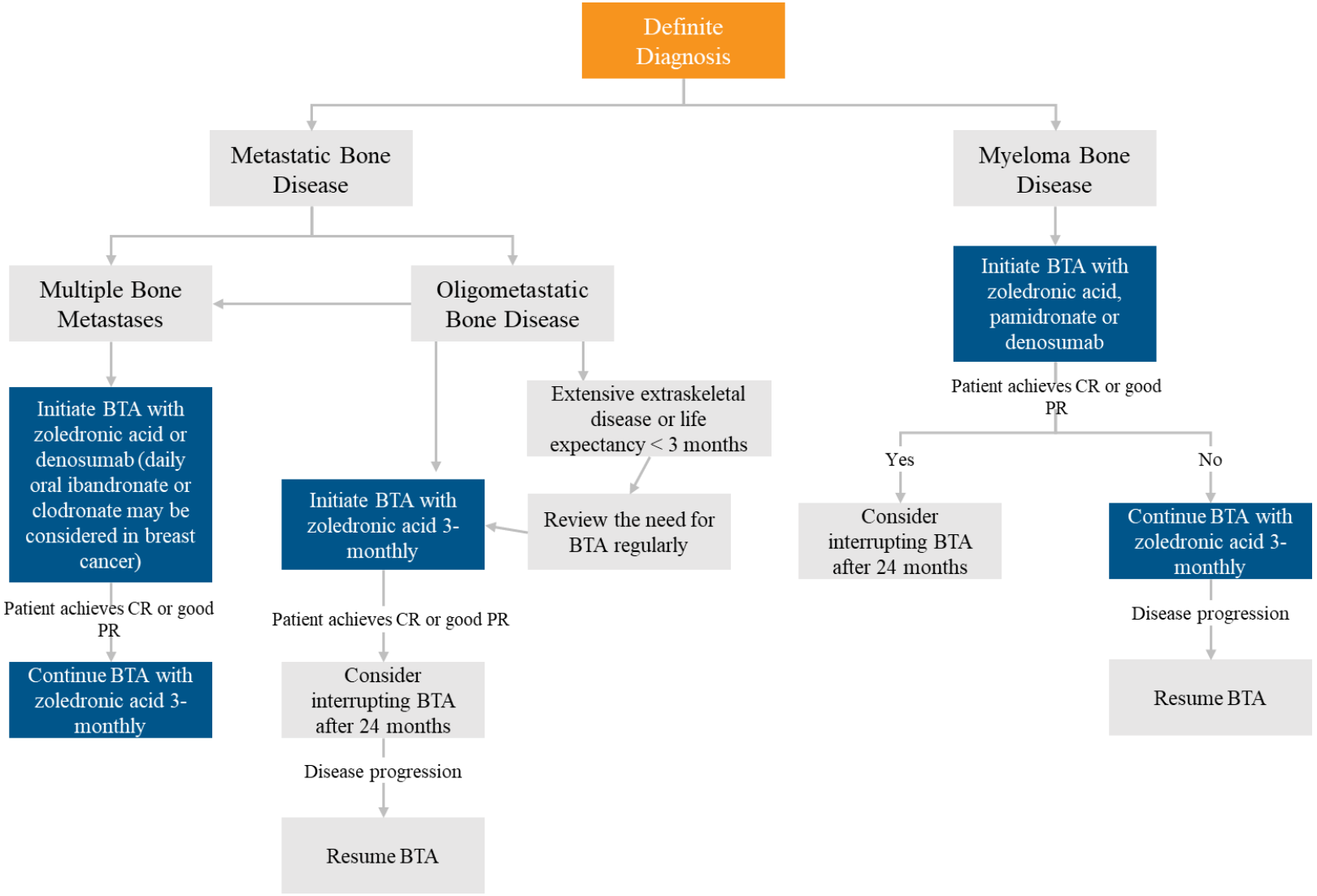
- Good prognostic factors (oligometastatic disease)
- Low risk of bone complications
- Durable response to systemic treatment

Source: Coleman, R et al. *Ann Oncol*. 2020;31(12):1650-1663; Stopeak AT et al. *J Clin Oncol*. 2010;28(35):5132-5139

Treatment Algorithm

Algorithm for use of bone-targeted treatments for bone metastases and myeloma bone disease

