Bisphosphonates in the Management of Myeloma Bone Disease

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Myeloma Bone Disease

Myeloma cells

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

(+) (++)

Osteoclast

Tumor-derived osteoblast inhibitory factors
- Dickkopf1
- IL-3
- sFRP2
- L-7

(-)

Stromal cells

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

Prevalence of Skeletal Complications in 21 months among MM Patients

- Total
- Pathologic fracture
- Radiation to bone
- Hypercalcemia of malignancy
- Surgery to bone
- Spinal cord compression

†9-month data.
‡Placebo arm of pamidronate randomized trial.
Results: Overall Survival

Clinical Consequences of Myeloma Bone Disease

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- Survival

*SREs- skeletal-related events

Berenson et al. Am J Hematol, in press
### Results

Predictors of Overall Survival from Time of MM diagnosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>n/N (%)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender = Female</td>
<td>129/300 (43%)</td>
<td>0.90 (0.51,1.60)</td>
<td>0.725</td>
</tr>
<tr>
<td>Race = White</td>
<td>230/300 (77%)</td>
<td>0.69 (0.36,1.32)</td>
<td>0.258</td>
</tr>
<tr>
<td>ISS Stage 2 or 3</td>
<td>135/300 (45%)</td>
<td>1.69 (0.97,2.94)</td>
<td>0.064</td>
</tr>
<tr>
<td>ISS Stage 3</td>
<td>50/300 (17%)</td>
<td>1.89 (0.91,3.91)</td>
<td>0.088</td>
</tr>
<tr>
<td>Calcium &gt; 10 mg/dL at diagnosis</td>
<td>66/294 (23%)</td>
<td>1.59 (0.84,3.03)</td>
<td>0.156</td>
</tr>
<tr>
<td>Creatinine &gt; 2 mg/dL at diagnosis</td>
<td>28/295 (9%)</td>
<td>3.35 (1.54,7.32)</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes</td>
<td>51/300 (17%)</td>
<td>1.17 (0.57,2.41)</td>
<td>0.677</td>
</tr>
<tr>
<td>History of Smoking</td>
<td>122/299 (41%)</td>
<td>0.80 (0.46,1.42)</td>
<td>0.450</td>
</tr>
<tr>
<td>History of Alcohol Use</td>
<td>83/299 (28%)</td>
<td>0.66 (0.33,1.33)</td>
<td>0.244</td>
</tr>
<tr>
<td>SRE (time dependent)</td>
<td></td>
<td>2.92 (1.64,5.22)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HR – Hazard Ratio, 95% CI – 95% Confidence Interval, P-value from Wald Chi-Square Test in Cox Regression

Berenson et al. Am J Hematol, in press

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### Reduced Multivariate Model for Survival in ZOL-Treated MM Patients—Continuous Variables

(Using inverse for Hgb)

- **Age (per 1-yr ↑)**
  - 1.03
- **Paraprotein vs IgG:**
  - IgA: 1.49
- **Prior SRE**
  - 1.93
- **NTX (per 100 ↑)**
  - 1.93
- **Hgb < 10**
  - 2.24

<table>
<thead>
<tr>
<th>Risk ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>4.0</td>
<td></td>
</tr>
</tbody>
</table>

Reduced risk of death | Increased risk of death

Terpos, Berenson, Cook, and Coleman, Leukemia, 2010
Bisphosphonates - inhibitors of bone loss
- potency varies greatly depending upon R1 & R2 side chains

<table>
<thead>
<tr>
<th></th>
<th>R1</th>
<th>R2</th>
<th>Relative 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 –(CH₂)₄ – CH₃</td>
<td>5,000</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>OH</td>
<td>(CH₂)₂N – (CH₂)₄ – CH₃</td>
<td>10,000</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>OH</td>
<td>–N –</td>
<td>100,000</td>
</tr>
</tbody>
</table>

Bisphosphonate Inhibition of Osteoclast Activity: Mechanism of Action

Bisphosphonates may modulate signaling from osteoblasts to osteoclasts
- Increased OPG production²
- Decreased RANKL expression³

Effect of Monthly Intravenous Pamidronate (90 mg) in Reducing Skeletal Events in Patients with Advanced Multiple Myeloma: A Phase III Trial

![Graph showing proportion of patients with skeletal events at 9 months and skeletal morbidity rate (events/year) at 9 months](image)


**Zoledronic Acid**

- Zoledronic acid belongs to a new class of highly potent bisphosphonates
  - Heterocyclic, nitrogen-containing bisphosphonate composed of:
    - A core bisphosphonate moiety
    - An imidazole-ring side chain containing 2 critically positioned nitrogen atoms

Zoledronic Acid in Multiple Myeloma and Breast Cancer Patients: Protocol 010 Trial Design

• 24-mo dosing regimen
  – Pamidronate 90 mg every 3 to 4 wk/120-min infusion
  – Zoledronic acid 4 mg and 8/4 mg
    • every 3 to 4 wk
    • 5-min amended to 15-min infusion
  – Double-blind, double-dummy
  – Study duration: 25 mo
• Patients received oral vitamin D 400 IU and calcium 500 mg

