Advances in Treatment of Bone Metastasis

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Objectives

- Physiology of Bone
- Pathophysiology of Bone Metastasis
- Treatment of Bone Metastasis
  - Bisphosphonate (no talk)
  - Non-bisphosphonate treatment
- Assessment of Treatment Response of Bone Metastasis
- Cancer-induced bone loss
- Advances in Treatment
- Summary
What are Normal Functions of Bone?

- Supports network for muscles/tendons
- Protects internal organs
- Creates blood cells
- Stores calcium and phosphorous
- Buffers numerous metabolic processes
Osteoclast

Osteoblast
Normal Bone Turnover: Bone Breakdown and Bone Formation Are in Equilibrium

Resorption
Osteoclasts break down bone mineral and matrix, creating an erosion cavity

Reversal
Mononuclear cells prepare bone surface for new osteoblasts to begin building bone

Formation
Osteoblasts form a matrix to replace resorbed bone with new bone

Resting
A prolonged resting period follows until a new remodeling cycle begins
“Bone metastasis is a catastrophic complication for most patients with cancer. Not only does it cause intractable pain and . . . fracture after trivial injury, spinal cord compression, and hypercalcemia, it also signifies that the malignant process is incurable.”

Gregory R. Mundy, MD
Type of Bone Metastasis

- **Osteolytic**: dominant activity of osteoclasts
- **Osteoblastic**: dominant activity of osteoblasts
- **Mixed**: No dominance between lytic and blastic.
Pathogenesis of Bone Metastasis

Immature osteoclasts

Mature osteoclasts

Bone

TGFs, IGFs

PTHrP

OPG

PTH, Vitamin D, IL-11, PGE₂

osteoblasts, marrow stromal cells
Consequences of Increased Bone Resorption

- Hypercalcemia
- Fracture
- Bone pain
- Impaired mobility

- Increased bone resorption

Bone

Cord compression, nerve root damage, bone marrow suppression
Treatment of Bone Metastases

**Rapid Decision needed to be made**
- Surgery
- Radiation Therapy
- Analgesics

**Decision needed to be made**
- Bisphosphonate
- Diet and Life Style
- Systemic Treatment for Metastatic Breast Cancer
Surgery

- **Objective:** Prevent pathological fractures, or spinal cord compression

- **When:**
  - Perform surgery before fracture.
  - 30 mm axial cortical involvement in weight bearing area (osteolytic) → needs surgery

- **Method:**
  - Make sure that you are not missing other impending pathological fracture.
  - Pathological fracture → stabilization (nail or rod), internal fixation
  - Surgery followed by external-beam radiation
External Beam Radiation Therapy

- **Objectives:** palliation of symptoms
  - Pain control (within 24-48 hours)
  - Bone lesion stabilization
  - Delay pathological fracture, spinal cord compression
- **Methods:**
  - RT dose of at least 30 Gy in 10 fractions
  - Short course RT dose should be considered in patients with short life expectancy
- **Side effects:** BMS, nausea/vomiting, diarrhea
Radiopharmaceutical

- **Objective:** Pain control
- **Methods**
  - Strontium chloride 89, Samarium 153
  - Response takes up to 3 weeks
  - Indicated for those who can survive more than 3 M
- **Side Effects**
  - 20% may have flare pain
  - Bone marrow suppression
Patient Education (Learn about)

- Fracture prevention, pain management, and maintenance of daily activities.
- Drugs available to minimize bone loss.
  - bisphosphonates
  - non pharmaceutical measures, maintaining body weight, increasing non–weight-bearing exercise, minimizing caffeine and alcohol intake, and stopping smoking
- Risks of falls and developing individualized
- Programs to increase physical stability are critical.
- Pain is a part of metastatic disease and that it can be controlled. To prevent undertreatment.
  - Many patients prefer to avoid strong opioids like morphine due to the fear of addiction.
  - Some patients express a desire to reserve the use of opioids in case pain worsens over time.
Patients are under-treated for Bone Metastasis

Due to Physicians
Due to Patients
Due to Family Members
Issues related addressing bone tumor response

- What is true response?
  Bone structural change?
  ...sclerotic change of lytic lesion....
  Metabolic change?
  ...activity down of hot spot....

- No reliable response criteria.

- Breast cancer patient with bone only metastasis will be excluded from the patient eligibility.
Response criteria for bone tumor response

- **UICC** (International Union Against Cancer; 1977) based on XR.
- **WHO** (World Health Organization; 1978) based on XR and SS.
- **RECIST** (Response Evaluation Criteria in Solid Tumors Group; 2000) does not cover bone lesions.

