Bone Health in the Cancer Patient

Stavroula Otis, M.D.
Primary Care and Oncology: Practical Lessons Conference
Brea Community Center
May 10, 2018
Overview

• Healthy bone is in a constant state of remodelling
  • Normal bone physiology

• Profound effects of cancer on bone health
  • Pathophysiology of bone metastases
  • Incidence/epidemiology of bone mets
  • Skeletal related events (SREs)

• Diagnosis of bone mets....

• ....
Normal bone physiology

• Healthy bone is a dynamic tissue in a constant state of remodeling
  • Involves bone resorption and formation
  • Preserves skeletal size, shape and structural integrity
  • Regulates mineral homeostasis

• Osteoclasts
  • Terminally differentiated myeloid cells
  • Express calcitonin receptors
  • Adapted to remove mineralized bone
  • CSF-1 and RANKL critical regulators

• Osteoblasts
  • Develop from pluripotent mesenchymal stem cells
  • Express PTH receptors
  • Roles in bone remodeling:
    • Express osteoclastogenic factors
    • Production of bone matrix proteins
    • Bone mineralization

Normal bone physiology

• Osteocytes
  • Terminally differentiated osteoblasts entombed in calcified bone matrix
  • Cocooned in fluid filled cavities
  • Long dendritic processes that interact with other cells
  • Detect bone microdamage and direct remodeling
    • Activation → resorption → reversal → formation → mineralization
Pathophysiology of bone metastases

- Primary tumor cells gain access to angiolymphatic vessels
- Tumor cells transported to distant organs via circulatory system
- Most disseminated tumor cells die
- Some tumor types have a particular affinity for bone
- Bone marrow microenvironment
  - May act as a reservoir for malignant cells
  - HSC niche is a site for dormant tumor cells that only result in relapse after many years

Pathophysiology of bone metastases

• In bone microenvironment
  • Tumor cells produce cytokines and GFs (PTHRP, prostaglandins, ILs, etc)
  • Results in increased production of RANKL
  • Activation of osteoclasts
  • As bone matrix is broken down, bone-derived GFs are released
  • Increased growth and proliferation of tumor cells
  • Self sustaining vicious cycle

• Ann Oncol. 2014;25(suppl_3):iii124-iii137
## Incidence and Epidemiology of Bone Metastases

### Metastatic Bone Disease

**Epidemiology - Etiology**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Estimated Number of Persons Living with Cancer¹</th>
<th>Number of New Cases in 2004¹</th>
<th>Incidence of Bone Metastases²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>2,184,125 (24%)</td>
<td>217,440 (16%)</td>
<td>65-75%</td>
</tr>
<tr>
<td>Prostate</td>
<td>1,838,653 (20%)</td>
<td>230,110 (17%)</td>
<td>65-75%</td>
</tr>
<tr>
<td>Bladder</td>
<td>521,945 (6%)</td>
<td>60,240 (4%)</td>
<td>40%</td>
</tr>
<tr>
<td>Lung</td>
<td>388,538 (4%)</td>
<td>173,770 (13%)</td>
<td>30-40%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>273,642 (3%)</td>
<td>23,600 (2%)</td>
<td>60%</td>
</tr>
<tr>
<td>Other</td>
<td>4,013,458 (43%)</td>
<td>705,160 (52%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>9,220,361 (100%)</td>
<td>1,368,030 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

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² Coleman, R.E., Cancer Treatment Reviews, 2001 37: 166-176
Clinical consequences of bone metastases

- **Skeletal Related Events (SREs)**
  - Pathologic fractures
  - Need for palliative radiation
  - Need for palliative surgery
  - Cord compression
  - Hypercalcemia
Clinical Consequences of Bone Metastases

- SREs associated with:
  - Loss of mobility and social functioning
  - Decrease in QOL
  - Increase in medical costs

- Across all tumor types, breast ca has highest incidence of skeletal complications
  - 2-4 events/year if no bone targeting treatment

  - Population based cohort study
  - 36,000 newly dx’d breast ca pts with 9 yr f/u
  - Median survival for pts w/ bone mets 16 mos, only 7 mos for pts with bone mets + SRE