Suggested from ESMO Guidelines

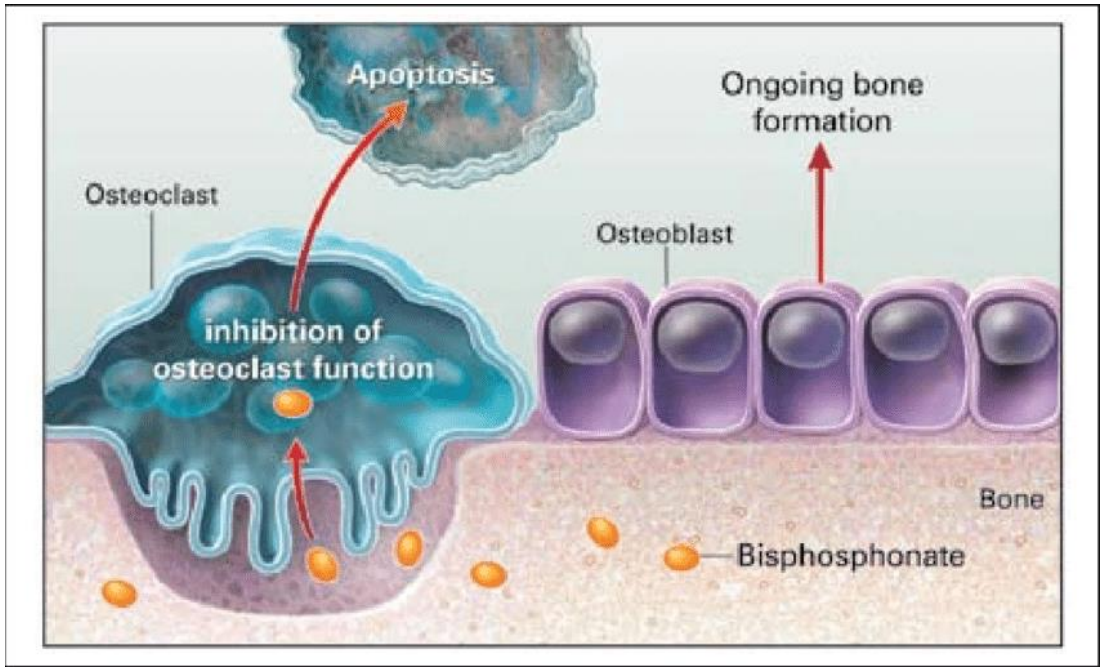


Source: Adapted from Coleman, R et al. *Ann Oncol*. 2020;31(12):1650-1663

Treatment: Bone-Targeted Agents

BISPHOSPHONATES

- Potent inhibitors of bone resorption
- Analogues of pyrophosphate, a natural inhibitor of bone demineralization
- May have antitumor and/or antiangiogenic effects – clinical relevance is controversial
- Additional treatment approach for bone pain, reduce risk of SREs, treat hypercalcemia of malignancy



Source: Coleman, R et al. *Ann Oncol*. 2020;31(12):1650-1663; Macedo F et al. *Oncol Rev*. 2017;11(1):321; Schmidt GA et al. *Am J Health Syst Pharm*. 2010;67(12):994-1001.

Bisphosphonates

IBANDRONATE

Breast cancer, metastatic bone disease

- IV: 6 mg over 1-2 hours Q3-4 weeks for 4 years

Hypercalcemia of malignancy

- IV: 2-6 mg single dose over 1-2 hours

Prostate cancer, metastatic bone pain (alternative agent if RT is not an option)

- IV: 6 mg as single dose over 15 min

ZOLEDRONIC ACID (ZOMETA®)

Bone metastasis, solid tumors

- IV: 4 mg every 3 to 4 weeks (may continue indefinitely)

Breast cancer, early stage, adjuvant therapy in postmenopausal females

- IV: 4 mg Q6 months (up to 3 to 5 years)

Hypercalcemia of malignancy (albumin corrected serum calcium ≥ 12 mg/dL)

- IV: 4 mg single dose, repeat in 7 days prn

Multiple Myeloma (active treatment or patients with osteolytic lesions, osteoporosis, osteopenia)

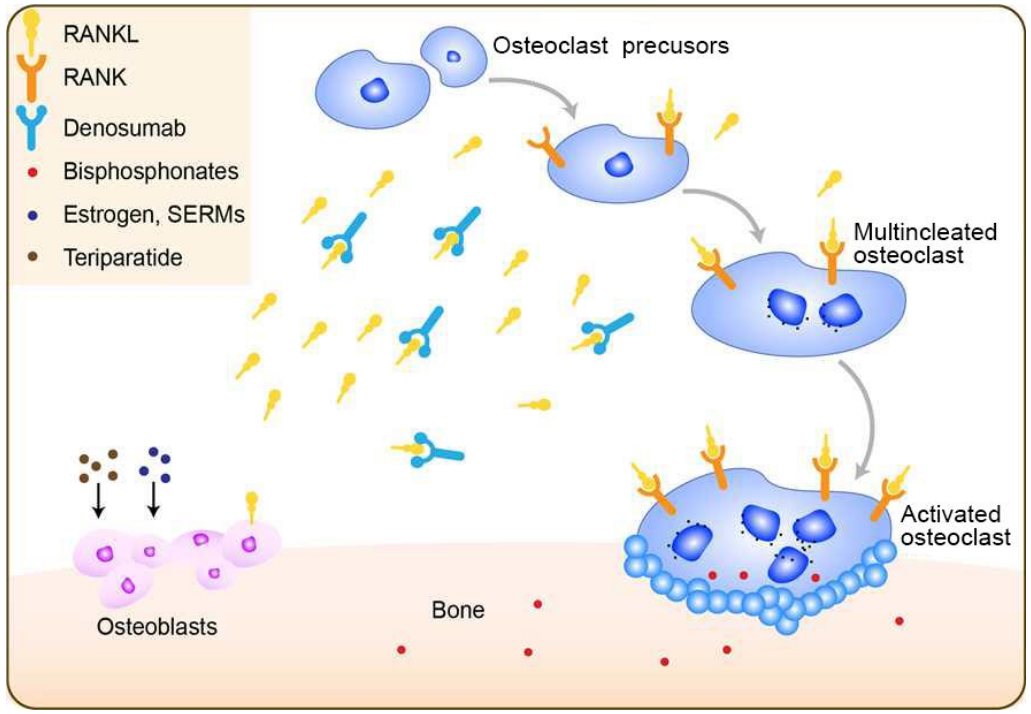
- IV: 4 mg Q3-4 weeks (up to 2-years)

Source: Coleman, R et al. *Ann Oncol*. 2020;31(12):1650-1663; Ibandronate. Lexi-Drugs. Hudson, OH: Lexicomp, 2022; Zoledronic Acid. Lexi-Drugs. Hudson, OH: Lexicomp, 2022

Treatment: Bone-Targeted Agents

DENOSUMAB (XGEVA®)

- Suppression of bone resorption
- Monoclonal antibody that binds avidly to RANKL, preventing its interaction with RANK receptor
- Reversible
- May exert antitumor effects and decrease mammary carcinogenesis in preclinical models



Source: Coleman, R et al. *Ann Oncol*. 2020;31(12):1650-1663; Macedo F et al. *Oncol Rev*. 2017;11(1):321; Creative Biolabs: Recombinant Antibody. Denosumab Overview 2022.

