Living Beyond Breast Cancer
Bone Metastases

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• Bayer: Research support to University of Michigan
• Royalties: UpToDate
Outline for presentation

• Introduction to bone as an organ
• Epidemiology of bone metastases
• Clinical management of bone metastases
  • Imaging
  • Interventions
• Potential side effects from bone directed therapies
• Research directions
• Dialog together, questions and answers
Importance of Bone Integrity

• Structural framework
• Mineral balance
• Bone marrow cells
• Bone metastases: morbidity & mortality:
  ◇ Pain
  ◇ Anemia
  ◇ Compromised mobility
  ◇ Skeletal Related Events (SRE)
  ◇ Bone matrix elaborates growth factors that may promote cancer growth
Osseous Metastases

Osteolytic

Osteoblastic

Mundy, Nature Reviews Cancer 2002
Common Sites of Bone Metastases
How did the breast cancer get to the bone?

Do cancer cells travel to the bone? How do they know which bone to go to? Are there bone-specific mechanisms involved in the development of bone metastasis?

- Pre-metastasis Niche in Organ-specific Metastasis?
- Homing by what mechanisms?
- Osteomimicry?

Is cancer a disease of self-seeding?

Norton & Massagué
Nature Medicine 2006
Imaging Bone Metastases

- Xray
- CT
- MRI
- Bone Scan
- PET-CT scan
Personal Impact of Bone Metastases

- Poor functional capacity
- Economic burden
- Impaired mobility
- Severe bone pain
- Long and painful recovery from fractures
- Hypercalcaemia
- Inconvenient hospital/clinic visits
- Pain and paralysis from spinal cord compression
Bone Pain

- Often worsened by motion, weight bearing
- Fracture risk
- Interventions
  - Analgesics (NSAIDs, Tylenol, Opiates, Lidoderm, etc)
  - Physical therapy
  - Radiation therapy
  - Procedures (kyphoplasty, vertebroplasty, etc)
  - Bisphosphonates
  - Other
Bone Metastases in Breast Cancer

Skeletal Related Events (SREs)
• Fracture
• Need for radiation to bone
• Need for surgery to bone
• Spinal Cord Compression
• Hypercalcemia of malignancy

Bone metastases also affect:
• Pain
• Mobility
• Quality of life
• Anemia secondary to compromised marrow
Cancer Induced Bone Disease

Local
- Anticancer therapy

Systemic
- Analgesics
- Osteoclast inhibition
- Clinical Trials

Surgery
- Radiation Therapy
- Clinical Trials
Cancer cells

Osteoclast

Bone

Vicious Cycle (1)

PTHrP
IL-6
IL-8
PGE₂
TNF-α
CSF-1

IL-6, PGE₂, TNF, M-CSF

BMP
PDGF
FGFs
IGFs
TGFβ
Vicious Cycle (2)  

**Cancer cells**

- IL-6, PGE2, TNF, M-CSF

**Anti-Cancer Therapy**

- BMP
- PDGF
- FGFs
- IGFs
- TGFβ

**Osteoclast**

- PTHrP
- IL-6
- IL-8
- PGE₂
- TNF-α
- CSF-1

**Bone**

**Osteoclast inhibition**
Bone Modifying Agents (Metastatic Bone Disease Osteoclast Inhibitors)

Skeletal Related Events (SRE) rates are reduced by BMA

- Denosumab
- Pamidronate (IV)
- Zoledronic acid (IV)

- Clodronate (IV, oral)
- Ibandronate (IV, oral)

Hypercalcemia of Malignancy (HCM):
Zoledronic acid > pamidronate (Major JCO 2001)
Denosumab for bisphosphonate refractory (HCM) (Hu JNCI 2013)
Pamidronate versus Placebo (Hortobagyi NEJM 1996): SRE in 1 y
  • 43% versus 56% p = 0.046

Pamidronate versus Zoledronic acid (Rosen J.Cancer 2001)
  • Breast chemotherapy SRE in 1 y: 44% versus 43%
  • Breast hormonal therapy SRE in 1 y: 42% versus 47%

Zoledronic Acid versus Placebo (Kohno JCO 2005)
  • SRE in 1 y
    • 29.9% versus 49.6% p=0.003

Denosumab versus Zoledronic acid
  • 0.45 events (denosumab) versus 0.58 events (zoledronic acid) per patient per year

Zoledronic acid every 4 weeks or every 12 weeks: CALGB 70604, ZOOM, & OPTIMIZE-2
  • SRE in 2nd y of dosing Ranges 15% to 29% p=0.004
No Anticancer Efficacy of BMA in Metastatic Breast Cancer