The reality is that most of oncologists using CT and/or MRI for the assessment of bone tumor response without published criteria.

Standardized criteria, which include CT, MRI, and PET/CT are needed.
<table>
<thead>
<tr>
<th>Response Type</th>
<th>UICC*1 Only cover XR</th>
<th>WHO *2 Only cover XR and SS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Response</strong></td>
<td>Disappearance of all known disease</td>
<td>Complete disappearance of all lesions</td>
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<tr>
<td></td>
<td>Lytic lesions should have radiologic</td>
<td>on X-ray or scan for at least 4 weeks</td>
</tr>
<tr>
<td></td>
<td>evidence of calcification</td>
<td></td>
</tr>
<tr>
<td><strong>Partial Response</strong></td>
<td><strong>Objective improvement</strong> in evaluable</td>
<td>Partial decrease in size of lytic lesions,</td>
</tr>
<tr>
<td></td>
<td>or non measurable lesions</td>
<td>recalification of lytic lesions, or</td>
</tr>
<tr>
<td></td>
<td>At least 50% decrease in size of</td>
<td>decreased density of blastic lesions</td>
</tr>
<tr>
<td></td>
<td>measurable lesions</td>
<td>for at least 4 weeks</td>
</tr>
<tr>
<td></td>
<td>No new lesions and progressive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lesions</td>
<td></td>
</tr>
<tr>
<td><strong>No Change (Stable Disease)</strong></td>
<td>Unchanged</td>
<td>“no change” at least for 8 week</td>
</tr>
<tr>
<td></td>
<td>Less than 25% increase or less than</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50% decrease in size of measurable lesions</td>
<td></td>
</tr>
<tr>
<td><strong>Progressive Disease</strong></td>
<td>Mixed; some lesions persist while others</td>
<td>Increase in size of existent lesions or</td>
</tr>
<tr>
<td></td>
<td>progress, or new lesions appear</td>
<td>appearance of new lesions</td>
</tr>
<tr>
<td></td>
<td>Failure; some or all lesions progress and/or new lesions appear</td>
<td></td>
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<tr>
<td></td>
<td>No lesions regress</td>
<td></td>
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</table>

### New criteria for the treatment response (MDA criteria)

| Complete Response | Complete fill-in or sclerosis of lytic lesion on XR and CT  
|                   | Disappearance of hot spots or tumor signal on SS, CT or MRI  
|                   | Normalization of osteoblastic lesion on XR and CT |
| Partial Response  | Sclerotic rim about initially lytic lesion or sclerosis of previously undetected lesion on XR or CT |
|                   | Partial fill-in or sclerosis of lytic lesion on XR or CT |
|                   | Regression of measurable lesion on XR, CT or MRI |
|                   | Regression of lesion on SS (exclude rapid regression) |
|                   | Decrease in blastic lesion on XR or CT |
| Stable Disease    | No change in measurable lesion on XR, CT or MRI |
|                   | No change in blastic lesion on XR, CT or MRI |
|                   | No new lesion on XR, SS, CT or MRI |
| Progressive Disease | Increase in size of any existing measurable lesions on XR, CT or MRI |
|                     | New lesion on XR, SS, CT or MRI (exclude flares) |
|                     | Increase in activity on SS (exclude flares) or blastic/lytic lesion on XR or CT |

# Imaging diagnosis of bone metastasis

<table>
<thead>
<tr>
<th>Diagnostic imaging</th>
<th>Pros</th>
<th>Cons</th>
<th>Examination order and purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS</td>
<td>High sensitivity (62-100%) Whole body</td>
<td>No anatomic detail Low specificity</td>
<td>1: Screening</td>
</tr>
<tr>
<td>XR</td>
<td>Bone anatomic detail Low cost</td>
<td>Low sensitivity (44-50%) Local bone image</td>
<td>2: Diagnosis</td>
</tr>
<tr>
<td>CT</td>
<td>High sensitivity (71-100%) Bone and tumor anatomic detail</td>
<td>Local image</td>
<td>3: Diagnosis</td>
</tr>
<tr>
<td>MRI</td>
<td>High sensitivity (82-100%)</td>
<td>Local image</td>
<td>3: Diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low cost</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No signal in bone</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>High cost ($1700 for total spine)</td>
<td></td>
</tr>
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</table>
Algorithm for Bone Metastasis

