Bisphosphonates and Breast Cancer
Bisphosphonates

- Analogues of pyrophosphate
- Carbon substitution makes them resistant to endogenous phosphatases in circulation
- Potent inhibitors of osteoclast growth, maturation and function
- Poorly absorbed via GI tract
- Structure function/potency relationship
Structure and Potency of Clinically useful Bisphophonates

![Diagram of bisphophonate structure with relative potencies and chemical structures](image)

When $R_1 = \text{OH}$, tridentate binding facilitates calcium binding.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$R_1$</th>
<th>Relative Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etidronate</td>
<td>-CH$_2$</td>
<td>1</td>
</tr>
<tr>
<td>Clodronate</td>
<td>Cl</td>
<td>10</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>-(CH$_2$)$_2$-NH$_2$</td>
<td>100</td>
</tr>
<tr>
<td>Alendronate</td>
<td>-(CH$_2$)$_2$-NH$_2$</td>
<td>100</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>-(CH$_2$)$_2$-N-(CH$_2$)$_2$</td>
<td>1,000</td>
</tr>
<tr>
<td>Risendronate</td>
<td>-(CH$_6$)-N-</td>
<td>1,000</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>-(CH$_6$)-N-</td>
<td>10,000</td>
</tr>
</tbody>
</table>
Structure and Potency of Clinically useful Bisphophonates
Bisphosphonate Mechanisms of Action

- Bind to hydroxyapatite crystals – inhibit breakdown
- Preferentially incorporated into active bone remodeling sites
- Promote osteoclast apoptosis – inhibit mevalonic acid pathway

Drake MT et al Mayo Clin Proc 2008;83:1032-1045
Metastatic Breast Cancer

- Pamidronate
- Zoledronic acid
- Ibandronate
- Clodronate
### Prospective randomized trials of bisphosphonates in bone metastasis from breast cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th># Pts</th>
<th>Placebo control</th>
<th>Agent/route</th>
<th>Fracture Risk</th>
<th>Radiation</th>
<th>Surgery</th>
<th>HCM</th>
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<td>↓</td>
<td>NR</td>
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<td>No diff</td>
<td>↓</td>
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<tr>
<td>Conte</td>
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<td>161</td>
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<td>No diff</td>
<td>No diff</td>
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<td>372</td>
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<td>↓</td>
<td>No diff</td>
<td>↓</td>
<td>↓</td>
<td>No diff</td>
</tr>
</tbody>
</table>

*12 month analysis
*24 month analysis

↓ - Decreased
NR – Not reported
No Diff – No difference
Prospective randomized trials of bisphosphonates in bone metastasis from breast cancer

References

Metastatic Breast Cancer

- Zoledronic acid vs pamidronate
- Randomized, double blind, trial
- 1648 patients
- Zoledronic acid 4 mg iv q 3-4 weeks OR
- Pamidronate 90 mg iv q 3-4 weeks
- Duration of study drug 24 months

Metastatic Breast Cancer
Zoledronic Acid vs. Pamidronate

Combination of 2 randomized controlled trials 1130 patients – breast cancer – osteolytic bone mets
Zoledronic acid 4mg IV q 3-4 weeks OR
Pamidronate 90 mg IV q 3-4 weeks
12 month observation

Results:
Proportion with skeletal related events (SRE)

<table>
<thead>
<tr>
<th>Zoledronic Acid</th>
<th>Pamidronate</th>
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<tbody>
<tr>
<td>43%</td>
<td>45%</td>
</tr>
<tr>
<td>48%</td>
<td>58%</td>
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</table>

<table>
<thead>
<tr>
<th>Time to first SRE (days)</th>
<th>overall</th>
<th>lytic disease</th>
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<tr>
<td>310</td>
<td>174</td>
<td></td>
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</tbody>
</table>

Rosen LS et al, Cancer 2004;100:36-43
## Metastatic Breast Cancer
### Zoledronic acid vs. Pamidronate – Long Term Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Zoledronic Acid</th>
<th>Pamidronate</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>SRE (%)</td>
<td>46%</td>
<td>49</td>
<td>NS</td>
</tr>
<tr>
<td>SRE (XRT)</td>
<td>19%</td>
<td>24%</td>
<td>0.037</td>
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<tr>
<td>Time to 1(^{st}) SRE (days)</td>
<td>376</td>
<td>356</td>
<td>NS</td>
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<tr>
<td>Time to 1(^{st}) SRE (days) brca endocrine</td>
<td>415</td>
<td>370</td>
<td>0.047</td>
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<tr>
<td>SMR</td>
<td>.9</td>
<td>1.49</td>
<td>0.125</td>
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</table>
Pamidronate or zoledronic acid (with calcium 1200-1500mg and vitamin D 400-800 IU daily supplement) should be given (category 1) in addition to chemotherapy or endocrine therapy if bone metastasis present, expected survival ≥ 3 months and creatinine ≤ 3.0 mg/dL.
Clinical Endpoints

- Decrease fracture risk
- Decrease need for radiation to bone
- Decrease need for surgery for bone
- Improve pain
Bisphosphonates and Metastases

- Established role in metastatic bone disease
- Data sources
  - Randomized, placebo controlled trials
  - Randomized controlled trials
  - Meta analyses
  - Cochrane reviews
Patient Supplements

- Calcium 1200 – 1500 mg po daily
- Vitamin D 400 – 800 IU po daily
- Pre-administration assessment
  - Serum creatinine (adjust bisphosphonate per FDA black box)
  - Dental evaluation and treatment as needed

Guidelines Revision Recommended

- Bisphosphonate for bone metastasis. Pamidronate 90mg IV over not less than 2 hours monthly (FDA approved) OR Zoledronic acid 4mg IV over not less than 15 minutes monthly (FDA approved).