Denosumab

Bone metastasis from solid tumors (prevention of SRE)

- Subq: 120 mg Q4 weeks

Giant cell tumor of bone

- Subq: 120 mg Q4 weeks

Hypercalcemia of malignancy, refractory to bisphosphonate therapy

- Subq: 120 mg Q4 weeks

Multiple Myeloma (prevention of SRE)

- Subq: 120 mg Q4 weeks

Source: Coleman, R et al. *Ann Oncol*. 2020;31(12):1650-1663; Denosumab. Lexi-Drugs. Hudson, OH: Lexicomp, 2022

Clinical Data

Breast Cancer with Bone Metastasis

Randomized, double-blind, double-dummy, active-controlled, international trial		
Purpose	Denosumab versus zoledronic acid in delaying or preventing SRE	
Population	No prior bisphosphonate therapy, 37% had SRE at enrollment, median time since diagnosis of bone metastasis was 2 months, ~82% of the population was post-menopausal in each arm	
Methods	**Treatment arms** (randomized 1:1) 1. Subq Denosumab 120 mg + IV placebo Q 4 weeks (n = 1,026) 2. IV Zoledronic acid 4 mg + subq placebo Q 4 weeks (n = 1,020) Calcium (≥ 500 mg) and vit D (≥ 400 IU) were encouraged	**Primary Endpoint** (non-inferiority) Time to first on-study SRE (pathologic fracture, radiation or surgery to bone, spinal cord compression) **Secondary Endpoint** (superiority) Time to first on-study SRE and subsequent SRE (21 days apart)
Results	○ Denosumab delayed time to first on-study SRE by 18% compared to zoledronic acid • [HR, 0.82; 95% CI 0.71 - 0.95; P < 0.001 noninferiority; P = 0.01 superiority] ○ Median time to first on-study SRE: 26.4 months for zoledronic acid vs not reached for denosumab ○ Denosumab delayed time to first on-study SRE and subsequent ones by 23% compared to zoledronic acid • [rate ratio 0.77; 95% CI 0.66 - 0.89; P = 0.001] ○ OS and disease progression were similar	

Source: Stopeck AT, et al. *J Clin Oncol*. 2010;28(35):5132-5139.

Prostate Cancer with Bone Metastasis

Randomized, double-blind, double-dummy, active-controlled, international trial		
Purpose	Denosumab versus zoledronic acid in delaying or preventing SRE	
Population	No prior bisphosphonate therapy and 24% had SRE at enrollment	
Patients and Methods	**Treatment arms** (randomized 1:1) 1. Subq Denosumab 120 mg + IV placebo Q 4 weeks (n = 950) 2. IV Zoledronic acid 4 mg + subq placebo Q 4 weeks (n = 951) Calcium (≥ 500 mg) and vit D (≥ 400 IU) were encouraged	**Primary Endpoint** (non-inferiority) Median time to first on-study SRE (pathologic fracture, radiation or surgery to bone, spinal cord compression) **Secondary Endpoint** (superiority) Time to first on-study SRE and subsequent SRE (21 days apart)
Results	○ Denosumab delayed time to first on-study SRE by 18% compared to zoledronic acid • [HR 0.82, 95% CI 0.71 – 0.95, *P* = 0.0002 noninferiority, *P* = 0.008 superiority] ○ Median time to first on-study SRE for Denosumab was 20.7 months verses for zoledronic acid was 17.1 months ○ OS and disease progression were similar	

Source: Fizazi K, et al. *Lancet*. 2011;377(9768):813-822.

Multiple Myeloma with Bone Metastasis

Randomized, double-blind, double-dummy, active-controlled, international trial		
Purpose	Denosumab versus zoledronic acid in delaying or preventing SRE	
Population	≤ 1 IV bisphosphonate therapy, 65% had SRE at enrollment, median time since diagnosis of bone metastasis was 4 months for denosumab and 5 months for zolendronic acid, ~75% of the population was ≥ 65-years	
Patients and Methods	**Treatment arms** (randomized 1:1) 1. Subq Denosumab 120 mg + IV placebo Q 4 weeks (n = 859) 2. IV Zoledronic acid 4 mg + subq placebo Q 4 weeks (n = 859) Calcium (> 500 mg) and vit D (400 IU) were encouraged	**Primary Endpoint** (non-inferiority) Median time to first on-study SRE (pathologic fracture, radiation or surgery to bone, spinal cord compression) **Secondary Endpoint** (superiority) Time to first on-study SRE and subsequent SRE (21 days apart)
Results	○ Denosumab delayed time to first on-study SRE compared to zoledronic acid • [HR 0.98, 95% CI 0.85 – 1.14, *P* = 0.01 noninferiority] ○ Median time to first on-study SRE for Denosumab was 22.8 months and for zoledronic acid was 24 months ○ Denosumab did not show superiority to zoledronic acid for first on-study SRE and subsequent ones • [rate ratio 1.01; 95% CI 0.89 – 1.15; P = 0.84] ○ OS and disease progression were similar	

Source: Raje, Noopur et al. *Lancet. Onc* vol. 19,3 (2018): 370-381.

