The management of bone metastases: role of bisphosphonate

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The management of bone metastases: role of bisphosphonate

- Incidence of bone metastases
- Complication of bone metastases
- Patophysiology of bone metastases
- Bisphosphonate in breast cancer
- Recommendation
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# Incidence of bone metastases

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloma</td>
<td>95-100</td>
</tr>
<tr>
<td>Breast</td>
<td>65-75</td>
</tr>
<tr>
<td>Prostate</td>
<td>65-75</td>
</tr>
<tr>
<td>Thyroid</td>
<td>60</td>
</tr>
<tr>
<td>Bladder</td>
<td>40</td>
</tr>
<tr>
<td>Lung</td>
<td>30-40</td>
</tr>
<tr>
<td>Renal</td>
<td>20-25</td>
</tr>
<tr>
<td>Melanoma</td>
<td>14-45</td>
</tr>
</tbody>
</table>

Coleman RE. Cancer 1997;80:1599-94
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Complication of bone metastases

- Bone pain
- Hypercalcemia
- Pathologic fractures
- Nerve compression syndrome
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Pathophysiology of bone metastases
Pathophysiology of bone metastases

- Breast:
  - Clonal proliferation
  - Invasion of local tissue
  - Induction of angiogenesis

- Blood vessel:
  - CXCL12
  - CXCR4
  - Detachment
  - Migration and entry into circulation

- Target tissue or organ:
  - CXCL12
  - Binding of CXCL12 and migration to normal tissue with high CXCL12 levels
  - Tumor

- Tumor
Pathophysiology of bone metastases
Pathophysiology of bone metastases: 2 ways

- Osteolytic:
  - Most common way
  - Stimulated normal bone resorbing cells: osteoclast
  - Breast ca, lung ca, myeloma

- Osteoblastic:
  - Stimulated new bone formation: osteoblast
  - Prostate ca, breast ca (occasionally)
Osteolytic
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Bone metastases: bisphosphonate

- Anti resoptive drugs for the treatment of diseases arising from excess bone resorption
- Bisphophonate:
  - Nitrogen containing
  - Non nitrogen containing
## Bisphosphonate: mechanism of action

<table>
<thead>
<tr>
<th>Nitrogen containing (pamidronate, etidronate, ibandronate, zoledronate)</th>
<th>Non-nitrogen containing (clodronate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not metabolized within osteoclast</td>
<td>Metabolized within osteoclast</td>
</tr>
<tr>
<td>Inhibit protein prenylation within osteoclast</td>
<td>Do not inhibit protein prenylation</td>
</tr>
<tr>
<td>Gradually causes apoptosis of osteoclast</td>
<td>Rapidly causes apoptosis of osteoclast</td>
</tr>
<tr>
<td>Not anti-inflammatory</td>
<td>Anti-inflammatory</td>
</tr>
</tbody>
</table>
Bisphosphonate: break the Vicious cycle

- Adhesion: E-cadherin αvβ3
- TGF-β, IGF-1
- RANKL
- Bisphosphonates
- Tumor cells
- Stromal cells
- Osteoclast precursors
- Chemotherapy ↓ Estrogen
- Growth factors
Bisphosphonate in bone metastatic

• Rosen LS (2001):
  – Phase III randomized trial
  – 4 or 8 mg zoledronic acid vs 90 mg pamidronate every 3 to 4 weeks in multiple myeloma or breast ca with lytic disease
  – No difference of skeletal related events (46%-48% with zoledronic acid vs 49% with pamidronate)
Bisphosphonate in primary breast ca with bone metastase : clodronate 1600 mg/day PO

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>100 Open, Randomized</td>
<td>144 Double blind, randomized, multicenter</td>
</tr>
<tr>
<td>Result</td>
<td>Bone fracture : 10 % vs 27,5 %</td>
<td>Prolongation by 35% of the time to bone disease progression (244 vs 180 days)</td>
</tr>
</tbody>
</table>
Bisphosphonate in primary breast ca without bone metastase : clodronate 1600 mg/day PO

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<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Randomized, non placebo</td>
<td>Double blind, randomized</td>
<td>Open randomized</td>
</tr>
<tr>
<td>Bone metastases</td>
<td>8% vs 17% (p=0.003)</td>
<td>3.8% vs 6.7% (p=0.016)</td>
<td>21% vs 17% (ns)</td>
</tr>
<tr>
<td>Visceral metastase</td>
<td>8% vs 19% (p=0.003)</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Relative risk</td>
<td>0.70</td>
<td>0.44</td>
<td></td>
</tr>
</tbody>
</table>
Bisphosphonate : adjuvant therapy

