Management of Bone Disease and Supportive Care

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Effects of Myeloma

Low Blood Counts

Bone Damage

Decreased Kidney Function
Bone Disease

- 85% of patients
- Bone pain and fractures
  - A result of lesions (weakening of the bone) adjacent to a large cluster of myeloma cells
- Bone destruction caused by:
  - Growth of myeloma cells that push aside normal bone-forming cells
  - Increased activity of osteoclasts (cells that normally break down old or damaged bone)

Bone Structure
Bone Remodeling: A Balance

Bone Resorption
(Osteoclasts remove bone)

Bone Formation
(Osteoblasts build bone)

Adults ‘replace’ their skeleton ~ every 7 years via remodeling

Normal Bone Remodeling is Coupled
Normal Bone Remodeling is Coupled

Bone Density Throughout Life
Normal Bone (age 20-50) | Osteoporosis (age 60+)
---|---
[Image of normal bone] | [Image of osteoporosis]

**Myeloma Bone Disease**

Why does bone loss occur in myeloma?
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’

- For ‘seed’ myeloma cells, this ‘soil’ is bone

- Lytic lesions occur adjacent to myeloma cells

Bone Marrow Microenvironment

- Myeloma cells
- Osteoclasts (Bone-resorbing cells)
- Bone
Bone Disease

Circular Network of Cells Lead to Bone Destruction

Myeloma cells \[\rightarrow\] Osteoclast \[\rightarrow\] Bone marrow stroma \[\rightarrow\] Osteoblast

Myeloma Bone Disease of the Spine

- Spine lesions are particularly common and problematic in patients with multiple myeloma
- Painful
- Loss of height due to collapse of bones
  - Bones can heal but height doesn’t return
  - Change in posture
    - Puts pressure on remaining bones, discs
  - Lack of room for lungs
    - Shortness of breath, pneumonia


STIR MRI Patterns at Diagnosis

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse</td>
<td>33%</td>
</tr>
<tr>
<td>Heterogeneous</td>
<td>33%</td>
</tr>
<tr>
<td>Focal</td>
<td>33%</td>
</tr>
<tr>
<td>Normal</td>
<td>&lt;5%</td>
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</tbody>
</table>
Clinical Consequences of Myeloma Bone Disease

- Pathological fractures
  - Non-vertebral
  - Vertebral compression
- Spinal cord compression/collapse
- Radiation therapy
- Surgery to bone
- Hypercalcemia
- Bone pain
- Use of analgesics
- Quality-of-life effects
- Survival

*SREs - skeletal-related events

Management Strategies

- Surgical procedures
  - Vertebroplasty
  - Balloon Kyphoplasty
- Radiotherapy
- Bisphosphonates
  - Aredia, Zometa

Treatment of myeloma
Vertebroplasty


Balloon Kyphoplasty: A Minimally Invasive Fracture Reduction Procedure

**KyphX Introducer Tool Kit:**
- Allows precise, minimally invasive access to the vertebral body.
- Provides working channel

**KyphX IBT inflation:**
- Reduces the fracture.
- Compacts the bone.
- May elevate endplates

**KyphX IBT Removal:**
- Leaves a defined cavity and trabecular dam that can be filled with an approved bone void filler of the physician’s choice
Tumor-Related VCFs
Balloon Kyphoplasty Procedure

- Minimally invasive
  - Bilateral, 1 cm incisions
- Typically one hour per treated fracture
- General or local anesthesia (supplemented by conscious sedation)
  - Among 155 elderly patients with osteoporosis and VCFs in prospective Kyphon U.S. study, only 1 complication was related to anesthesia.¹
- May require an overnight hospital stay

Lieberman and Reinhardt Study
Parameters

- 63 patients with osteolytic collapse
  - 52 with multiple myeloma
  - 11 with osteolytic metastases
- 264 vertebral bodies treated with kyphoplasty
- Mean follow-up
  - 18 weeks in multiple myeloma patients
  - 3 weeks in patients with metastases

**Lieberman and Reinhardt Study**

*Myeloma Patient Outcomes*

![Visual Analog Scale](chart.png)

Mean Self-Rated Pain (0 to 10)

- pre-op: 6.18
- post-op: 2.84

0 = no pain


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**Radiation Therapy**

- **Useful in specific situations**
  - Pain control
  - Prevent impending fracture
  - Spinal Cord Compression
  - Solitary Plasmacytomas

- **Can delay treatment of the rest of the body**

- **May injure healthy bone marrow**

- **Best to use sparingly**
Bisphosphonates
(Medicine to prevent bone problems)

Approved for Multiple Myeloma

- Pamidronate (Aredia®)
- Zoledronic Acid (Zometa®)

- Reduce activity of cells responsible for bone destruction (osteoclasts)
  - Prevents development
  - Induces osteoclast cell death
  - Reduces production of substances that stimulate MM activity
- Possible direct effect against myeloma cell growth