Cancer Treatment-Induced Bone Loss

Cancer Treatment Effects on Bone

Osteoporosis –

- Low bone mass
- Micro-architectural deterioration in structural integrity of bone tissue resulting in high risk of fracture
- Estrogen deficiency is a major cause of accelerated bone loss

Hormone deprivation state resulting from certain cancer therapies enhances osteoclastic bone resorption leading to bone loss

Breast cancer is associated with increased rates of osteoporosis and fractures

- 2.72% annual incidence of vertebral fractures in 352 patients with newly diagnosed breast cancer

Source: Gralow, Julie R et al. *J Natl Compr Canc Netw*. 2013;11 Suppl 3:S1-S51

Risk Factors

CANCER THERAPY RELATED

Chemotherapy-induced menopause

Gonadotropin-releasing hormone (GnRH) suppression of gonadal function
- Goserelin, Leuprolide, Triptorelin

Antiestrogen and androgen-deprivation therapies
- Aromatase Inhibitors: Anastrozole, Letrozole, Exemestane
- Antiandrogen therapies: Enzalutamide, Apalutamide, Darolutamide

Glucocorticoids

Radiation therapy

OSTEOPOROSIS RELATED

Age

Prior fracture history

Family history of fracture

Smoking

Excess alcohol intake

Inadequate weight-bearing exercise

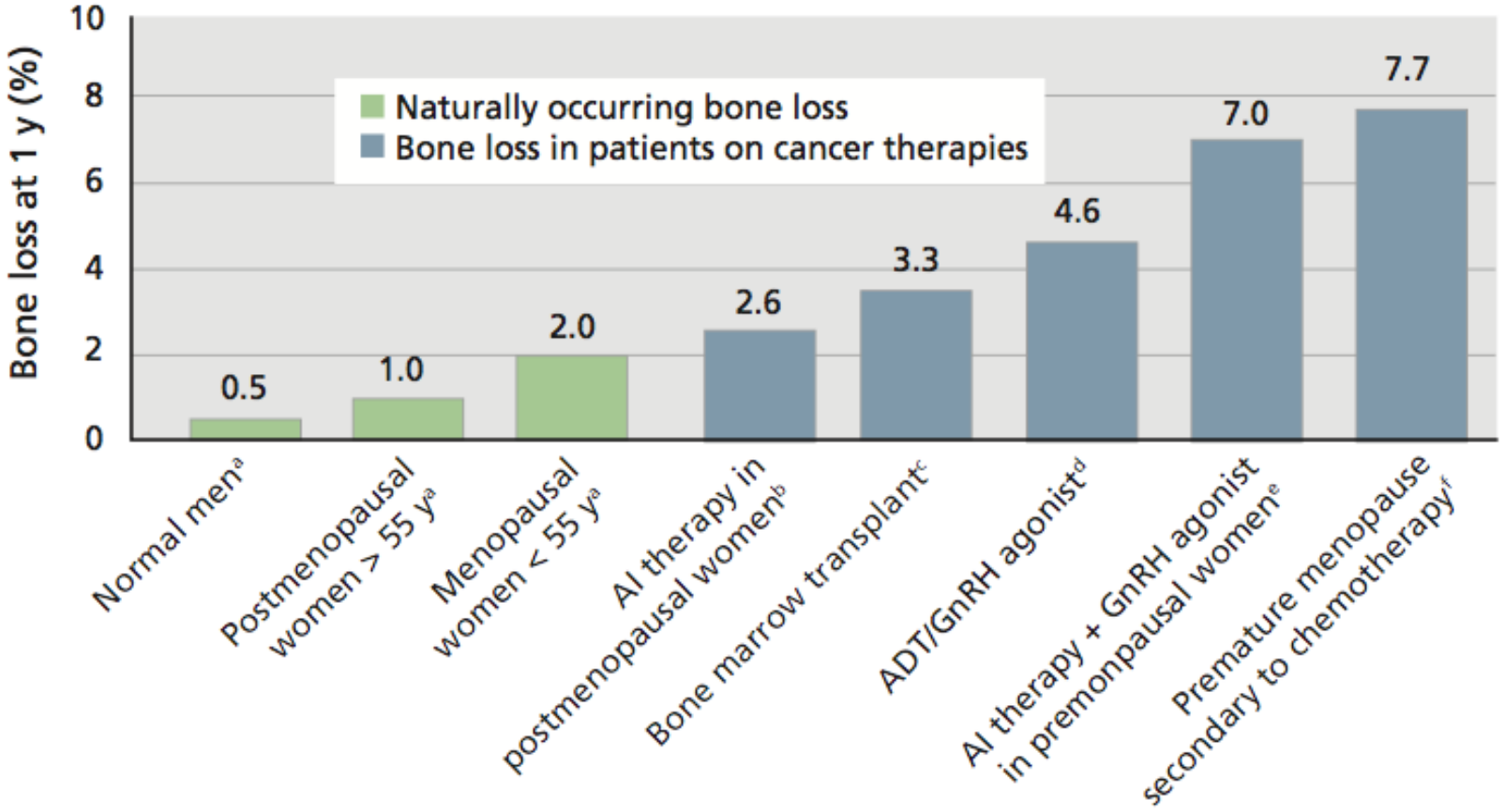
Low calcium intake

Vitamin D deficiency

Source: Gralow, Julie R et al. *J Natl Compr Canc Netw*. 2013;11 Suppl 3:S1-S51

Cancer Therapy Related Risk Factors

Bone loss associated with chemotherapy-induced menopause is several-fold higher than seen with natural menopause or AI therapy-induced bone loss in postmenopausal women



Source: Gralow, Julie R et al. *J Natl Compr Canc Netw*. 2013;11 Suppl 3:S1-S51

Diagnosis: Osteoporosis

Fracture Risk Assessment Tool (FRAX)

