Advances in the Biology and Treatment of Myeloma Bone Disease

G. David Roodman MD PhD
Indiana University
Oct. 22, 2015
## Relationship between primary molecular cytogenetic abnormalities and specific CRAB feature at diagnosis

<table>
<thead>
<tr>
<th>FISH abnormality</th>
<th>Overall (n=484)</th>
<th>Hypercalcemia (n=59)</th>
<th>Renal insufficiency (n=98)</th>
<th>Anemia (n=242)</th>
<th>Bone disease (n=336)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy (ies) without IgH abnormality</td>
<td>201 (42%)</td>
<td>26 (44.1%)</td>
<td>33 (33.7%)</td>
<td>100 (41.3%)</td>
<td>146 (43.5%)</td>
</tr>
<tr>
<td>IgH abnormality without trisomy (ies)</td>
<td>146 (30%)</td>
<td>21 (35.6%)</td>
<td>44 (44.9%)</td>
<td>84 (34.7%)</td>
<td>95 (28.3%)</td>
</tr>
<tr>
<td>t(11;14)</td>
<td>74 (15%)</td>
<td>7 (11.9%)</td>
<td>16 (16.3%)</td>
<td>38 (15.7%)</td>
<td>52 (15.5%)</td>
</tr>
<tr>
<td>t(4;14)</td>
<td>28 (6%)</td>
<td>7 (11.9%)</td>
<td>10 (10.2%)</td>
<td>18 (7.4%)</td>
<td>18 (5.4%)</td>
</tr>
<tr>
<td>t(14;16)</td>
<td>19 (4%)</td>
<td>3 (5.1%)</td>
<td>9 (9.2%)</td>
<td>15 (6.2%)</td>
<td>10 (3.0%)</td>
</tr>
<tr>
<td>t(14;20)</td>
<td>1 (&lt;1%)</td>
<td>0 (0.0%)</td>
<td>1 (1.0%)</td>
<td>1 (0.4%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Unknown partner/deletion of IgH region</td>
<td>24 (5%)</td>
<td>4 (6.8%)</td>
<td>9 (9.2%)</td>
<td>13 (5.4%)</td>
<td>15 (4.5%)</td>
</tr>
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<td>IgH abnormality with trisomy (ies)</td>
<td>74 (15%)</td>
<td>6 (10.2%)</td>
<td>7 (7.1%)</td>
<td>33 (13.6%)</td>
<td>47 (14.0%)</td>
</tr>
<tr>
<td>t(11;14)</td>
<td>12 (3%)</td>
<td>1 (1.7%)</td>
<td>1 (1.0%)</td>
<td>5 (2.1%)</td>
<td>7 (2.1%)</td>
</tr>
<tr>
<td>t(4;14)</td>
<td>19 (4%)</td>
<td>2 (3.4%)</td>
<td>2 (2.0%)</td>
<td>11 (4.5%)</td>
<td>10 (3.0%)</td>
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<tr>
<td>t(14;16)</td>
<td>5 (1%)</td>
<td>0 (0.0%)</td>
<td>1 (1.0%)</td>
<td>4 (1.7%)</td>
<td>3 (0.9%)</td>
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<td>3 (&lt;1%)</td>
<td>0 (0.0%)</td>
<td>1 (1.0%)</td>
<td>1 (0.4%)</td>
<td>2 (0.6%)</td>
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<td>Unknown partner/deletion of IgH region</td>
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<td>3 (5.1%)</td>
<td>2 (2.0%)</td>
<td>12 (5.0%)</td>
<td>25 (7.4%)</td>
</tr>
<tr>
<td>Monosomy 14 in absence of IgH translocations or trisomy (ies)</td>
<td>22 (4.5%)</td>
<td>2 (3.4%)</td>
<td>4 (4.1%)</td>
<td>9 (3.7%)</td>
<td>17 (5.1%)</td>
</tr>
<tr>
<td>Other cytogenetic abnormalities in absence of IgH translocations or trisomy (ies) or monosomy 14</td>
<td>26 (5.5%)</td>
<td>3 (5.1%)</td>
<td>5 (5.1%)</td>
<td>10 (4.1%)</td>
<td>18 (5.4%)</td>
</tr>
<tr>
<td>Normal</td>
<td>15 (3%)</td>
<td>1 (1.7%)</td>
<td>4 (4.1%)</td>
<td>5 (2.1%)</td>
<td>12 (3.6%)</td>
</tr>
</tbody>
</table>

Abbreviations: FISH, fluorescence in situ hybridization; IgH, immunoglobulin heavy chain.
Possible Myeloma from Nubia, ca. 200 AD
Bone Remodeling is Uncoupled in MM