- Ibandronate 6mg IV over 1-2 hours monthly (not FDA approved)


Bisphosphonates
Cancer Treatment Induced Bone Loss (CTIBL)

- NCCN Guideline – None
- Background
  - Chemotherapy and ovarian ablation result in bone loss
  - Presumed mechanism hypoestrogenism
  - Aromatase inhibitors result in bone less and increased fracture risk
## CTIBL – Studies with Bisphosphonates

### Risedronate

<table>
<thead>
<tr>
<th>Study</th>
<th># Pt</th>
<th>End Point</th>
<th>Agents</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBRCT</td>
<td>53</td>
<td>BMD-LS, hip</td>
<td>Risedronate/placebo 30mg daily x 2 weeks, 10 weeks rest x 8 cycles</td>
<td>Improved BMD LS/hip with risedronate</td>
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<tr>
<td>DBRCT</td>
<td>87</td>
<td>BMD LS/hip</td>
<td>Risedronate 35 mg weekly/or placebo</td>
<td>Improved BMD LS/hip</td>
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<tr>
<td>DBRCT</td>
<td>216</td>
<td>BMD LS</td>
<td>Risedronate 35 mg/weekly or placebo</td>
<td>No difference in BMD LS at 12 mos</td>
</tr>
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</table>

### Ibandronate

<table>
<thead>
<tr>
<th>Study</th>
<th># Pt</th>
<th>End Point</th>
<th>Agents</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBRCT</td>
<td>131</td>
<td>BMD</td>
<td>Ibandronate 150mg/placebo</td>
<td>Improved BMD LS/hip</td>
</tr>
</tbody>
</table>
CTIBL – Studies with Bisphosphonates

References


Lester, D, Dodwell, D., Purohit, O. P., gutcher, A, ellis, R, thorpe, j. m., horsman, j. e., brown, r. a., hannon, r. e., and col. Use of monthly oral ibandronate to prevent anastrozole-induced bone loss during adjuvant treatment for breast cancer: Two-year results from ABIRON study. *jco* 26, 19s. 5-20-2008.
## CTIBL – Studies with Bisphosphonates

<table>
<thead>
<tr>
<th>Type Study</th>
<th># Pts</th>
<th>Endpoint</th>
<th>Agent</th>
<th>Result</th>
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<tbody>
<tr>
<td>DBRCT</td>
<td>40</td>
<td>BMD LS/hip</td>
<td>Pamidronate 60mg IV q 3 months/placebo</td>
<td>Improved BMD LS/hip</td>
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<tr>
<td>RCT</td>
<td>401</td>
<td>BMD/LS</td>
<td>Zoledronic acid 4mg IV q 6 mos.</td>
<td>Prevented LS bone loss</td>
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<tr>
<td>RCT</td>
<td>602</td>
<td>BMD LS/hip</td>
<td>Zoledronic acid 4mg IV q 6 months x 5 years up front vs. delayed</td>
<td>Up front prevented BMD loss LS/hip</td>
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<tr>
<td>RCT</td>
<td>1065</td>
<td>BMD LS/hip</td>
<td>Zoledronic acid 4mg IV q 6 months x 5 years up front vs. delayed</td>
<td>Up front improved LS/hip BMD</td>
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<tr>
<td>RCT</td>
<td>166</td>
<td>BMD LS</td>
<td>Zoledronic acid 4mg IV q 3 months vs. nil</td>
<td>Improved LS BMD</td>
</tr>
</tbody>
</table>
CTIBL – Studies with Bisphosphonates

References


Conclusions

- Bisphosphonates preserve BMD lumbar spine and hip in pre menopausal women with amenorrhea and/or ovarian failure.
- Bisphosphonates preserve BMD lumbar spine and hip in post menopausal women treated with an aromatase inhibitor.
- No data on fracture risk reduction
Recommended Guideline Modification

NOT APPROVED

- Consider use of bisphosphonate in the adjuvant setting for preservation of BMD
  - Pre-menopausal women treated with gonadotoxic therapy – chemotherapy, ovarian ablation
  - Post - menopausal women treated with aromatase inhibitor
Recommended
Guideline Modification
NOT APPROVED

- Zoledronic acid 4mg IV q3 months for up to 12 months for pre menopausal women receiving gonadotoxic chemotherapy or treated with oophorectomy/ovarian suppression with or without an aromatase inhibitor in the adjuvant setting.