Used to evaluate a patient's 10-year fracture risk

Includes clinical risk factors that predict fracture risk:

- Age, sex, body mass index (BMI), smoking, alcohol use, prior fracture, parenteral history of hip fracture, use of glucocorticoids, rheumatoid arthritis, secondary osteoporosis and femoral neck BMD if available

Results may be used to identify patients who require diagnostic evaluation with a DXA scan

- Not a definitive tool for deciding to treat a patient

Increased risk of osteoporosis on the FRAX tool is indicated by a 10-year probability ≥3% for hip fracture or ≥20% for major osteoporotic fracture

Source: Camacho PM. et al. *Endocrine Prac*. 2020;2(Suppl 1):1-46

Diagnosis: Osteoporosis

Dual-Energy-X-ray Absorptiometry (DXA)

- Gold standard for osteoporosis diagnosis
- It is recommend obtaining baseline and repeating every 1 - 2 years until findings stabilize

Bone Mineral Density (BMD)

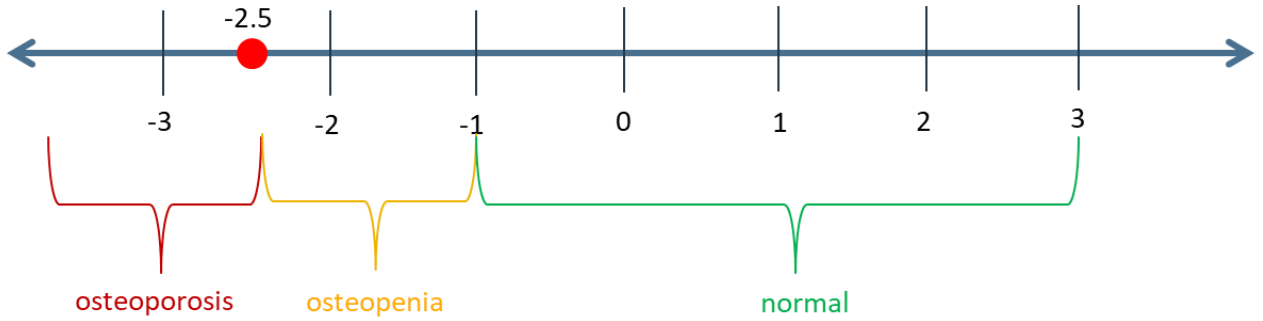
- Measured by dual-energy-X-ray absorptiometry (DXA)
- Abnormalities in the bone remodeling process can lead to loss of BMD
- Fractures represent one of the most important negative manifestations associated with low BMD and osteoporosis

Source: Camacho PM. et al. *Endocrine Prac*. 2020;2(Suppl 1):1-46; United States by the numbers: DXA Testing. National Osteoporosis Foundation. 2018

Diagnosis: Osteoporosis

T-scores - based on the mean BMD for a <u>healthy young man or woman</u>

- "Normal": -1.0 or above
- Osteopenia: between -1.0 and -2.5
- Osteoporosis: ≥ 2.5 SDs below the mean value
- Severe or established osteoporosis: -2.5 or below *with fragility fracture*



Source: Lane NE. *Am J of Obstet and Gynecol.* 2006;194:S3-11.

NCCN Recommendations for Screening

In oncology patients, changes in DXA scan in response to antiresorptive medication occur over a long period

NCCN guidelines recommend evaluating fracture risk with DXA every 24 months

- When bone loss risks have changed for a major therapeutic intervention has been undertaken, 12-month DXA follow-ups may be reasonable

Baseline and follow-up history and physical examinations should include:

- Assessment of vertebral fractures
- History of falls
- Annual height measurement
- Evaluation of new back pain