Obtain XR, CT, PET/CT or MRI as a baseline before initiating treatment

Metastatic Disease

Positive
- Multiple focal typical (randomly distributed) lesions
- Multiple atypical lesions
- Solitary lesion (or small number)
- Diffuse involvement
- Photon-deficient lesion

Or Negative
- With symptoms
  - (+) metastatic disease demonstrated

No Metastatic Disease

Negative
- No symptoms
- No lesions
- Typical non-metastatic lesions

Confirmation of benign process that explains findings and symptoms

No Metastatic Disease

(+)

XR

(+)

MR

PET/CT

CT

MR

PET/CT

a These lesions can be diagnosed as "metastatic disease". However, XR images are needed as a baseline for future assessment of bone tumor response and complications like pathologic fracture.
b Can be caused by metabolic disease (osteoporosis, Cushing's syndrome, osteomalacia), trauma, arthritis, inflammatory disease (osteomyelitis), Paget's disease, or infarction.
c Bone biopsy may be required for confirmation.
d CT is indicated for lesions in weight-bearing, chest-wall or complex structure bones, and MRI is indicated for spinal lesions.
We continue to improve our ability to assess Tumor Response in Bone Metastasis

Due to Imaging Technology
Due to Response Criteria
Causes of Cancer Treatment Induced Bone Loss (CTIBL)

- Aromatase inhibitors (Breast & Ovarian Cancers)
- Chemotherapy (All Cancers)
- Corticosteroids (BMT, Multiple Myeloma, Leukemia)
- GnRH agonists (Breast & Prostate Cancers)
- Radiotherapy (All Cancers)
- Bone Loss

- Bilateral Oophorectomy, orchietectomy (Breast, Prostate, & Ovarian Cancers)

BMD

- BMD is compared with “young normal” (optimal or peak density of a 30-year-old healthy adult)
- Standard deviation (SD): the difference between patient’s BMD and that of a healthy young adult
  - For every 1 SD decrease, there is a relative risk of fracture increase of 1.5- to 2.5-fold

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>T Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt;-1</td>
</tr>
<tr>
<td>Low bone mass (Osteopenia)</td>
<td>-1 to -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>≥-2.5</td>
</tr>
<tr>
<td>Severe osteoporosis</td>
<td>≥-2.5 and ≥1 fracture</td>
</tr>
</tbody>
</table>

Relative Potency of Bisphosphonates

Potency relative to pam disodium in vivo (hypercalcemic rat)

- Tiludronate: 0.041
- Pamidronate: 0.051
- Clodronate: 1.0
- Alendronate: 2.77
- Olpadronate: 7.44
- Ibandronate: 35.9
- Risedronate: 43.6
- Zoledronic acid (ZA): 847

Treatment of Bone Loss

- Bisphosphonates
  - Alendronate (Fosamax) Oral
  - Risedronate (Actonel) Oral
  - Pamidronate (Aredia) IV
  - Zoledronic acid (Zometa) IV
  - Ibandronate
  - Clodronate

- In randomized clinical trials, bisphosphonates have achieved greater increases in BMD than other treatments.
Summary and Conclusions

- Cancer treatments cause bone loss in women and men
- Bone loss is associated with an increase risk of fracture and can be identified early
- Bone complications are debilitating, painful and negatively impact on QOL
- Zoledronic acid prevents bone loss and increase BMD
- Further study with zoledronic acid will optimize treatment strategies to protect bone
Need to recognize bone loss is a major problem in cancer treatment

If you are going to control or cure cancers for long-term, you need to think about bone loss prevention
Some thoughts

- Can we cure bone only metastatic disease?
  - Oligometastasis
  - Multiple bone metastasis

- Can we develop drugs that target bone metastasis?
  - Mechanism
  - Potential new drugs
Background of Oligo bone metastasis

- **Initial presentation**, about 18% of breast cancer patients had disease only in the bone. Survival is better in patients with bone only disease:
  - bone only H.R. 1.0;
  - bone & other organs H.R. 1.4,
  - other organs initially H.R. 2.5, p < 0.001

- **Solitary metastasis** in 20-40% of patients with bone only disease
  - The spine and sternum were common sites
  - 5 year survival
    - Initial solitary bone (with or without other organ metastasis) : ~38%
    - multiple bone metastases: ~20%
  - ~ 56% eventually develop additional bone metastasis.

