Management of Skeletal Health in Patients with Cancer, Cancer Treatment, and Cancer Survivors

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22nd Annual Santa Fe Bone Symposium
August 5-6, 2022
Disclosure

Commercial interest
• None

Off label usage
• None
Learning Objectives

The learner will be able to:

• Recognize that cancers are associated with bone loss and increased fracture risk

• List ways in which cancer-specific effects and cancer therapies induce bone loss

• Describe both pharmacologic and non-pharmacologic approaches to reduce bone loss and fracture risk in cancer patients
Question for the Audience

Bone health management should be an integral component in the care of patients with which types of cancers?

1. Breast cancer
2. Prostate cancer
3. Multiple Myeloma
4. Childhood cancers
5. All of the above
Bone Remodeling: A Balance

Bone Resorption (Osteoclasts)  Bone Formation (Osteoblasts)

Adults ‘replace’ their skeleton ~ every 7-10 years
Bone Remodeling in Healthy Subjects

- Oc Precursor
- Osteoclast
- Mononuclear Cells
- Ob Precursors
- Osteoblast
- Resting Bone Surface
- “Activation”
- Resorption
- Reversal
- CL
- Bone Formation
- OS
- BRU
- Mineralization

~3 WEEKS

LC = Lining Cells  CL = Cement Line  OS = Osteoid  BRU = Bone Remodeling Unit

~3 MONTHS
Cancer is a Major Risk for Bone Loss

- Bone mineral density (BMD) measured in 1,041 adult cancer patients in Germany
  - Mean age 57.1 years
  - Mean 22.5 months since diagnosis
  - 16% had osteoporosis
  - 44% had osteopenia
- Low BMD was independent of sex or cancer type
- This rate is substantially higher than in the general population

Risk for Bone Loss in Cancer

- Bone loss in cancer results from multiple causes
  - Direct cancer cell effects
  - Effects of cancer therapies
    - Chemotherapy
    - Corticosteroids
    - Aromatase inhibitors (AI’s)
    - Androgen deprivation therapy (ADT)
- Therapies have led to improved patient survival and longevity
  - Treatment can have significant skeletal effects
BMD Loss with Cancer Therapies

- Normal men: 0.5%
- Late menopausal women: 1.0%
- Early menopausal women: 2.0%
- Aromatase inhibitor (AI) therapy: 2.6%
- Bone marrow transplant: 3.3%
- Androgen deprivation therapy: 4.6%
- AI therapy + GnRH agonist: 7.0%
- Ovarian failure due to chemotherapy: 7.6%

Uluckan et al. (2009) Primer Metab. Bone Disease Disord. Miner. Metab. 386.
Cancer Cell Growth in Bone

• Cancer cells grow within bone
  • Induce osteoblasts and osteoclasts to produce factors which stimulate further cancer cell growth

• Skeleton is the most common site of metastasis
  • Post-mortem incidence rates
    • Breast 73%; prostate 68%; thyroid 42%; lung 36%;
    • Renal 35%; melanoma 35%; head/neck 12%; GI 5%

Seed and Soil Hypothesis

• Proposed by Stephen Paget in 1889

• Tumor cells (the seeds) interact with a specific organ/tissue microenvironment (the soil) and grow there due to specific interactions between the ‘seed’ and ‘soil’
Skeletal-Related Events (SREs) Across Cancer Types

*21-month data except for surgical intervention and spinal cord compression, for which only 9-month data are available; NSCLC = non-small cell lung carcinoma.

Breast Cancer and Bone

• Median age at breast cancer diagnosis is 61 yrs
  • 95% of women aged > 40 yrs

• Morbidity due to bone disease can have a major impact in breast cancer patient quality of life due to the often long clinical course
  • Highest incidence of skeletal complications
  • Mean skeletal related events/year ~ 2.2 to 4.0
    • Fractures, need for XRT, surgery, spinal cord compression, hypercalcemia

Estrogen, Bone, and Breast Cancer

- Essential role for estrogen in bone homeostasis through effects at the estrogen receptor (ER)
  - Limits bone resorption before menopause
  - Menopausal ↓ in estrogen leads to bone loss
- ~ 75% of breast cancers are ER+
- Hormonal therapies in breast cancer affect estrogen action
- 5 years of endocrine therapy is considered adjuvant standard of care
- In metastatic disease, therapy often used until disease progression or intolerable toxicity
Selective Estrogen Receptor Modulators

