Metastasis

**Primary tumor:**
1) Breast
2) Lung
3) Prostate
4) Thyroid
5) Kidney

- Brain
- Lung
- Bone
- Liver
- Pelvis
- Spine
- Long Bones
- Skull
- Ribs
What are bisphosphonates?
Background

- Bisphosphonate is a class of drug that inhibits the resorption of bone by osteoclasts.
- Bisphosphonates are structural analogs to pyrophosphate.
- Pyrophosphate is a normal product of metabolism when ATP is hydrolyzed to AMP.
The replacement of the O with a C makes bisphosphonates resistant to hydrolysis and are chemically extremely stable.
Two classes of Bisphosphonates

- Non-N containing
  - Less potent
  - Etidronate - 1
  - Clodronate - 10
  - Tiludronate - 10

- N containing
  - More potent
  - Pamidronate - 100
  - Neridronate - 100
  - Olpadronate - 500
  - Alendronate - 500
  - Ibandronate - 1000
  - Risedronate - 2000
  - Zoledronate - 10000
Two classes of Bisphosphonates

Biochemical Structure of Different Bisphosphonates

- Etidronate
- Pamidronate
- Alendronate
- Tiludronate
- Risedronate

Non-N containing

N containing
Mechanism of action

- Bisphosphonates have a high affinity for hydroxyapatite and thus bony surfaces.
- The bisphosphonates are “ingested” by the osteoclasts and their function (ie bone resorption) is inhibited once inside the cell.
- The two classes have different mechanisms of action.
Mechanism of action

- Non-N containing
  - These bisphosphonates are metabolized in the cell to compounds that compete with ATP in the cellular energy metabolism.
Mechanism of action

- N containing
  - These bisphosphonates inhibit the production of cholesterol – which is an essential component to making a proper cell membrane and cytoskeleton.
  - The "ruffled border" - the area with which the cell makes contact with bone and resorbs bone – cannot be maintained.
Is there evidence to support the use of bisphosphonates in the treatment of metastatic bone disease?

YES
Systematic review of role of bisphosphonates on skeletal morbidity in metastatic cancer

BMJ. 2003 Aug 30;327(7413):469

Ross JR, Saunders Y, Edmonds PM, Patel S, Broadley KE, Johnston SR.

Department of Palliative Medicine, Royal Marsden Hospital, London
Methods

- Reviewed RCTs of patients with malignant disease (breast, prostate, MM and mixed dx) and bone metastases who were treated with bisphosphonates vs placebo or standard care.
- Looking specifically at skeletal morbidity:
  - Pathological fractures
  - Spinal cord compression
  - Hypercalcemia
  - Need for orthopedic surgery
  - Need for radiation
- 30 studies were meta-analyzed.
Results

- > 6 mos of treatment
  - DECREASE in the risk of
    - Fractures
    - Hypercalcemia
    - Need for radiation
  - NO DIFFERENCE
    - Need for orthopedic surgery
    - Spinal cord compression
Results

- > 1 year of treatment
  - DECREASE in the risk of
    - Needing orthopedic surgery
- Also found
  - Increased time to first skeletal event
  - But does not increase survival
Bisphosphonates for breast cancer

- Cochrane Database Syst Rev.
  2002;(1):CD003474

- Pavlakis N, Stockler M.
Methods

- Reviewed RCTs evaluating skeletal events in women with early and metastatic breast cancer treated with bisphosphonates
  - Skeletal events (primary outcomes)
    - New bone metastases
    - Pathologic fractures
    - Spinal cord compression
    - Need for orthopedic surgery
    - Need for radiation
    - Bone pain

- 19 studies were meta-analyzed
Results

- Overall decrease in the risk of developing a skeletal event
- Significant delay in time to first skeletal event
Can bisphosphonates stop metastasis?

PERHAPS
3 clodronate trials

- Adjuvant clodronate treatment improves the overall survival of primary breast cancer patients with micrometastases to bone marrow – a longtime follow-up.
  - Jaschke A, Bastert G, Solomayer EF et al.