Treatment of MM Bone Disease

- Bisphosphonates
- Surgical procedures
  - Vertebroplasty
  - Balloon Kyphoplasty
- Radiotherapy
- Treatment of myeloma
Bisphosphonate Therapy in Myeloma

- Bisphosphonates (pamidronate and zoledronic acid) decrease pain and minimize bone-related complications
  - Use in all patients with symptomatic myeloma, regardless of documented bone disease[1]
  - Zoledronic acid has been reported to increase OS in the Myeloma IX trial[2]
  - Monitor for renal dysfunction
  - Monitor for osteonecrosis of the jaw
  - Monitor vitamin D levels; consider vitamin D and calcium supplements

Fracture Incidence in Myeloma Patients

**Melton et al. JBMR 20:487, 2005**

**Terpos E, Blood 122,2013 abstract**

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### Fracture Incidence in Myeloma Patients

**Diagnosis**

- **Osteolytic Disease**: 284/400 (71%) during 1st Rx
- **SREs**: 167 (26%) during 1st Relapse
- **Fractures**: 104 (26%) during 1st Relapse
- **Surgery**: 21 (5.5%)
- **XRT**: 21 (5.2%) during 1st Relapse

<table>
<thead>
<tr>
<th></th>
<th>During 1st Rx</th>
<th>1st Relapse</th>
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<td>Osteolytic Disease</td>
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<td>7 (1.8%)</td>
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<tr>
<td>Fractures</td>
<td>104 (26%)</td>
<td>3/176 (1.7%)</td>
</tr>
<tr>
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<td>21 (5.5%)</td>
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<tr>
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<td>21 (5.2%)</td>
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</tbody>
</table>

*Rx: Imid-43%, Bort-20%, VTD/RVD-28%, other-9% 369/400 BP treated. Median F/u 39 m*
Myeloma Bone Disease

Myeloma cells

Tumor-derived osteoclast activating factors
- Macrophage inflammatory protein 1α
- Interleukin-3

(+) (+) (−)

Stromal cells
- RANKL
- Interleukin-6

Tumor-derived osteoblast inhibitory factors
- DKK1, IL3, sFRP2, IL-7, TNF
- Sclerostin

Osteoclasts
Osteoblasts
Bone
Osteocytes
Activin A

Randomized double-blind study of Denosumab versus Zol in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma

- Human monoclonal antibody that binds RANKL
- Inhibits formation and activation of osteoclasts
- Denosumab was non-inferior to Zol in delaying time to first SRE on study
- Overall survival for all patients similar, but inferior for MM subgroup
- ONJ rates similar
- Hypocalcemia more frequent with denosumab

Henry, DH et al, JCO 29:1125, 2011
Issues with BP or Denosumab

- Osteonecrosis of the jaw
- Decrease skeletal events but patients still progress at slower rate
- Do not induce new bone formation or repair lytic lesions.
Optimal Therapy for Myeloma Bone Disease

Targeting both

- Myeloma Cells
- Increased osteoclast activity/formation and osteoblast suppression
Osteoblast Inhibitors in Myeloma


Soluble factors
- Dkk-1
- Sclerostin
- sFRP-2
- sFRP-3
- TNF-α
- IL-3
- IL-7

Direct cell-cell contact
- Notch
- Integrin

Osteoblasts
- MM cells
- MSCs

Osteoclasts
- MIP-1α
- MIP-1β
- RANKL
- TNF-α
- IL-3
DKK1 and sFRP-2 in Myeloma Bone Disease

- Inhibitors of the WNT signaling pathway
- WNT signaling is a critical pathway for OBL differentiation
- Secreted by myeloma cells
- Marrow plasma from patients with high levels of DKK1 or sFRP-2 inhibit murine OBL differentiation
- DKK1 gene expression levels correlated with extent of bone disease in MM patients

Anti-DKK1 Increases Bone Formation in the SCID-Rab Multiple Myeloma Model


BMD, bone mineral density
Phase I/II Study of BHQ880, an Anti-DDKK1 Human Monoclonal Antibody, in Relapsed/Refractory MM Patients Treated with Zoledronic Acid and Anti-Myeloma Therapy and a Phase II Study in Smoldering Myeloma Have Been Completed.
Activin stimulates osteoclasts, leading to increased bone resorption.

Activin inhibits osteoblasts, resulting in reduced bone formation and decreased bone mineral density and strength.