• Tamoxifen is an ER antagonist in breast tissue
  • Used in ER+ patients and as prophylaxis in high-risk patients
  • PreM women lose BMD
  • May act as an ER agonist in bone in PostM women to increase BMD vs. placebo

• STAR trial showed no difference in fracture incidence between raloxifene and tamoxifen in PostM women

• Bottom Line: SERMs affect BMD but likely not fracture risk in breast cancer patients

Aromatase Inhibitors (AI’s)

• Low circulating estrogen levels occur in PostM women due to androgen aromatization to estrogens

• Third generation AI’s (anastrozole, exemestane, letrozole) block this peripheral conversion

• AI’s decrease cancer recurrence and improve disease-free survival vs. SERMs

Aromatase Inhibitors

• Most study have shown that Al’s increase bone loss and fracture incidence
  • ATAC trial demonstrated a 5 year fracture rate of 11% (anastrozole) vs 7.7% (tamoxifene); p < 0.0001
  • BIG 1-98 trial showed a 5 year fracture incidence of 211 fractures (letrozole) vs. 141 fractures (tamoxifene); p<0.001
• MAP.3 trial of exemestane vs. placebo did not show differences in fracture incidence at a median follow-up of 35 months

Limiting Bone Disease in Breast Cancer

• Z-FAST trial
  • Upfront vs delayed zoledronic acid in PostM women on adjuvant AI (letrozole) for early-stage breast cancer
  • Lumbar spine BMD was 4.4% higher and hip BMD 3.3% higher in patients who received zoledronic acid at randomization vs. after one year of letrozole

• Denosumab
  • Delayed time to first skeletal-related event vs. zoledronic acid in patients with breast cancer

Prostate Cancer

• Median age at prostate cancer diagnosis is 67 yrs
  • 70% of prostate cancers are androgen dependent
• Androgen-deprivation therapy (ADT) is a mainstay of treatment
  • Orchiectomy
  • Chemical (GnRH agonist) castration
    • Also anti-androgens (bicalutamide/flutamide)
    • Abiraterone (blocks adrenal androgen production)
  • Commonly used at initial diagnosis to manage intermediate to high risk prostate cancer
ADT and Skeletal Health

• ADT leads to bone loss
  • 2-8% annual LS BMD loss
  • 1.8-6.5% annual hip BMD loss
  • May be up to 10% loss in the first year with surgical castration

• Likely due to decreased androgen to estrogen conversion

• Hypogonadism also reduces muscle mass and increases fall risk

• ADT increases fracture risk at 5 years (SEER)
  • 19.4% men with prostate cancer receiving ADT
  • 12.6% men with prostate cancer not receiving ADT

Rates of BMD Testing After ADT Initiation

Limiting Bone Loss in Prostate Cancer

• BP’s prevent bone loss or increase bone mass
  • Zoledronic acid ↑ BMD by 5.6%
  • Placebo ↓ 2.2%

• One dose of zoledronic acid prevented GnRH agonist induced bone loss at one year

• Raloxifene ↑ hip BMD by 1.1% in GnRH agonist treated men vs. 2.6% ↓ with placebo

• Androgen receptor antagonist (bicalutamide) ↑ serum testosterone and estrogen levels
  • ↑ Hip and spine BMD

Denosumab Increases BMD in Prostate Cancer Patients Receiving ADT

Denosumab also prolongs time to first skeletal-related event (20.7 months vs. 17.1 months) compared to zoledronic acid.

Preventing Bone Loss in Prostate Cancer

• Bisphosphonates have been shown to work in many studies
  • Alendronate, risedronate, ibandronate
  • Only zoledronate is FDA-approved for men receiving ADT at risk for fracture

• Denosumab is also FDA approved for men on ADT and at risk for fracture
  • Denosumab is also FDA approved for use in men with bone metastases from prostate cancer to prevent the occurrence of skeletal-related-events

• Radium-223 is FDA-approved for use in metastatic castrate resistant prostate cancer