Bisphosphonates

Pamidronate: Reduces Bone Complications

Pamidronate compared to Placebo

- Reduced pain people experienced by 40%
  - TOOK 3 MONTHS TO NOTICE A DIFFERENCE
- Cut the chance to develop a bone problem by 40%
  - Fracture, Need for Radiation, Need for surgery
  - TOOK 6 MONTHS TO NOTICE A DIFFERENCE
- TAKES TIME TO WORK
- DIDN’T STOP THINGS COMPLETELY
- NOT PERFECT

Bisphosphonates
Why Not a Pill, Why so much

- Poorly absorbed when swallowed
  - ONLY 1-2% of drug swallowed makes it into the bloodstream
    - Enough to treat osteoporosis
    - Likely not enough to stop damage from myeloma
- 50% gets urinated out - rest stays in bone for years
  - Builds up
    - Took 3 months to decrease bone pain
    - Took 6 months to reduce chance of fractures
- Doesn’t get into bones evenly
Bisphosphonates

- Side effects
  - Flu like symptoms (fever), bone pain when first given IV
    - Symptoms diminish with further use
  - Doses intravenously over 1 mg per minute can be harmful to kidneys
    - Pamidronate 90 mg over 2 hours
    - Zoledronic Acid 4 mg over 15 minutes
  - Can stop healing of infected bone
    - Osteonecrosis of jaw
  - ? Brittle bones with long-term use

Bisphosphonate Backbone

<table>
<thead>
<tr>
<th></th>
<th>R₁</th>
<th>R₂</th>
<th>Relative in vivo potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etidronate</td>
<td>OH</td>
<td>– CH₃</td>
<td>1</td>
</tr>
<tr>
<td>Clodronate</td>
<td>Cl</td>
<td>– Cl</td>
<td>10</td>
</tr>
<tr>
<td>Tiludronate</td>
<td>H</td>
<td>– S – ☐ – Cl</td>
<td>10</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>OH</td>
<td>–(CH₂)₂ – NH₂</td>
<td>100</td>
</tr>
<tr>
<td>Alendronate</td>
<td>OH</td>
<td>–(CH₂)₃ – NH₂</td>
<td>1,000</td>
</tr>
<tr>
<td>Risedronate</td>
<td>H</td>
<td>–CH₂ – ☐ N</td>
<td>5,000</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>OH</td>
<td>(CH₂)₂·N·(CH₂)₄·CH₃</td>
<td>10,000</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>OH</td>
<td>H</td>
<td>100,000</td>
</tr>
</tbody>
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Breast Cancer and Multiple Myeloma

Zoledronic acid not enough better to say it is superior

Unanswered Questions

- Duration of studies = 2 years
  - How much is enough?
    - Inconvenient
  - Still needed if in remission?
    - Works best as prevention not as a fix for a weak bone
  - Problems with long term use?
    - ONJ risk increases
      - Keep teeth in good shape
  - Markers to decide on amount needed
    - Urine NTX measures whole body bone breakdown
MRC Myeloma IX—
Analysis Schematic for ZOL vs CLO

1960 Myeloma Patients
NEWLY DIAGNOSED

Zoledronic acid (4 mg IV)
Every 3-4 weeks

Clodronate (1,600 mg/d PO)
Every DAY

Treatment continued at least until disease progression

MRC Myeloma IX—
ZOL Significantly Reduced SREs vs CLOa

24% relative reduction

P = .0004

Abbreviations: CLO, clodronate; SRE, skeletal-related event; ZOL, zoledronic acid.

a SREs were defined as vertebral fractures, other fractures, spinal cord compression, and the requirement for radiation or surgery to bone lesions or the appearance of new osteolytic bone lesions.
### MRC Myeloma IX—
ZOL Improved OS and PFS vs CLO\(^a\)

- ZOL significantly reduced the relative risk of death by 16% vs CLO
  (IMPROVED MEDIAN SURVIVAL BY 5.5 MONTHS)

<table>
<thead>
<tr>
<th></th>
<th>Risk reduction</th>
<th>(P) value</th>
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</thead>
<tbody>
<tr>
<td>OS</td>
<td>16%</td>
<td>.0118</td>
</tr>
<tr>
<td>PFS</td>
<td>12%</td>
<td>.0179</td>
</tr>
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**Abbreviations:** CI, confidence interval; CLO, clodronate; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; ZOL, zoledronic acid.

\(^a\) Cox model adjusted for chemotherapy, and minimization factors.

### MRC Myeloma IX—
Adverse Events (Safety Population)

<table>
<thead>
<tr>
<th></th>
<th>Intensive pathway</th>
<th>Non-intensive pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZOL</td>
<td>CLOD</td>
</tr>
<tr>
<td><strong>Acute renal failure</strong></td>
<td>5.2%</td>
<td>5.9%</td>
</tr>
<tr>
<td><strong>ONJ(^b)</strong></td>
<td>3.8%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

**Abbreviations:** CLO, clodronate; ONJ, osteonecrosis of the jaw; SAE, serious adverse event; ZOL, zoledronic acid.

\(^a\) Statistical significance determined by Fisher’s exact test.