Source: Gralow, Julie R et al. *J Natl Compr Canc Netw*. 2013;11 Suppl 3:S1-S51

Treatment

Treatment: Bone-Targeted Agents

BISPHOSPHONATES

Alendronate

Risedronate

Ibandronate

Zoledronic acid

MONOCLONAL ANTIBODY

Denosumab

Source: Gralow, Julie R et al. *J Natl Compr Canc Netw*. 2013;11 Suppl 3:S1-S51

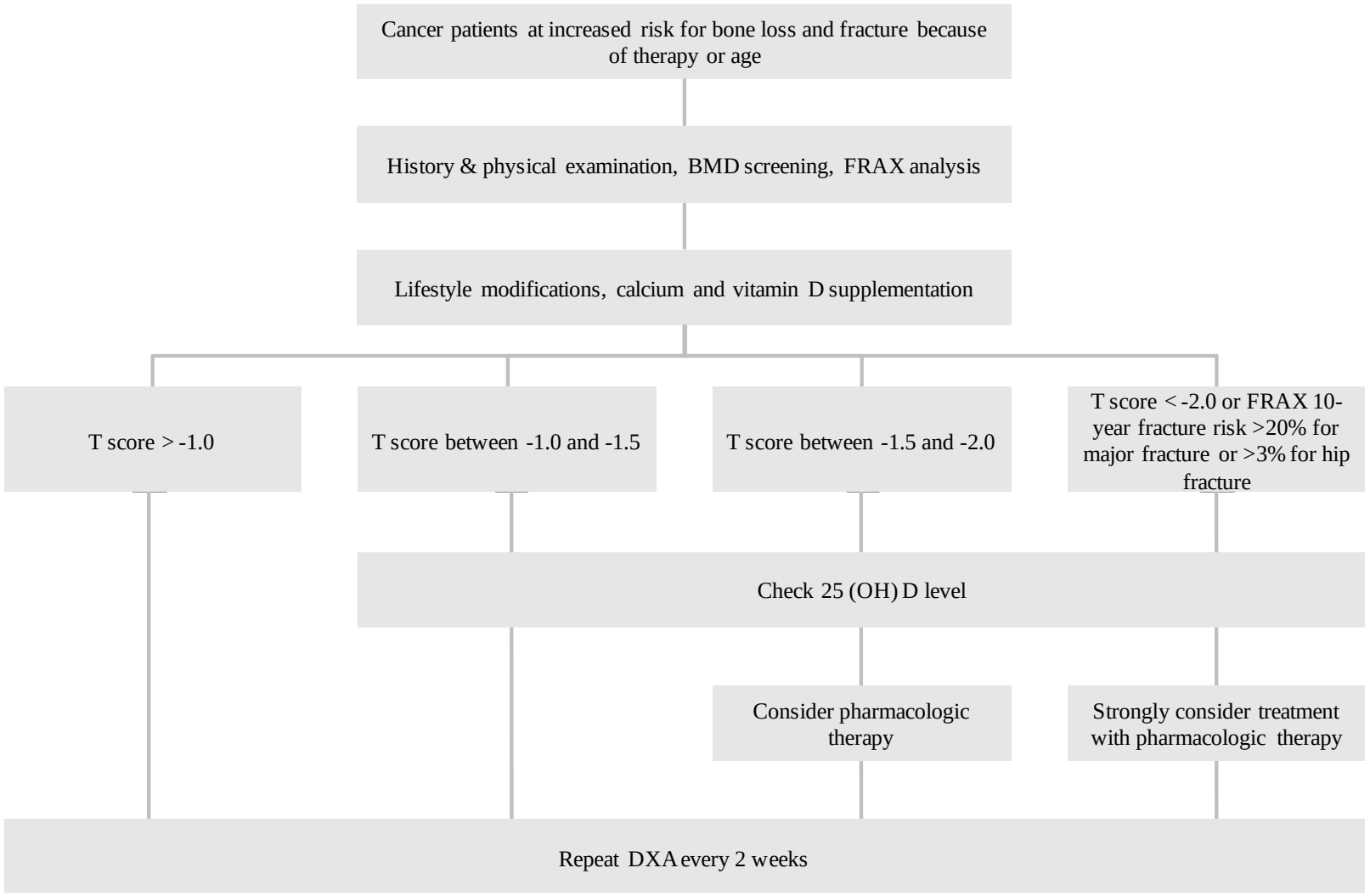
Bone-Targeted Agents

	Alendronate	Risedronate	Ibandronate	Zoledronic Acid (Zometa®)	Denosumab (Prolia®)
Prostate Cancer	Prostate cancer, bone loss associated with ADT – use in males without bone metastasis with a: 1. T-score of ≤ -2.5 2. prior fragility fracture 3. -1 < T-score > -2.5 Dose: 70 mg PO Q weekly	Prostate cancer, bone loss associated with ADT – use in males without bone metastasis with a: 1. T-score of ≤ -2.5 2. prior fragility fracture 3. -1 < T-score > -2.5 Dose: 35 mg PO Q weekly	Prostate cancer, bone loss associated with ADT – use in males without bone metastasis with a: 1. T-score of ≤ -2.5 2. prior fragility fracture 3. -1 < T-score > -2.5 Dose: 150 mg PO Q monthly	Prostate cancer, bone loss associated with ADT – use in males without bone metastasis with a: 1. T-score of ≤ -2.5 2. prior fragility fracture 3. -1 < T-score > -2.5 Dose: 5 mg IV Q12 months or 4 mg Q6-12 months (up to 36 months)	ADT-induced bone loss in males with prostate cancer, treatment[1] Dose: 60 mg subq Q6 months
Breast Cancer			Breast cancer, bone loss from AI therapy with a: 1. T-score of ≤ -2.5 2. prior fragility fracture 3. -1 < T-score > -2.5 Dose: 150 mg PO Q monthly	Breast cancer, bone loss from AI therapy with a: 1. T-score of ≤ -2.5 2. prior fragility fracture 3. -1 < T-score > -2.5 Dose: 4 mg IV Q6 months (up to 3 to 5 years)	AI-induced bone loss in females with breast cancer, treatment[1] Dose: 60 mg subq Q6 months

[1]FDA approved treatment

Source: Coleman, R et al. *Ann Oncol*. 2020;31(12):1650-1663; Denosumab. Lexi-Drugs. Hudson, OH: Lexicomp, 2022.; Ibandronate. Lexi-Drugs. Hudson, OH: Lexicomp, 2022; Zoledronic Acid. Lexi-Drugs. Hudson, OH: Lexicomp, 2022; Alendronate. Lexi-Drugs. Hudson, OH: Lexicomp, 2022; Risedronate. Lexi-Drugs. Hudson, OH: Lexicomp, 2022; Denosumab. Lexi-Drugs. Hudson, OH: Lexicomp, 2022

Bone Health Maintenance: Algorithm



Source: Gralow, Julie R et al. *J Natl Compr Canc Netw*. 2013;11 Suppl 3:S1-S51

Clinical Data

Bisphosphonate Therapy

Alendronate - Men with non-metastatic prostate cancer receiving androgen deprivation therapy

- 70 mg/week increased BMD of the hip and spine by 2.3% and 5.1% after 12 months

Risedronate - Postmenopausal women with early breast cancer receiving aromatase inhibitor therapy

- 35 mg/week increased BMD of the hip and spine by 2.2% and 1.8% compared to -1.8% and -1.1% with placebo at 24 months

Ibandronate - Postmenopausal women with early breast cancer receiving aromatase inhibitor therapy

- 150 mg/month increased BMD[1] of the hip and spine by 1.19% and 5.01% after 12 months