- NSABP trial B34:
  - 2400 early stage breast ca
  - Clodronate vs placebo
- North American Intergroup: S0307
  - Oral clodronate vs risedronate, zoledronic acid
### Bisphosphonate: Toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin disorders</td>
<td>14.3</td>
</tr>
<tr>
<td>Upper gastrointestinal</td>
<td>22.3</td>
</tr>
<tr>
<td>Hepatic</td>
<td>7</td>
</tr>
<tr>
<td>Renal</td>
<td>5.3</td>
</tr>
</tbody>
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## Bisphosphonate: recommendation: ASCO 2003

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<th>Specific guidelines</th>
<th>Recommendation</th>
</tr>
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<tr>
<td>lytic disease (+) (rontgen)</td>
<td>Pamidronate 90 mg IV (2 h) or zoledronic acid 4 mg (15 min) every 3-4 weeks</td>
</tr>
<tr>
<td>Bone scan (+), normal rontgen, bone destruction on CT/MRI</td>
<td>Considered reasonable</td>
</tr>
<tr>
<td>Bone scan (+) only</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Duration</td>
<td>Continued until substantial decline in performans status</td>
</tr>
</tbody>
</table>
### Bisphosphonate recommendation: ASCO 2003

<table>
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<th>Recommendation</th>
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</thead>
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<tr>
<td><strong>Safety</strong></td>
<td>Creatinine $&lt;3$ mg/dl: no change in dosage or interval monitor: creatinine (prior to each dose)</td>
</tr>
<tr>
<td><strong>Biochemical markers</strong></td>
<td>Ca, phosphate, magnesium, Hb</td>
</tr>
<tr>
<td><strong>Pain control secondary to bone metastases</strong></td>
<td>Not suggested for routine care</td>
</tr>
<tr>
<td></td>
<td>Current standard care, concurrent with chemotherapy and/or hormonal</td>
</tr>
<tr>
<td>Specific guidelines</td>
<td>Recommendation</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Ekstraskeletal metastases</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td>Not recommended outside of clinical trial</td>
</tr>
<tr>
<td>Osteoporosis prevention in breast ca</td>
<td>Recommended an algorithm</td>
</tr>
</tbody>
</table>
Bisphosphonate : Cohrane Breast Cancer Review Group

- 8 studies: 1962 women with advanced breast cancer and bone metastases
  - Bisphosphonate reduced the risk of skeletal event by 14%
  - For IV pamidronate 90 mg, the reduction was 23%
  - For oral clodorate, the reduction was 16%
  - Compared with placebo, bisphosphonates reduced the skeletal event rate by 30%
Bisphosphonate: Cancer Care Ontario (2002)

- Women with breast cancer who have bone metastases should be offered treatment with oral clodronalate or intravenous pamidronate.
- Intravenous zoledronic acid was considered an alternative to pamidronate when a shorter infusion time (15 minutes) is important.
Osteoporosis risk in breast ca

- Age > 65 years
- Age 60-64 years with:
  - Family history
  - Body weight < 70 kg
  - Prior non-traumatic fracture
  - Other risk factors
- Premenopausal women with therapy associated premature menopause
Management strategy in non metastatic breast ca

Osteoporosis risk

Low risk

Life style, Ca, vit D

Monitor annually

High risk

BMD hip ± spine

T score

≤ -2.5

Le de style, Ca, vit D, Alendronate/risedronate/zoledronic acid/raloxifene

Between -1 and -2.5

Life style, Ca, vit D

Repeat BMD annually

> -1

Life style, Ca, vit D
Take home messages

- Bone metastases in breast cancer is a complex process, involving interaction:
  - Breast cancer cells
  - Osteoclasts
  - Bone marrow stroma
  - Bone matrix
Take home messages

- Breast cancer cells produce PTHrP which stimulates osteoclast
- Bone resorption by osteoclast produces growth factors which stimulates cancer growth
Take home messages

• Bisphosphonate:
  – Osteoclast activity inhibition
  – Apoptosis cancer cell
  – Angiogenesis inhibition

• Bisphosphonate effective in reducing skeletal events in breast cancer patients with bone metastases

• Ongoing studies to determine the role of bisphosphonate as adjuvant therapy in early breast cancer