\(^b\) ONJ cases were confirmed by an independent adjudication committee.
Osteonecrosis of the Jaw (ONJ): Clinical Presentation

Clinical Features of Suspected ONJ
- Exposed bone in maxillofacial area that occurs in association with dental surgery or occurs spontaneously, with no evidence of healing*

Working Diagnosis of ONJ
- No evidence of healing after 6 weeks of appropriate evaluation and dental care
- No evidence of metastatic disease in the jaw or osteoradionecrosis

*Refer for appropriate dental evaluation and care as soon as possible.

Osteonecrosis of the Jaw

Pathophysiology
- Jaw is susceptible to infection
  - Direct exposure to mouth flora following tooth extraction
- Mandible and maxilla are generally bisphosphonate seeking bones
  - Continued wear and tear from chewing action
  - Increase in skeletal turn over
  - Higher levels of bisphosphonates resulting in marked osteoclast inhibition
- Infected bone not readily cleared by osteoclasts resulting in chronic infections
Minimizing the Risk of Jaw Osteonecrosis

- Excellent oral hygiene is the best prophylaxis
- Limit alcohol and tobacco use
  - Dry mouth
- Patients starting IV BPs should be evaluated by a dentist first
  - Dental procedures (extraction or implants) should be done prior to starting IV BPs if possible
- Avoid invasive dental procedures after starting IV BPs
- If extraction is necessary
  - Hold bisphosphonates temporarily
  - Consider the use of prophylactic antibiotics

Mechanism of Action for Denosumab

Adapted from Boyle WU, et al. Minerva. 2002;423:317-42
**Denosumab**

- Given monthly by subcutaneous shot
- Denosumab compared to Zoledronic Acid in large randomized trial of patients with Breast Cancer and Myeloma
  - Approximate 15% reduction in skeletal bone events in denosumab group
  - Survival similar in the Breast Cancer + Myeloma groups as a whole
    - Survival trended worse for MM patients
  - ONJ risk about the same
  - Less flu like reactions with denosumab

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**Advances in the Treatment of Myeloma Bone Disease (Summary)**

- Prevention is best!
  - Control of the myeloma
  - Ambulation
  - Bisphosphonates
    - Side effects can be lessened
      » Good oral hygiene, no extractions
      » Prolong infusion times, be hydrated when given
      » ? Break in treatment, give less often after 2 years
      » ? Urine NTX to guide treatment
  - New drugs on horizon (Denosumab)
  - Vitamin D (often low)
    - Radiation Therapy
    - Vertebroplasty
    - Kyphoplasty
Low Blood Counts

- Low red blood cells often results in anemia
- Low levels of infection-fighting white blood cells (neutropenia) can lead to infection
- Low levels of platelets (thrombocytopenia) can cause blood clotting problems/easy bruising

Anemia

- Present in 60% of patients at diagnosis
- Symptoms:
  - Fatigue
  - Difficulty breathing
  - Rapid heartbeat
  - Dizziness
  - Depression/mood changes
  - Weight loss
  - Nausea
  - Difficulty sleeping
- Low levels of iron, folate, and vitamin B-12 can also cause anemia
- Treatment:
  - Identify and treat causes other than myeloma
  - If needed: iron, folate, vitamin B12 supplements
  - Moderate anemia: medications to increase number of red blood cells (Procrit, Epogen Aranesp)
  - Severe anemia: blood transfusions
### Infection Resulting from Low White Blood Cells

#### Preventing infection
- Vaccination (pneumonia, flu)
- Treatment with antibodies such as intravenous immunoglobulin IgG
- Antifungal medications and preventive herpes, in some cases

#### Treatment
- Medications to stimulate production of white blood cells (Leukine, Neupogen, Neulasta)
- Antibiotics to treat infections
- Antifungal medications, if needed for fungal infections

### Decreased Kidney Function

#### Detection
- Decreased amount of urine is one sign
- Blood test: increase in creatinine and other proteins

#### Other causes beside myeloma
- Hypertension
- Diabetes
- Some medications

#### Treatment
- Fluids
- Avoid NSAIDs: non-steroidal anti-inflammatory drugs such as Aleve (naproxen), Advil/Motrin (ibuprofen)
- Treat other causes
- Dialysis (severe)
Summary: Supportive Care for Patients with Multiple Myeloma

- Various approaches are used to reduce the impact of common multiple myeloma complications
  - Bone damage/loss
  - Anemia
  - Infection due to low white blood counts
  - Reduced kidney function

Partner with your healthcare team to determine the best management plan for you

Updated Recommendations from the IMWG

International Myeloma Working Group Recommendations for the Treatment of Multiple Myeloma–Related Bone Disease