- Zoledronic acid 4mg IV q6 months for up to 5 years beginning with start of aromatase inhibitor adjuvant therapy.
Monitoring of Bone Health

- Monitor BMD at baseline, 12 months and annually
- Calcium 1200 – 1500 mg po daily
- Vitamin D 400 – 800IU daily
- Dental exam and treatment prior to bisphosphonate use
- Monitor serum creatinine per FDA recommendation
Adjuvant Bisphosphonate

- Potential to reduce recurrence and death from breast cancer
- Moot point if bisphosphonate used for BMD preservation.
Oral Clodronate for Primary Breast Cancer

- 1069 patients
- Oral clodronate 1600 mg/day or placebo
- 2 years of therapy – start within 6 months
- Endpoint – bone relapse

Results
Powles et al.

- During clodronate – significant decrease in bone mets
- Significant reduction in mortality during follow-up (23% reduction)

Atula S et al. Drug Safety 2003; 26:661-671
Reductions in New Metastases in Breast Cancer with Adjuvant Clodronate

- 302 patients primary breast cancer
- Bone marrow positive by cytokeratin (at least one cell)
- Clodronate 1600 mg daily or nil
- 2 years treatment
- Endpoints – distant mets, survival

### Results

**Diel et al.**

<table>
<thead>
<tr>
<th>Category</th>
<th>Clodronate</th>
<th>Nil</th>
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</thead>
<tbody>
<tr>
<td>Distant mets</td>
<td>21</td>
<td>42</td>
</tr>
<tr>
<td>Deaths</td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td>Bone mets</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>36 months</td>
<td></td>
</tr>
</tbody>
</table>

Diel IJ et al. Cancer 2000;3080-3088
Adjuvant clodronate treatment does not reduce skeletal metastases in node positive breast cancer

- 299 patients – node positive breast cancer
- Clodronate 1600 mg daily or nil
- 3 years of treatment
- 5 years follow-up
- Endpoints – distant mets, survival

## Results

Saarto et al.

<table>
<thead>
<tr>
<th></th>
<th>Clodronate</th>
<th>Nil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone mets</td>
<td>29</td>
<td>24</td>
</tr>
<tr>
<td>Non-bone mets</td>
<td>60</td>
<td>36</td>
</tr>
<tr>
<td>Survival</td>
<td>70%</td>
<td>83%</td>
</tr>
</tbody>
</table>

- Powles
  - Clodronate improved 5 year survival for stage II and III disease 76.7% vs. 69.2%.
  - At 10 years risk of death 23% overall and 26% in stage II and III disease.
- Diel
  - Survival advantage at 103 months follow-up.
- Saarto
  - Study criticized for imbalance of randomization ER status, PR status.
  - ER(-) postmenopausal women treated with tamoxifen.
Zoledronic acid in Premenopausal Women Treated with Adjuvant Ovarian Suppression + Tamoxifen or Ovarian Suppression + Aromatase Inhibitor, + Zoledronic acid 4mg IV q 6 months

- 1801 premenopausal women endocrine responsive breast cancer
- End points
  - Primary DFS
  - Secondary RFS, OS
  - Exploratory bone mets free survival
- Median Follow-up 60 months
  - Results
    - DFS improved with zoledronic acid (HR=0.64 [0.46-0.91])  p = 0.01
    - Improved RFS  p = 0.10
- Conclusion – zoledronic acid has anti-tumor activity

Gnant, M., Mlineritsch, B., Schippinger, W., Luschin-Ebengreuth, G., Poestlberger, S., Menzel, C., Jakesz, R., Kubista, E., and Marth, C. Adjuvant ovarian suppression combined with tamoxifen or anastrozole, alone or in combination with zoledronic acid, in premenopausal women with endocrine-responsive, stage I and II breast cancer: First efficacy results from ABCSG-12. jco 26(18s), 1006s. 6-20-2008.
Zoledronic acid in post menopausal women with endocrine responsive primary breast cancer treated with adjuvant letrozole

- 1667 patients
- Zoledronic acid 4mg IV q 6 months (up front vs. delayed)
- End point 1° BMD LS at 12 months of study
  - 2° time to recurrence
  - Total hip BMD
  - Changes in bone tumor markers
  - safety
- Results
  - Improved BMD - LS and total hip
  - Fracture rates similar
- Recurrences
  - 7 in upfront group
  - 17 in delayed group P=0.0401

NSABP B-34

- Primary breast cancer
- Clodronate vs. placebo
- 3323 subjects
- Closed to accrual March 31, 2004
- Analyses pending
Bone Metastases Prevention

- SWOG – RCT adjuvant bisphosphonate within 12 weeks of surgery (6000 participants)
  - Clodronate 1600mg po daily
  - Zoledronic acid 4mg IV q 4 weeks for 6 months, then q 3 months for 2.5 years
  - Ibandronate 50mg po daily
AZURE Trial

3360 participants
Adjuvant chemotherapy and/or endocrine therapy

Zoledronic acid 4 mg IV vs nil
q 3-4 weeks x 6 doses
q 3 months x 8 doses
q 6 months x 5 doses
Recommendation

No guideline additions pending large RCT data