Activin decreases bone mineral density and strength.
IL-3 induces Osteoclasts via Activin A


“Phase II Study of Sotatercept (Activin A Receptor Antagonist) on bone mass and turnover in patients with multiple myeloma”
RAP-011 Prevents Development of Myeloma Bone Lesions

Normal Mice  Mice + tumor  Mice + tumor + RAP-011

Croucher et al. 2007 X1th International Myeloma Workshop
Phase IIA Sotatercept Study in Myeloma

Maximum percent change from baseline in bALP by use of bisphosphonates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo ($n = 6$)</th>
<th>0.1 mg/kg ($n = 8$)</th>
<th>0.3 mg/kg ($n = 8$)</th>
<th>0.5 mg/kg ($n = 8$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No bisphosphonates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n$</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>bALP, max. mean change from baseline (%)</td>
<td>39·2</td>
<td>22·7</td>
<td>36·9</td>
<td>104·4</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n$</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>bALP, max. mean change from baseline (%)</td>
<td>25·6</td>
<td>348·5</td>
<td>11·3</td>
<td>6·6</td>
</tr>
</tbody>
</table>

bALP, bone-specific alkaline phosphatase.
OBL Suppression in Myeloma

What is the mechanism(s) responsible for long term osteoblast suppression in myeloma?
OBL differentiation by stromal cells from MM-injected mice is suppressed

Saline

No injection

5TGM1

Runx2

Fold change

Reg media

Differentiating media

Multiple putative Gfi1 binding sites [AA(T/G)C] are located on this portion of the Runx2 promoter, a master gene for osteoblast differentiation.

Gfi1 is a transcriptional repressor that recruits histone modifying enzymes and co-repressors to target genes.

Since Gfi1 can modify chromatin structure, Gfi1 is a good candidate to serve as a long-term Runx2 repressor.
Gfi-1 is upregulated in stromal cells from MM patients

GFI1 knockdown increased Runx2, Ocn, and Bsp mRNA in MM patient BMSC

Gfi-1 Repression of the Runx2 Promoter is Independent of the Normal DNA Binding Site and Requires HDAC Activity
Adhesive Interactions Increase Myeloma Growth, Chemoresistance and Bone Destruction
Multiple Signaling Pathways Are Activated via p62 in the MM Microenvironment
p62 Acts as a Platform for Formation of Multiple Signaling Complexes
XRKF2

MW: 363.5
**Summary**

- **p62-ZZ Antagonist**
  - MM Viability
  - OCL Formation
  - Hematopoietic Cell Growth: No Effect
  - Stromal Cell Growth: No Effect
  - VCAM-1 Expression
  - IL-6 Production
  - PKCζ/NF-κB Signaling
  - p38MAPK Signaling: No Effect

Teramachi J et al, Leukemia. 2015 Aug 19
XRKF2 Treatment Protocol

5TGM1-GFP cells (murine) → Stratification by Tumor Burden → IP 5days/week

C57BL/KaLwRij (immunocompetent) → Vehicle → XRFK2 → Outcomes

Time: 0 → Week 2 → Week 4 → Week 6

Outcomes:
- IgG_{2b}
- Toxicity
- PK
- μQCT
- X-ray
- Histology

Teramachi J et al, Leukemia. 2015 Aug 19
XPK3 Induces Dramatic New Bone Formation in Myeloma Bearing Bones

IT tumor + Vehicle
Contralateral tibia + XPKF2
IT tumor + XPKF2
Histology of Bones from p62-ZZ Antagonist Treated Mice

Teramachi J et al, Leukemia. 2015 Aug 19
Bortezomib / Lenalidomide in MBD

Roodman GD JCI 2008 118:462-4
Novel Approaches for MM Bone Disease

<table>
<thead>
<tr>
<th>Target</th>
<th>Potential Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>RANKL</td>
<td>Denosumab</td>
</tr>
<tr>
<td>MIP-1 alpha</td>
<td>CCR1 Receptor antagonist</td>
</tr>
<tr>
<td>DKK1/sFRP-2</td>
<td>Anti-DKK1, Bortezomib</td>
</tr>
<tr>
<td>Activin A</td>
<td>ACE-011</td>
</tr>
<tr>
<td>Sclerostin</td>
<td>Anti-Sclerostin</td>
</tr>
<tr>
<td>GFI-1</td>
<td>HDAC1 inhibitors</td>
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</table>
Acknowledgements

L  Ehrlich          R  Silbermann
A  Huston          N  Giuliani
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D  DelPetre        S  Choi
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Y  Hiruma          F  Wang
J  Teramachi       J  Anderson
X  Xie             J  Eiseman
J  Beumer          J  Windle

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