Source: Smith MR, et al. J Urol 2003;169:2008–2012; Michaelson MD, et al. J Clin Oncol 2007;25:1038–1042; Greenspan SL, et al. Ann Intern Med 2007;146:416–424.; Klotz LH, et al. Eur Urol 2012;63:927–935; Lester JE et al. *J Bone Oncol*. 2012;1(2):57-62; Van Poznak et al. *J Clin Oncol*. 2010;28(6):967-975

Synergy Trials: Zoledronic Acid

	Design/Arm	Results
Z-FAST	Compare the effects of zoledronic acid (4 mg IV every 6 months) administered concomitantly with letrozole (2.5 mg PO QD) therapy versus delayed administration at the first sign of bone loss: 1. Letrozole + Zoledronic acid 2. Letrozole + delayed Zoledronic acid (T-Score fell below < -2.0 or non-traumatic facture occurred)	61 months: Adjusted mean differences in lumbar spine and total hip BMD between the upfront and delayed groups were 8.9% and 6.7% (P<.0001, for both).
E-ZO-FAST		12 months: Increases BMD, with a mean increase of 2.7% at the lumbar spine and 1.7% at the hip with upfront administration.

Source: Brufsky AM, et al. *Clin Breast Cancer*. 2009;9(2):77-85; Coleman R, et al. *Ann Oncol*. 2013;24(2):398-405; Llombart A, et al. *Clin Breast Cancer*. 2012;12(1):40-48

ABCSG-18 Trial: Denosumab

Prospective, randomized, placebo-controlled, double-blind phase III trial		
Purpose	Effects of adjuvant denosumab on fracture risk in women receiving aromatase inhibitors	
Population	Postmenopausal with early, hormone receptor-positive, non-metastatic breast cancer (median age 64-years) receiving aromatase inhibitor therapy	
Patients and Methods	**Treatment arms** (randomized 1:1) 1. Subq Denosumab 60 mg Q 6 months (n = 1,711) 2. Placebo (n = 1,709)	**Primary Endpoint** Time to first clinical fracture from randomization
Results	○ Denosumab group had a delayed time to first clinical fracture • [HR 0.50; 95% CI 0.39 – 0.65; *P* < 0.0001] • First clinical fractures rates at 84 months were 11.1% (denosumab) vs 26.2% (placebo) ○ Mean lumbar spine BMD at 36 months: + 7.27% (denosumab) vs -2.75% (placebo)	

Source: Gnant M, et al. *Lancet*. 2015;386(9992):433-443

HALT Trial: Denosumab

Randomized, double-blind, placebo-controlled, phase III trial		
Purpose	Effects of denosumab on BMD and fracture in men receiving ADT for non-metastatic prostate cancer	
Population	Men with prostate cancer at increased risk of fracture (age ≥ 70 years, low BMD T-Score < -1, history of osteoporotic fracture) receiving androgen deprivation therapy	
Patients and Methods	**Treatment arms** (randomized 1:1) 1. Subq Denosumab 60 mg Q 6 months (n = 734) 2. Subq Placebo (n = 734)	**Primary Endpoint** % change in BMD[1] at the lumbar spine
Results	○ Mean lumbar spine BMD at 24 months: + 5.6% (densoumab) vs - 1.0% (placebo) (p <0.001) ○ Patients treated with denosumab also had decreased incidence of new vertebral fracture at 12, 24, and 36 months • 3-year risk of new vertebral fractures was reduced by 62%	

Source: Smith M, et al. *NEJM*. 2009;361:745-755.

Non-Pharmacologic Therapy

Non-Pharmacologic Therapy

Calcium

- Women ≥ 50-years old: 1,200 mg/day
- Men 51 to 70-years old: 1,000 mg/day
- Patients > 70-years old: 1,200 mg/day

Vitamin D

- 1,000 international units (IU)/day

Multifactorial fall prevention

- Assessment and management

Exercise

- Walking
- Low impact
- Strength training
  - At least 30 minutes/day

Social Habits

- Smoking cessation/avoidance
- Limited to moderate alcohol intake (< 2 drinks/day)
  - 120 mL of wine, 30 mL of liquor, or 260 mL of beer

Source: Coleman, R et al. *Ann Oncol*. 2020;31(12):1650-1663

Pharmacologic Therapy Review

Bisphosphonates

	Alendronate	Risedronate	Ibandronate	Zoledronic Acid
Administration	• Oral • Take with 6-8 oz water • Separate by at least 30 minutes before food/drink/other medication • do not lie down for ~ 30 minutes after		• Intravenous • Consider acetaminophen after administration to reduce incidence of acute reaction (eg, arthralgia, fever, flu-like symptoms, myalgia)	
Warnings/SE	Osteonecrosis of the jaw; hypocalcemia; upper GI irritation; severe bone/joint/muscle pain; atypical femur fractures			
Monitoring	BMD; serum calcium; vitamin D; serum creatinine; serum electrolytes			
Drug Interactions	• Aspirin and NSAID drug use may worsen GI irritation • Caution with calcium supplements, antacids, or medications containing multivalent cations		• Aspirin and NSAID drug use may worsen GI irritation	
Pearls	• Renal impairment considerations (not recommended if CrCl < 30 mL/min)			• Fetal harm • Renal impairment considerations (not recommended if CrCl < 30 mL/min)

Source: Coleman, R et al. *Ann Oncol*. 2020;31(12):1650-1663; Denosumab. Lexi-Drugs. Hudson, OH: Lexicomp, 2022.; Ibandronate. Lexi-Drugs. Hudson, OH: Lexicomp, 2022; Zoledronic Acid. Lexi-Drugs. Hudson, OH: Lexicomp, 2022; Alendronate. Lexi-Drugs. Hudson, OH: Lexicomp, 2022; Risedronate. Lexi-Drugs. Hudson, OH: Lexicomp, 2022.