Hematologic Malignancies and Bone

- Multiple myeloma (MM) is the second most common hematologic malignancy
  - 10% of all hematologic malignancies
- Skeletal complications are large source of pain and disability
  - Osteolytic lesions
  - Bone loss – osteopenia and osteoporosis
- 2/3 of patients present with bone pain
  - Pathologic fractures are present in > 50%
  - Fracture rates 16-fold higher the year before diagnosis
Fracture Incidence in Myeloma

![Graph showing cumulative incidence of fractures over years following diagnosis.](graph.png)
Bone Disease in Multiple Myeloma

- Even with disease remission, osteolytic lesions rarely heal
- Myeloma cell produced factors ↑ osteoclast activity and ↓ osteoblast activity
  - Lesions are almost purely osteolytic
Myeloma Cells Disrupt Bone Remodeling

Net Result = Bone Loss
Pharmacologic Management of Myeloma Bone Disease

• Current recommendations
  • Pamidronate 90 mg/monthly
  • Zoledronic acid 4 mg/monthly
  • Denosumab 120 mg/monthly

• Anti-resorptives improve skeletal outcomes
  • Bone pain
  • Hypercalcemia
  • Fractures
  • Need for surgical intervention
Skeletal Related Event Risk – Zoledronate vs. Pamidronate

Reduced Bisphosphonate Dosing May Benefit Cancer Patients

- Randomized trial of MM patients who had completed ~1 year of initial bisphosphonate therapy, continued monthly treatment did not reduce skeletal-related-events vs placebo.

- Monthly bisphosphonate therapy significantly ↑ ONJ risk vs monthly therapy for one year followed by ↓ to an every 3 month schedule, with no differences in the composite endpoint of skeletal-related events.

- Monthly dosing was equivalent to every 3-month dosing for skeletal related events in a metastatic breast, metastatic prostate and myeloma cohort.

Myeloma Primary Endpoint: Non-inferiority for Time to First On-Study Skeletal-Related Event

$\text{HR (95\% CI)} = 0.98 (0.85, 1.14); \textit{P}=0.01$ (Noninferiority)

Figure. Proportion of Denosumab Doses Administered to Medicare Beneficiaries With Multiple Myeloma
Bone Loss With Denosumab Discontinuation

Tsourdi et al. (2017) Bone 105:11
Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS.


AUTHOR INFORMATION

ABSTRACT

INTRODUCTION: The optimal duration of osteoporosis treatment is controversial. As opposed to bisphosphonates, denosumab does not incorporate into bone matrix and bone turnover is not suppressed after its cessation. Recent reports imply that denosumab discontinuation may lead to an increased risk of multiple vertebral fractures.

METHODS: The European Calcified Tissue Society (ECTS) formed a working group to perform a systematic review of existing literature on the effects of stopping denosumab and provide advice on management.

RESULTS: Data from phase 2 and 3 clinical trials underscore a rapid decrease of bone mineral density (BMD) and a steep increase in bone turnover markers (BTMs) after discontinuation of denosumab. Clinical case series report multiple vertebral fractures after discontinuation of denosumab and a renewed analysis of FREEDOM and FREEDOM Extension Trial suggests, albeit does not prove, that the risk of multiple vertebral fractures may be increased when denosumab is stopped due to a rebound increase in bone resorption.

Fracture Risk and Management of Discontinuation of Denosumab Therapy: A Systematic Review and Position Statement by ECTS

Denosumab Therapy Considerations

- Denosumab does not cause osteoclast apoptosis like bisphosphonates; rather it prevents pre-osteoclasts from becoming active osteoclasts.

- Therefore, any treatment with denosumab must be followed by a bisphosphonate (such as a dose of zoledronic acid) to limit rebound bone resorption. The timing of bisphosphonate treatment relative to the last dose of denosumab is not clear.