Solitary vs Multiple Bone Metastasis

Treating Oligo-metastasis

Study Schema: Initial Evaluation

Whole body:
- skeletal scintigraphy (Whole body bone scan)

Oligo-Metastases Site:
- Magnetic resonance imaging
- SPECT-CT
- Radiography (plain X-ray)

Rule out other distant metastasis:
- PET-CT

Biopsy
Treating Oligo-metastasis
Study Schema: Treatment Plan

Evaluation by:
Multidisciplinary Clinic
1. Orthopedic Surgeon
2. Radiation Oncologist
3. Medical Oncologist
4. Radiologist

Definitive Surgical Resection
Surgical Fixation and RT
Definitive Radiation Therapy

Follow-up at 1 M, then q3M:
1. MRI
2. PET-CT

Determine the PFS after definitive local therapy

CTV 45 Gy (3 Gy x 15 fx) + GTV 60 Gy (3 Gy x 20 fx)
27 Gy (9 Gy x 3 fx) allowed for vertebrae only

• No Chemotherapy
• Give endocrine therapy and trastuzumab in appropriate patients
Phase II Study of $^{153}\text{Sm-EDTMP}$ Followed by Autologous Peripheral Blood Stem Cell Transplantation for Breast Cancer Patients with Bone Only Metastases (2006-0349)

- $^{166}\text{Ho-DOTMP}$, 2 out of 6 pt had no progression for > 5 y, minimum toxicities
- Eligibility: bone only metastatic breast cancer
- Treatment: $^{153}\text{Sm-EDTMP}$ with autologous stem cell transplant
- Eradication of bone only disease by high-dose radiation targeting only the bone
Some thoughts

- Can we cure bone only metastatic disease?
  - Oligometastasis
  - Multiple bone metastasis

- Can we develop drugs that targets bone metastasis?
  - Mechanism
  - Potential new drugs
What Is Denosumab?

• Fully human monoclonal antibody
  – Lower risk of allergic reactions
  – Stable PK profile

• IgG₂

• High affinity for human RANK ligand
  – Kd 3 x 10⁻¹² M

• Does not bind to TNFα, TNFβ, TRAIL, or CD40L
Bone Resorption is Dependent on RANKL

RANKL is the primary mediator of osteoclast formation, function and survival

- CFU-M = colony forming unit macrophage
- Pre-Fusion Osteoclast
- Multinucleated Osteoclast
- Activated Osteoclast

Growth Factors, Hormones, Cytokines

Denosumab Mechanism of Action

Denosumab inhibits osteoclast formation, function and survival

- **Osteoblast**
- **Osteoclast**
- **Growth Factors**
- **Hormones**
- **Cytokines**

**Key Molecules**
- **denosumab**
- **OPG**
- **RANKL**
- **RANK**

**Bone**
- **CFU-M**
- **Pre-Fusion Osteoclast**
- **Multinucleated Osteoclast**
- **Mature Osteoclast**
Summary

• Denosumab is a fully human monoclonal antibody to RANK Ligand
• RANK Ligand is essential for osteoclast formation, function, and survival
• Denosumab inhibits osteoclast bone resorption in osteoblastic and osteolytic tumors
• Denosumab in preclinical models prevented bone metastasis and delayed progression of established metastases in breast and prostate cancer
Rapamycin inhibitor
Minimal Bone Destruction in AP24170-Treated Mouse

AP24170 14 mg/kg qw

Left leg

Right leg

Minimal cortical lysis

No cortical lysis, but tumor evident

Rt leg

Small tumor deposits

Right leg
Osteolytic Bone Metastasis “Vicious Cycle”

- **Osteoclast**
  - TGFβ
  - Ca²⁺
  - c-Fms
  - M-CSF
  - RANKL
  - RANK

- **Osteoblasts**
  - PTHrP
  - IL-6
  - PGE₂

- **Tumor Cell**
  - Release of osteoclast-promoting factors
  - EGFR
  - MMP-9
  - MMP-2

- **Bone**

- **Osteoclast precursors**

- **Osteoblasts**
Opportunities and Challenges

- Need for standardization of care to all research-driven clinical care
- Mechanism-based preclinical research
  - More potent bisphosphonates
  - More targeted specific drugs
  - Need for preclinical model
- Bone, homing ground for bad cancer cells?
- Prevention of recurrence?
- Improved imaging and response criteria?
- Need for Multidisciplinary approach
Acknowledgment

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It takes a team to take care of bone-related problems.

Thank you!

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