  - Risk factors that increase fracture risk in postmenopausal women w/ breast ca
    - Aromatase inhibitor treatment
    - BMD T-score < -2.5
    - Increasing age (>65)
    - Oral corticosteroid use >6 mos
    - Low BMI (<20kg/m2)
    - Family hx of hip fracture
Diagnosis of Bone Metastases

• Early detection of skeletal mets is critical
  • Accurate staging and optimal treatment
  • Implementing treatments to reduce risk of SREs
    • Surgical fixation
    • Radiotherapy
    • Bisphosphonate therapy

• Most common sites of bone mets are axial skeleton

• Lytic lesions
  • Radiolucent areas in bone
  • Aggressive
  • Myeloma, lung, thyroid, and renal cell ca
  • Tumor cells release factors that upregulate osteoclast activity
    • PTHRP, TNF alpha or beta, IL-1, IL-6
    • Net osteolysis

• Blastic lesions
  • Radiopaque areas in bone
  • Slower progression
  • Lymphomas, prostate and breast cancer
  • Tumor cells release factors that upregulate osteoblasts
    • EGF, TGR alpha and beta, insulin-like GFs
    • Net osteosclerosis

• Mixed lesions – combination of both processes occurring

• Plain radiographs are an insensitive test for axsatic bone mets
  • A destructive lesion can only be seen if >1cm and 50-70% loss of bone mineral content
Diagnosis of bone metastases

- **18F FDG-PET**
  - Sensitivity 98%, specificity 56% (increases to >90% for PET/CT)
  - Functional imaging (vs anatomic)
- **MRI**
  - Sensitivity 95%, specificity 90%
  - Excellent soft tissue resolution
  - Ideal for assessing spread in/extension from marrow cavity
  - Preferred when evaluating for cord compression
- **CT scan**
  - Sensitivity 74%, specificity 56%
  - Excellent resolution of cortical and trabecular bone
  - Preferred for evaluating the ribs
  - Reduces burden of imaging
  - Can be used to guide perc biopsy
- **Bone scintigraphy (bone scan)**
  - Sensitivity 78%, specificity 48%
  - Widespread availability
  - Images the entire skeleton
  - Can detect bone mets up to 18 mos earlier than plain films
  - Nonspecific, false positives, treatment flare
  - Need additional imaging (CT or MRI) for correlation
  - False negative, “super scan”

Sensitivity and specificity of imaging modalities in bone metastasis

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18F NaF-PET/CT</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>MRI</td>
<td>95</td>
<td>90</td>
</tr>
<tr>
<td>SPECT</td>
<td>87</td>
<td>91</td>
</tr>
<tr>
<td>18F FDG-PET</td>
<td>98</td>
<td>56</td>
</tr>
<tr>
<td>CT</td>
<td>74</td>
<td>56</td>
</tr>
<tr>
<td>Bone Scintigraphy</td>
<td>78</td>
<td>48</td>
</tr>
</tbody>
</table>

PET: Positron emission tomography; CT: Computed tomography; MRI: Magnetic resonance imaging; SPECT: Single photon emission tomography; 18F FDG: Fluorine 18 labelled fluorodeoxyglucose; 18F NaF: Fluorine 18 labelled sodium fluoride.
Treatment of bone metastases: **Palliative Radiation**

- Highly effective for bone pain
- Overall RR 85%, w/ complete relief in 50%
- 50% of responders show benefit in 1-2 weeks
- If no improvement after 6 weeks, unlikely
- No difference in outcomes between fractionated and single fraction

- Targeted radiotherapy in certain tumor types
  - I-131 for follicular carcinoma of thyroid
  - Radium chloride (Xofigo) for prostate cancer
    - Minimal systemic effects
    - Randomized phase III trial showed addition of radium chloride to best supportive care in CRPC pts showed 3.6 mo improvement in OS and improvement in QoL
Treatment of Bone Metastases: Bone targeted agents