- Oral clodronate for adjuvant treatment of operable breast cancer: results of a randomized, double-blind, placebo-controlled multicenter trial.
  - Powles T, McCloskey E, Kurkilahti M.
  - Proc Am Soc Clin Oncol 2004;23:8

- Ten-year follow-up of a randomized controlled trial of adjuvant clorionate treatment in node-positive breast cancer patients.
  - Lipton A, Theriault RL, Hortobagyi GN et al.
  - Cancer 2000;88:1082-1090
## Results

Table 3. Clinical trials of oral clodronate for the prevention of bone metastases

<table>
<thead>
<tr>
<th>Trial</th>
<th>n of patients</th>
<th>Duration (years)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Treatment</td>
<td>Median follow-up</td>
</tr>
<tr>
<td>Diel et al. [43, 61]</td>
<td>302</td>
<td>2</td>
<td>3.0</td>
</tr>
<tr>
<td>Saarto et al. [38, 63]</td>
<td>299</td>
<td>3</td>
<td>5.0</td>
</tr>
<tr>
<td>Powles et al. [44, 62]</td>
<td>1,069</td>
<td>2</td>
<td>5.5</td>
</tr>
</tbody>
</table>

All trials compared oral clodronate (1,600 mg/day) with placebo.

*aComparison favored placebo over oral clodronate.

Abbreviation: NS = not significant.
Ongoing trials

- NSABP (National Surgical Adjuvant Breast and Bowel Project) trial
  - Effect of 1600mg/day PO clodronate vs placebo 3400 pts with stage I and II breast ca

- AZURE (Adjuvant Zoledronate to Reduce Recurrence) trial
  - Standard therapy vs standard therapy + different regiments of zoledronate in 3300 pts with stage II and III breast ca
  - 4mg zoledronate IV
    - Q monthly x 6
    - Q 3 months x 3
    - Q 6 months x 5

- Also trials planned looking at effect of Zoledronate on metastases in prostate and renal cell carcinoma
Is there radiologic evidence bisphosphonates improves bone quality?

YES
Improvement of Paget Bone Lesions With Risedronate Treatment: A Radiologic Study

- Bone. 2000 Mar;26(3):263-
- Brown JP, Chines AA, Myers WR, Eusebio RA, Ritter-Hrncirik C, Hayes CW.
- Le Centre Hospitalier Universitaire de Quebec, Sainte-Foy, Canada
Methods

- 26 patients with Pagets (ALP >3x normal)
- Treated with 30mg/day PO risedronate x 84 days
- Radiographs of affected bones taken at baseline, 6 mos and 12 mos post treatment
- Radiographs examined by 1 blinded radiologist and classified as
  - No change
  - Improvement
  - Deterioration
Results

Table 2. Summary of radiographic changes in pagetic lesions

<table>
<thead>
<tr>
<th>Radiographic changea</th>
<th>Baseline to 6 months</th>
<th>Baseline to 12 months</th>
<th>6 to 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement</td>
<td>22 (16)</td>
<td>17 (11)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>No change</td>
<td>24 (17)</td>
<td>16 (11)</td>
<td>24 (14)</td>
</tr>
<tr>
<td>Deterioration</td>
<td>3 (3)</td>
<td>2 (2)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>(p) valueb</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

aData are the number of pagetic lesions and the number of patients (in parenthesis).
bProportion of improved vs. deteriorated lesions.

Broken down by body part:

1) Most improvement seen in Femur and tibia
2) No change in Pelvis
Figure 3. (a) Lateral radiograph of the left mid-femur showing pagetic changes with a lytic leading edge (arrows). (b) Six months later, after 3 months of risedronate treatment, there is significant healing in the lytic front.

Figure 4. (a) Lateral radiograph of the left tibia showing marked pagetic changes with a lytic edge (arrow). (b) Six months later, after 3 months of risedronate treatment, there is marked healing of the lytic edge.
Are there guidelines to surgical treatment of metastatic bone disease?

YES
An approach to the Management of the Patient with Metastatic Bone Disease

- AAOS Instructional Course Lectures Volume 53, 2004
- Weber KL, Lewis VO, Randall RL, Lee AK, Springfield D.
- Section of Orthopaedic Oncology, University of Texas, MD Anderson Cancer Center, Houston, Texas, USA
Primary goals of surgical treatment of bone metastases

1) Restore skeletal stability
2) Regain or improve function
3) Alleviate pain
Surgical options

- Method of fixation would be the same as if stabilizing a non-pathological fracture
- Have to consider joint reconstruction
Conclusion

- There is good evidence to use bisphosphonates in the treatment of metastatic bone disease – much new research on the way.

- However, no literature to date on the direct impact of bisphosphonates on metastatic bone surgery.