- No change to cancer outcomes in metastatic breast cancer
- No survival difference between zoledronic acid and denosumab
<table>
<thead>
<tr>
<th>Study name</th>
<th>Drug</th>
<th>Tumor Type</th>
<th>Primary Endpoint</th>
<th>Ref</th>
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<td>ZOOM</td>
<td>Zol (open label)</td>
<td>MBC, MBC, MPCA, MM</td>
<td>SRE per patient per year</td>
<td>Amadori Lancet Oncology 2013</td>
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<td>Non-inferiority</td>
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<td>Optimize 2</td>
<td>Zol (placebo)</td>
<td>MBC, MBC</td>
<td>SRE rate</td>
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<td>CALGB 70604</td>
<td>Zol (open label)</td>
<td>MBC, MBC, MPCA, MM</td>
<td>SRE within 2 years</td>
<td>Himmelstein JAMA 2017</td>
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<td>Non-inferiority</td>
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<tr>
<td>SAKK 96 /12</td>
<td>Denosumab</td>
<td>MBC, MPCA</td>
<td>Time to first SSRE</td>
<td>Open to enrollment, NCT 02051218</td>
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<td>4w v 12w</td>
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Choice & Dosing of Bone Modifying Agent
Challenges in Evaluating Bone

Bone Scan
- Flare (response)?
- Progression?

CT Vertebral Body
Lytic to sclerotic
- Healing?
- Progression?
Osteoclast Inhibitors (cancer dosing)
Side Effects

IV administration (bisphosphonates):
- Acute phase reactions
- Hypocalcemia [5% ≥ grade 2]
- Renal insufficiency
- Osteonecrosis of the jaw (ONJ) [1.3%]
- Atypical fracture [rare]

Subcutaneous administration (denosumab)
- Hypocalcemia [12% ≥ grade 2]
- Osteonecrosis of the jaw (ONJ) [1.8%]
- Atypical fracture [rare]

Uncommon Adverse Events Associated with Bone Modifying Agents but Cause(s) Unknown

Atypical Fractures

Osteonecrosis of the Jaw (ONJ)
Vertebroplasty & Kyphoplasty: Compression Fracture

*polymethylmethacrylate (PMMA)*

Vertebroplasty
- Needle + Cement/PMMA

Kyphoplasty
- Balloon + Cement/PMMA
To Operate, Most Surgeons Consider:

Consider surgery:
- Size of lesion: ≥ 2.5 cm
- Lesion: ≥ 50% bone diameter
- Lesion is a Lesser trochanter avulsion
- Patient has ≥ 6 weeks life expectancy

Scoring system to predict pathologic fractures: clinically not often used

Preemptive surgery for impending fracture vs. surgery for completed fracture (favors pre-fracture tx)
- Shorter hospital stays (7 vs 11 days)
- Greater likelihood of discharge home (vs extended care) (79% vs 56%)
- Greater likelihood of support-free ambulation (35% vs 12%)

Mirels Clin Ortho 2003
Ward CORR 2003
LIQUID BIOPSY

A new, noninvasive technique that can detect disease biomarkers in:

- Blood
- Urine
- Sputum

LIQUID BIOPSY CAN BE USEFUL WHEN:

- Not enough tissue sample is available
- Not enough tumor tissue is in a sample
- A tumor is hard to reach
- Regular monitoring is needed

LIQUID BIOPSIES CAN BE ANALYZED FOR:

- The presence of cancer cells
- DNA
- Other materials released by cancer cells
Research

Blood
- CTCs
- Plasma

Marrow
- DTC
- Hematopoietic cells
- Aspirate fluids
- Bone cells

Bone
- Bone cells
- Imaging bone
- Imaging Matrix
- Bone strength
Take Home Points

• Metastatic Bone Disease \(\rightarrow\) interdisciplinary approach

• Pain control
  • RX: NSAIDs, Opiates
  • External beam radiation & Radiopharmaceuticals
  • Osteoclast inhibition (supportive therapy)

• Skeletal Related Events
  • Can be emergencies
  • Can be prevented by use of a BMA

• Quality of Life & Survival
  • SREs carry significant morbidity & mortality
  • Osteoclast inhibition has not been associated with increased survival
  • Duration of osteoclast inhibition therapy is generally indefinite

• Problems/questions remain \(\rightarrow\) Design & participate in trials
It Takes A Village

- Researchers
- Pharmacists
- Advanced Practice Providers
- Techs
- Medical Assistants
- Administration
- Medical Oncology
- Social Work Psych-Onc
- Nursing
- Primary Care
- Friends and Family
- Genetic Counselor
- Clerical Staff: Call Center Schedulers Intake Coordinators
- Radiology
- Radiation Oncology
- Pathologist
- Surgery
- Nutritionist
- Advocates
- Physicists
- Financial Planning
- Researchers
- Social Work Psych-Onc
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- Radiation Oncology
- Pathologist
- Surgery
- Nutritionist
- Advocates
- Physicists
- Financial Planning
Thank you!

Now it’s time for Questions