• Bisphosphonates
  • Specifically inhibit osteoclasts
  • Concentrate in skeleton
    • Primarily at active remodeling sites
    • Limited distribution
  • Interrupt “viscious cycle”
    • Inhibiting osteoclast activity
    • Inhibiting differentiation
    • Inhibiting maturation
    • Directly inducing apoptosis

• Denosumab
  • Fully humanized moab
  • Binds to RANKL w/ high affinity
  • Inhibits binding of RANKL to RANK
  • As a circulating antibody, reaches all sites w/in bone
Lipton et al. European Journal of Cancer 53 (2016) 75-81

- Phase III trial
- Breast ca, prostate ca, or other solid tumors
- > or = 1 bone met
- Denosumab was superior to ZA in preventing SREs in pts with bone mets regardless of
  - ECOG PS
  - number of bone mets
  - presence/absence of visceral mets
- Overall HR 0.74-0.88, p < 0.0001
• Risk of first on study SRE

<table>
<thead>
<tr>
<th>ECOG performance status</th>
<th>Zoledronic Acid n/N</th>
<th>Denosumab n/N</th>
<th>HR* (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>360/1120</td>
<td>341/1141</td>
<td>0.79 (0.69-0.92)</td>
<td>0.0020</td>
</tr>
<tr>
<td>≥1</td>
<td>633/1640</td>
<td>547/1631</td>
<td>0.84 (0.74-0.94)</td>
<td>0.0025</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location of bone metastases</th>
<th>Zoledronic Acid n/N</th>
<th>Denosumab n/N</th>
<th>HR* (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial only</td>
<td>260/872</td>
<td>226/706</td>
<td>0.83 (0.69-1.00)</td>
<td>0.0443</td>
</tr>
<tr>
<td>Appendicular only</td>
<td>144/345</td>
<td>134/387</td>
<td>0.78 (0.61-0.99)</td>
<td>0.0428</td>
</tr>
<tr>
<td>Axial and appendicular</td>
<td>340/833</td>
<td>278/804</td>
<td>0.81 (0.69-0.95)</td>
<td>0.0104</td>
</tr>
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<tbody>
<tr>
<td>&lt;2</td>
<td>596/1696</td>
<td>520/1689</td>
<td>0.84 (0.74-0.94)</td>
<td>0.0033</td>
</tr>
<tr>
<td>≥2</td>
<td>436/1072</td>
<td>370/1086</td>
<td>0.78 (0.68-0.90)</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presence or absence of visceral metastasis</th>
<th>Zoledronic Acid n/N</th>
<th>Denosumab n/N</th>
<th>HR* (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
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<tr>
<td>Yes</td>
<td>40/3152</td>
<td>35/1185</td>
<td>0.80 (0.69-0.93)</td>
<td>0.0026</td>
</tr>
<tr>
<td>No</td>
<td>63/21616</td>
<td>539/1590</td>
<td>0.82 (0.73-0.93)</td>
<td>0.0011</td>
</tr>
</tbody>
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<thead>
<tr>
<th>uNTx level†</th>
<th>Zoledronic Acid n/N</th>
<th>Denosumab n/N</th>
<th>HR* (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥43.7 nmol/l</td>
<td>474/2222</td>
<td>436/1254</td>
<td>0.96 (0.75-0.98)</td>
<td>0.0025</td>
</tr>
<tr>
<td>&lt;43.7 nmol/l</td>
<td>458/1246</td>
<td>357/1229</td>
<td>0.94 (0.84-0.98)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Overall</td>
<td>1032/2768</td>
<td>890/2775</td>
<td>0.82 (0.75-0.89)</td>
<td>&lt;0.0001</td>
</tr>
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• Risk of subsequent SRE