- May be a good option for patients with renal dysfunction or limited life expectancy.
Bone Loss Also Occurs in Monoclonal Gammopathy of Undetermined Significance (MGUS)

- MGUS is a common pre-malignant condition with an ~1% annual risk of progression to MM
- MGUS prevalence increases with age and affects ~3 million Americans
  - 3.2% adults aged ≥ 50 years
  - 7.5% adults aged ≥ 85 years
- Fractures are ↑ in MGUS
  - Vertebral: 6.3-fold ↑
  - Any axial: 2.7-fold ↑
  - Femur: 1.6-fold ↑

MGUS Patients have Decreased Volumetric Bone Mineral Density and Skeletal Microstructure

<table>
<thead>
<tr>
<th></th>
<th>Controls (Mean±SEM)</th>
<th>MGUS (Mean±SEM)</th>
<th>Difference (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average vBMD (mg/cm³)</td>
<td>335±7</td>
<td>300±10</td>
<td>-10.4%</td>
<td>0.005</td>
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<td>Trabecular BMD (mg/cm³)</td>
<td>161±4</td>
<td>150±6</td>
<td>-6.8%</td>
<td>0.080</td>
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<td>Cortical vBMD (mg/cm³)</td>
<td>862±7</td>
<td>822±12</td>
<td>-4.7%</td>
<td>0.001</td>
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<tr>
<td>Cortical Thickness (mm)</td>
<td>0.88±0.03</td>
<td>0.80±0.03</td>
<td>-9.5%</td>
<td>0.029</td>
</tr>
<tr>
<td>Trabecular Thickness (mm)</td>
<td>0.074±0.001</td>
<td>0.068±0.001</td>
<td>-8.1%</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Ng et al. (2011) *Blood* 118:6529
MGUS is Associated with Increased Cortical Porosity

MGUS Patients have Reduced Bone Strength

Apparent Modulus

P < 0.05

control

MGUS

Mpa

Farr et al. (2014) Blood 123:647.
Bone Loss in Multiple Myeloma

- Factors associated with myeloma bone disease include:
  - Osteoblast inhibition
    - Dickkopf 1 (DKK1) [Wnt pathway inhibitor]
  - Osteoclast activation
    - Macrophage inflammatory protein-1α (MIP-1α)

The Osteoblast Inhibitor DKK1 and Osteoclast Activator MIP-1α are Increased in MGUS

Ng et al. (2011) Blood 118:6529.
Unveiling Skeletal Fragility in Patients Diagnosed With MGUS: No Longer a Condition of Undetermined Significance?

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ABSTRACT

Monoclonal gammopathy of undetermined significance (MGUS) is a common finding in clinical practice, affecting greater than 3% of adults aged 50 years and older. As originally described, the term MGUS reflected the inherent clinical uncertainty of distinguishing patients with a benign stable monoclonal plasma cell disorder from subjects destined to progress to malignancy. There is now clear epidemiologic evidence, however, that patients with MGUS suffer from a significantly increased fracture risk and that the prevalence of MGUS is increased in patients with osteoporosis. Despite this relationship, no clinical care guidelines exist for the routine evaluation or treatment of the skeletal health of patients with MGUS. Recent work has demonstrated that circulating levels of at least two cytokines (CCL3/MIP-1α and DKK1) with well-recognized roles in bone disease in the related monoclonal gammopathy multiple myeloma are also increased in patients with MGUS. Further, recent imaging studies using high-resolution peripheral quantitative CT have documented that patients with MGUS have substantial skeletal microarchitectural deterioration and deficits in biomechanical bone strength that likely underlie the increased skeletal fragility in these patients. Accordingly, this Perspective provides evidence that the “undetermined significance” portion of the MGUS acronym may be best replaced in favor of the term “monoclonal gammopathy of skeletal significance” (MGSS) in order to more accurately reflect the enhanced skeletal risks inherent in this condition.


KEY WORDS: MGUS; OSTEOPOROSIS; FRACTURE; DXA; HRPQCT
Skeletal Complications of Childhood Cancers

- With improved therapies, more children are surviving cancer into adulthood
  - 5 year survival all cancers ~ 80%
  - Acute lymphocytic leukemia (ALL) ~ 87%
- 40% of peak bone mass obtained in adolescence
- Nutritional and physical activity deficits are common in children with cancer
- Intracranial XRT can affect hormonal function
  - Growth hormone deficits; hypogonadism
- Chemotherapy (particularly corticosteroids) can affect skeletal development

Bone Health in Childhood ALL

- BMD Z-score < 1.0 affects 10-46% at diagnosis
- Fractures present in 10% at diagnosis
- Chemotherapy reduces BMD
  - Dexamethasone and methotrexate
  - Inhibit bone formation, affect calcium absorption
- Fracture rates 6-fold higher than normals
- Some ‘catch-up’ in BMD in most following treatment discontinuation
- Studies with bisphosphonates are limited, although in general appear to limit BMD loss