Breast Cancer and Multiple Myeloma Efficacy Summary

<table>
<thead>
<tr>
<th></th>
<th>Proportion with SRE, %</th>
<th>Time to first SRE (median)*</th>
<th>Mean skeletal morbidity rate*</th>
<th>Multiple-event analysis hazard ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zol acid 4 mg</td>
<td>47</td>
<td>376</td>
<td>1.04</td>
<td>0.841</td>
</tr>
<tr>
<td>Pam 90 mg</td>
<td>51</td>
<td>356</td>
<td>1.39</td>
<td>—</td>
</tr>
<tr>
<td>P value</td>
<td>.243</td>
<td>.151</td>
<td>.084</td>
<td>.030</td>
</tr>
</tbody>
</table>

*Hypercalcemia of malignancy is included as a skeletal-related event.
Zoledronic Acid 4 mg Infused over 15 minutes Compared to Pamidronate 90 mg Given over 2 hours Shows a Similar Time to First Serum Creatinine Increase in Breast Cancer and Multiple Myeloma

<table>
<thead>
<tr>
<th>Time, days†</th>
<th>Patients without increase, %</th>
<th>Zol 4 mg</th>
<th>Pam 90 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>272</td>
<td>268</td>
</tr>
<tr>
<td>120</td>
<td>80</td>
<td>226</td>
<td>213</td>
</tr>
<tr>
<td>240</td>
<td>60</td>
<td>197</td>
<td>182</td>
</tr>
<tr>
<td>360</td>
<td>40</td>
<td>152</td>
<td>138</td>
</tr>
<tr>
<td>480</td>
<td>20</td>
<td>81</td>
<td>73</td>
</tr>
<tr>
<td>600</td>
<td>0</td>
<td>68</td>
<td>59</td>
</tr>
<tr>
<td>720</td>
<td>0</td>
<td>30</td>
<td>27</td>
</tr>
</tbody>
</table>

†After start of study drug.

Other Measures to Reduce the Development of SREs

- Reduce the risk of falls
  - Decrease the risk/severity of neuropathy
  - Make home/work conducive to prevent
- Vitamin D
  - 800-1200 IU daily
  - Check levels in all patients
    - Approximately 1/3rd of MM patients are low
    - If low, supplement with more
- Calcium
  - 1,000 mg daily
Monoclonal Gammopathy of Undetermined Significance (MGUS)

• Definition:
  – Serum monoclonal protein ≤ 3 g/dL
  – < 10% plasma cells in the bone marrow
  – Absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the plasma cell proliferative process

• Incidence:
  – 3% of individuals over 50 years of age
  – 5% over 70 years of age

• Risk of bone-related problems:
  – Elevated rate of bone resorption
  – Increased prevalence of osteopenia/osteoporosis
  – Heightened risk of fractures especially vertebral compression fractures

Zoledronic Acid for Treatment of Cancer Patients w/o Metastatic Bone Disease

• Improves BMD for patients with cancer-treatment induced bone loss
  – Increased BMD in gonadotropin agonist-induced osteoporosis
    • Prostate CA without metastatic bone disease
    • Every 3 months at 4 mg
  – Increased BMD in women receiving aromatase inhibitor therapy for breast CA
    • Every 6 months at 4 mg

• Decreased mets and delay in disease progression in premenopausal breast CA in adjuvant setting
  – Every 6 months at 4 mg

• No agents studied to date for osteopenia/osteoporosis in MGUS
Phase II Study of Zoledronic Acid for MGUS Patients w/ Osteopenia/Osteoporosis

- MGUS patients w/ a T-score worse than -1 as verified by a DEXA scan either in L-spine or hip
- Treatment:
  - ZOL at 4 mg was administered IV over 15 minutes at 0, 6 and 12 months
- Efficacy:
  - DEXA scans and skeletal surveys were conducted at screening and one month after the final ZOL infusion (13 months)


### Evaluable Patient Responses

<table>
<thead>
<tr>
<th>Measure</th>
<th>Median Δ (Range)</th>
<th>% Improvement (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Δ L-spine T-score (Range), n=44</td>
<td>+0.30 (-0.38 - +3.91)*</td>
<td>+22% (-18% - +1140%)</td>
</tr>
<tr>
<td>% L-spine Improvement (Range), n=44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Δ Hip T-score (Range), n=44</td>
<td>+0.19 (-2.40 - +2.03)</td>
<td>+8% (-350% - +150%)</td>
</tr>
<tr>
<td>% Hip Improvement (Range), n=44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Δ Serum M-protein (Range), g/dl, n=54</td>
<td>0.00 (-2.50 - +2.10)</td>
<td></td>
</tr>
<tr>
<td>Patients with New Fractures, n=54</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Patients Progressing to Myeloma, n=54</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* P =
MGUS: Consensus Panel Recommendations

• Perform SPEP/UPEP
  – Age-inappropriate osteoporosis or osteopenia w/o additional risk factors
    • Premenopausal females
    • Males < 65 years of age

• MGUS patients
  – assess bone disease
    • Bone survey
    • If no evidence of bone disease, perform bone densitometry
  – If evidence of bone loss (T score < -1), treat
    • Zoledronic acid
    • Oral bisphosphonates

Berenson et al. Brit J Haematol 2010