Denosumab

	Denosumab
Administration	Subcutaneous
Warnings/SE	Hypocalcemia; serious infections; dermatologic reactions; osteonecrosis of the jaw; suppression of bone turnover; atypical femoral fracture; diarrhea; nausea
Monitoring	Serum calcium, BMD; vit D; phosphorus, magnesium, HBV screening
Pearls	May cause fetal harm

Source: Coleman, R et al. *Ann Oncol*. 2020;31(12):1650-1663; Denosumab. Lexi-Drugs. Hudson, OH: Lexicomp, 2022

Safety Considerations for Bone-Targeted Agents

Calcium balance

- Inhibition of bone resorption may cause hypocalcemia
- Monitor calcium and vitamin d levels

Osteonecrosis of the jaw

- More common when used on monthly basis for metastasis control
- Patients with poor oral hygiene at greater risk
- Similar for zoledronic acid and denosumab at ~1%

Atypical femoral fractures

- Absolute risk low at 3.2 to 50 cases/100,000 person years
- More common in long-term treatment (median 7-years)

Rebound osteolysis

- Denosumab does not incorporate into the bone matrix and bone turnover is not suppressed after its cessation
- Rapid decrease in BMD
- Consider bisphosphonate therapy to reduce or prevent risk of fractures

Source: Coleman, R et al. *Ann Oncol*. 2020;31(12):1650-1663

Therapy Selection

FACTORS TO CONSIDER

Drug and potential interactions

Dose and dosing interval

Route of administration

Access to agents

Risk for SRE

Overall status of tumor

RECOMMENDATIONS

Denosumab is favorable in terms of

- Efficacy
- Convenience
- Renal health perspectives

Bisphosphonates are favorable in terms of

- Health economic standpoint
- Lack of rebound osteolysis concern

Source: Coleman, R et al. *Ann Oncol*. 2020;31(12):1650-1663

Pharmacist’s Role

Pharmacist's Role

Therapy Choice

Side Effect Management

Medication Adherence

- Review adherence at least every 6 months
  - One-half of patients being treated with a bisphosphonate will self-discontinue therapy within the first 6 months due to:
    - Side effects or concerns about side effects, poor understanding of benefits, inconvenience, and use of multiple medications
- Pharmacists should continually assess for medication adherence

Counseling

- Educate patients about risks, encourage healthy lifestyle modifications, and supplementation with calcium and vitamin D

Source: Coleman, R et al. *Ann Oncol*. 2020;31(12):1650-1663; Adler RA et al. *J Bone Miner Res*. 2016;31(1):16-35.

Conclusions

- Pharmacologic therapy in the bone metastasis setting can help reduced time to SRE
- Pharmacologic therapy for individuals with a T score < -1.5 who have lost significant BMD as a result of cancer therapy
- Educate patients about risks, encourage healthy lifestyle modifications, and supplementation with calcium and vitamin D
- Treatment recommendations based on expert guidance and small studies in cancer patients

Additional Resources

Bone Health Management: ESMO Clinical Practice Guidelines	https://www.esmo.org/guidelines/supportive-and-palliative-care/bone-health-in-cancer-patients
NCCN Task Force Report: Bone Health in Cancer Care	https://jnccn.org/view/journals/jnccn/11/suppl_3/article-pS-1.xml
Cancer Therapy Education Sheets	Oralchemoedsheets.com
DDIs and Dose Modifications	Prescribing Information Tertiary resources

Assessment Question 1

Which of the following is not associated with osteolytic bone metastasis?

a. Intractable bone pain
b. Nerve compression syndromes
c. Hypocalcemia
d. Pathological fracture

Assessment Question 1: Correct Response

Which of the following is not associated with osteolytic bone metastasis?

a. Intractable bone pain

b. Nerve compression syndromes

c. Hypocalcemia

d. Pathological fracture

Assessment Question 2

Paula is a 70-year-old patient who has breast cancer with a history of diabetes, hypertension and has been a smoker for over 10-years. Her current medications include simvastatin 40 mg daily, aspirin 81 mg daily, lisinopril 5 mg daily, metformin 1000 mg daily, prednisone 5 mg 10-day taper only, acetaminophen 500 mg every 6 hours as needed, and anastrozole 1 mg daily. Which of following is NOT a risk factor for developing bone complications in this patient?

a. Advanced age

b. Smoking

c. Use of an aromatase inhibitor

d. Glucocorticoid use

Assessment Question 2: Correct Response

Paula is a 70-year-old patient who has breast cancer with a history of diabetes, hypertension and has been a smoker for over 10-years. Her current medications include simvastatin 40 mg daily, aspirin 81 mg daily, lisinopril 5 mg daily, metformin 1000 mg daily, prednisone 5 mg 10-day taper only, acetaminophen 500 mg every 6 hours as needed, and anastrozole 1 mg daily. Which of following is NOT a risk factor for developing bone complications in this patient?

a. Advanced age

b. Smoking

c. Use of an aromatase inhibitor

d. Glucocorticoid use

Assessment Question 3

Which of the following is a side effect of concern with bisphosphonate therapy?

a. Rebound osteolysis

b. Atypical femoral fractures

c. Hot flashes

d. Hyperglycemia

Assessment Question 3: Correct Response

Which of the following is a side effect of concern with bisphosphonate therapy?

a. Rebound osteolysis

b. Atypical femoral fractures

c. Hot flashes

d. Hyperglycemia

Thank you!

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