Bone Care of Childhood Cancers

• Address modifiable factors
  • Optimize nutrition (calcium + vitamin D)
  • Increase physical activity
  • Early identification of deficiencies
    • Growth hormone
    • Hypogonadism

• Children’s Oncology Group provides general recommendations

Complications of Pharmacologic Therapies for Limiting Bone Loss in Cancer

• Osteonecrosis of the jaw (ONJ)
• Atypical femoral fractures
• Renal impairment
• Hypocalcemia
Risk Factors for Osteonecrosis of the Jaw

- Invasive dental procedures
  - Extractions
  - Surgery
- Poor oral hygiene or active dental disease
- Prolonged bisphosphonate exposure (> 2 years)
- Rates appear comparable between zoledronate and denosumab in cancer patients
Management of Jaw Osteonecrosis

- Conservative approach is recommended
  - Oral rinses
  - Pain control
  - Antibiotics (consider prophylactically)
  - Limited surgical intervention

- Most cases heal with conservative treatment
Preventive Measures Reduce ONJ Incidence in Bisphosphonate Treated Cancer Patients

- Retrospective review of bisphosphonate-treated patients who did not receive preventative measures (Pre Group)
- Preventive dental measures implemented in 154 patients treated with bisphosphonate (Post Group)

Atypical Femoral Fractures

- Relatively uncommon
  - Mostly case reports in the oncologic literature
- Relationship to anti-resorptives is not clear, but may relate to oversuppression of bone remodeling

Kidney damage

• Relatively uncommon complication of intravenous bisphosphonate use

• Some factors can be modified to limit risks
  • Dose
  • Delivery volume
  • Duration of delivery
  • Choice of bisphosphonate
Hypocalcemia

- More common in patients receiving intravenous bisphosphonates
  - Rates with denosumab appear ~ similar to zoledronate
- Limits risk by optimizing intake/levels of
  - Calcium
  - Vitamin D
  - Magnesium
Current Treatment of Cancer Bone Disease

• Bisphosphonate or denosumab therapy
• Radiation therapy for localized bone pain
• Surgical procedures
  • Vertebroplasty or balloon kyphoplasty
• Avoidance of high fracture risk activities
  • Falls and limited lifting
• Physical therapy for muscle strengthening
• Diet and nutrition (calcium, vitamin D)
• Treatment of the cancer itself (chemotherapy)
Pharmacologic Treatment Options

- Bisphosphonates
  - Most studies have used IV bisphosphonates
    - Zoledronate or pamidronate

- Denosumab
  - FDA-approved for the prevention of fractures and skeletal-related events in patients with bone metastases from solid tumors
    - Delayed time to first SRE vs. zoledronate in patients with breast or prostate cancer
    - No difference in time to first SRE in myeloma

Cancer Patients Have Increased Risks for Falls and Fractures

- Dehydration (lung or urinary infections)
- Medications (sedatives, blood pressure)
- Inactivity/muscle weakness
- Falls (ice, rugs, steps, ladders, extension cords)
- Lifting
Calcium and Vitamin D

- Once bisphosphonate therapy is started and resolution of any hypercalcemia occurs, adequate dietary calcium (1000-1500 mg/day total daily intake) is important for optimal skeletal health.

- Daily vitamin D intake should be at least 800-1200 IU.
Treatment of Hypercalcemia of Malignancy

- Endocrine Society Clinical Practice Guidelines – currently in progress

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- Public comment period ended August 1, 2022
- Expected publication – Fall 2022
Summary

• Bone loss is common in cancer patients and results from many factors
  • Cancer-mediated effects
  • Chemotherapy effects
    • Including corticosteroids
  • Effects on hormonal status
    • Androgen deprivation, aromatase inhibitors
• Dietary changes
• Reduced physical activity
Question for the Audience

Bone health management should be an integral component in the care of patients with which types of cancers?

1. Breast cancer
2. Prostate cancer
3. Multiple Myeloma
4. Childhood cancers
5. All of the above
Conclusions

• Careful monitoring of bone health must be an essential component of the treatment plan for any cancer patient

• This is best done with a proactive approach
Research Support

Mayo Center for Clinical and Translational Science (CCaTS)