<table>
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<tr>
<th>ECOG performance status</th>
<th>Zoledronic Acid n/N</th>
<th>Denosumab n/N</th>
<th>RR* (95% CI)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>0</td>
<td>612/1120</td>
<td>496/1141</td>
<td>0.76 (0.66-0.88)</td>
<td>0.0002</td>
</tr>
<tr>
<td>≥1</td>
<td>949/1640</td>
<td>794/1631</td>
<td>0.83 (0.74-0.92)</td>
<td>0.0007</td>
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<tr>
<td>Axial only</td>
<td>363/872</td>
<td>316/706</td>
<td>0.84 (0.71-0.99)</td>
<td>0.0422</td>
</tr>
<tr>
<td>Appendicular only</td>
<td>205/345</td>
<td>200/387</td>
<td>0.81 (0.65-1.02)</td>
<td>0.0715</td>
</tr>
<tr>
<td>Axial and appendicular</td>
<td>577/833</td>
<td>441/804</td>
<td>0.78 (0.67-0.91)</td>
<td>0.0018</td>
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<td>&lt;2</td>
<td>867/1696</td>
<td>717/1689</td>
<td>0.81 (0.72-0.91)</td>
<td>0.0002</td>
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<tr>
<td>≥2</td>
<td>698/1072</td>
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<th>Denosumab n/N</th>
<th>RR* (95% CI)</th>
<th>P Value</th>
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<tr>
<td>Yes</td>
<td>576/1152</td>
<td>483/1186</td>
<td>0.79 (0.69-0.91)</td>
<td>0.0007</td>
</tr>
<tr>
<td>No</td>
<td>990/1616</td>
<td>811/1590</td>
<td>0.81 (0.72-0.91)</td>
<td>0.0003</td>
</tr>
</tbody>
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</thead>
<tbody>
<tr>
<td>≥43.7 nmol/l</td>
<td>755/2222</td>
<td>664/1254</td>
<td>0.83 (0.73-0.94)</td>
<td>0.0035</td>
</tr>
<tr>
<td>&lt;43.7 nmol/l</td>
<td>659/1246</td>
<td>492/1229</td>
<td>0.74 (0.65-0.86)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Overall</td>
<td>1566/2768</td>
<td>1294/2775</td>
<td>0.81 (0.74-0.88)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Hazard Ratio: Favors denosumab, Favors zoledronic acid
Rate Ratio: Favors denosumab, Favors zoledronic acid
Prevention of SREs

• For breast cancer:
  • It is recommended to start zolendronic acid or denosumab in all patients with
    bone metastases, whether they are symptomatic or not.

• For prostate cancer:
  • It is recommended to start zolendronic acid or denosumab in all patients with
    CRPC and bone metastases, whether they are symptomatic or not.

• For other solid tumors:
  • It is recommended to start zolendronic acid or denosumab in selected pts
    with advanced lung ca, renal cell ca, and other solid tumors w/ bone mets if
    they have a life expectancy >3 months and are considered high risk for SREs.
Safety concerns

• Both bisphosphonates and denosumab are generally well tolerated
• Side effects to be aware of
  • Hypocalcemia
    • More frequent and more likely to be symptomatic with denosumab than ZA
    • Patients should be on calcium and vitamin D3 supplements
      • Calcium 1000mg daily
      • Vitamin D3 (cholecalciferol) 1000 units daily
    • Regularly monitor serum calcium levels
  • Acute phase response (musculoskeletal pain, nausea, fatigue, fevers/rigors)
    • More frequent with ZA than denosumab
• Renal toxicity
  • More frequent with ZA than denosumab
Safety concerns: **Osteonecrosis of the Jaw**

- Manifests as exposed jaw bone
- The exposed bone does not get blood supply and dies
- Symptoms include pain in jaw or tooth, swelling, infection
- More common in pts getting rx for bone mets than osteoporosis
  - (1-2% vs < 0.0001)
- Risk increased with trauma to the jaw, esp invasive dental procedures like tooth extraction or implants
- Other risk factors:
  - Advanced age
  - Smoking
  - Steroid use
  - Diabetes
  - Gum disease
Safety concerns: Osteonecrosis of the Jaw

Treatment of ONJ

- If mild, treat conservatively with rinses, antibiotics and analgesics
- If severe, surgical debridement can be necessary

Prevention of ONJ

- Good oral hygiene and regular dental care
- Complete dental exam prior to starting bisphosphonates or denosumab
- Tell patients to tell their dentist
- If extractions not necessary, prefer less invasive procedures (like root canal)
- If extraction is necessary, delay starting rx until site has fully healed and pt asymptomatic
Prevention of metastases