**Review: Bisphosphonates prevent or delay skeletal events in women with advanced breast cancer and bone metastases**


**Clinical impact ratings**: Oncology ★★★★★✩

**Question**
In women with early or advanced breast cancer, do bisphosphonates reduce the incidence of skeletal events, decrease bone pain, improve quality of life, and increase survival?

**Methods**
Data sources: Cochrane Breast Cancer Group specialized register, EMBASE/Excerpta Medica, CancerLit, selected journals, lists of conference abstracts, bibliographies of relevant studies, pharmaceutical companies, authors of included studies, and other researchers in the field.

Study selection and assessment: Randomized controlled trials (RCTs) that compared a bisphosphonate with placebo or no bisphosphonate (control) or with another bisphosphonate in women with advanced breast cancer, with or without bone metastases, or early breast cancer. Individual study quality was assessed using the 13-item MERGE criteria.

**Outcomes**: Skeletal events (new bone metastases, pathologic fractures, spinal cord compression, irradiation of or surgery on bone, development or progression of bone pain [and, in some studies, hypercalcemia]), quality of life, and survival.

**Main results**
21 RCTs met the inclusion criteria: 15 RCTs (n = 5187) in women with advanced breast cancer and clinically evident bone metastases (category 1), 3 RCTs (n = 320) in women with advanced breast cancer without bone metastases (category 2), and 3 RCTs (n = 1670) in women with early breast cancer (category 3). In category 1, risk for skeletal events was reduced with bisphosphonates (Table) and time to the first event was longer in 7 of 10 RCTs, compared with control. The exclusion of hypercalcemia as a skeletal event and the route of administration (oral or intravenous) did not affect the benefit of treatment. 6 of 10 RCTs showed less bone pain in category 1 women receiving bisphosphonates than in control-group women. Bisphosphonates did not prevent the occurrence of new bone metastases in category 2 or 3 (Table). 2 of 6 RCTs in women with advanced breast cancer showed improved quality of life with bisphosphonate treatment. Survival increased with bisphosphonate use in women with early, but not advanced, breast cancer (Table).

**Conclusion**
In women with advanced breast cancer and clinically evident bone metastases, bisphosphonates reduce the incidence of skeletal events but have no effect on survival.

**Source of funding**: Not stated.

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**Bisphosphonates (treatment) vs placebo or no bisphosphonates (control) in women with breast cancer***

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Stages of breast cancer</th>
<th>Number of comparisons (n)</th>
<th>Weighted event rates</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skeletal events</td>
<td>Advanced, bone metastases</td>
<td>10 (3065)</td>
<td>54%</td>
<td>65%</td>
<td>16% (11 to 21)</td>
</tr>
<tr>
<td></td>
<td>New bone metastases</td>
<td>3 (320)</td>
<td>24%</td>
<td>24%</td>
<td>1% (−47 to 33)</td>
</tr>
<tr>
<td></td>
<td>Early</td>
<td>3 (1653)</td>
<td>15%</td>
<td>18%</td>
<td>18% (−1 to 34)</td>
</tr>
<tr>
<td>Death</td>
<td>Advanced</td>
<td>9 (1968)</td>
<td>62%</td>
<td>64%</td>
<td>2% (−3 to 8)</td>
</tr>
<tr>
<td></td>
<td>Early</td>
<td>3 (1653)</td>
<td>21%</td>
<td>26%</td>
<td>18% (3 to 31)</td>
</tr>
</tbody>
</table>

*Abbreviations defined in Glossary; weighted event rates, RRR, NNT, and CI calculated from data in article using a fixed-effects model.

**Commentary**
Bisphosphonates have a wide spectrum of uses in breast cancer. Pavlakis and colleagues reviewed the use of bisphosphonates in 3 specific breast cancer–related situations. They noted that the use of bisphosphonates in patients with bone metastases definitively reduces the rate of skeletal-related events (SREs). Zoledronate, the most potent bisphosphonate currently available, is at least as effective as pamidronate in preventing SREs and has a much-reduced infusion time (1).

Considerable interest exists in the use of bisphosphonates in the adjuvant setting, not only to reduce the rate of bone metastases, but to prolong disease-free and overall survival. The findings of available trials conflict, but Pavlakis and colleagues noted significantly improved survival when the results of these trials were combined. However, meta-analysis of the available trials did not provide evidence that the incidence of bone metastases is reduced by the prophylactic use of bisphosphonates in either early-stage or advanced breast cancer.

So how should medical oncologists use bisphosphonates in their clinical practice? Clearly, patients with bone metastases should be treated with a bisphosphonate to reduce the rate of SREs until their performance status declines. Either zoledronic or pamidronate given intravenously are reasonable options, and ongoing trials with oral agents will elucidate their role. In patients with early-stage breast cancer, the benefits of bisphosphonates on survival are encouraging but need confirmation before off-trial use can be recommended. Several ongoing studies are exploring this issue. The NSABP B-34 trial, which has completed accrual, randomized patients with early-stage breast cancer to oral clodronate or placebo for 3 years; disease-free survival is the primary endpoint. A current Intergroup trial is randomizing patients with early-stage breast cancer to 3 different bisphosphonates, zoledronate, ibandronate, or clodronate, after adjuvant chemotherapy.

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**Reference**