Clodronate reduced the incidence of bony and visceral metastases in patients with breast cancer and tumour cells in the bone marrow


Question
In patients with breast cancer, what is the effectiveness of oral clodronate in preventing the development of bony metastases?

Design
Randomised controlled trial with median 36-month follow-up.

Setting
University hospital in Heidelberg, Germany.

Patients
302 women (median age 51 y, 63% postmenopausal) who had primary breast cancer classified as stage T1, T2, T3, or T4 and histologically classified as stage N0, N1, or N2; and ≥ 1 tumour cell in a bone-marrow aspirate analysed by immunocytochemistry. Exclusion criteria were confirmed distant metastasis, secondary malignant disease, neoadjuvant chemotherapy or hormone therapy, skeletal disease, serious liver or kidney disorders, or pregnancy. 284 patients with skeletal disease, serious liver or kidney disease, or pregnancy. 284 patients (94%) completed the study.

Main outcome measures
Distant (bone or visceral), bony, and visceral metastases; and death.

Clodronate vs control therapy for primary breast cancer at median 36-month follow-up*

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Clodronate</th>
<th>Control</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distant metastases</td>
<td>13.4%</td>
<td>29%</td>
<td>54% (27 to 71)</td>
<td>6 (4 to 15)</td>
</tr>
<tr>
<td>Bony metastases</td>
<td>7.6%</td>
<td>17.2%</td>
<td>56% (16 to 77)</td>
<td>10 (6 to 45)</td>
</tr>
<tr>
<td>Visceral metastases</td>
<td>8.3%</td>
<td>18.6%</td>
<td>56% (18 to 76)</td>
<td>10 (5 to 37)</td>
</tr>
<tr>
<td>Death</td>
<td>3.8%</td>
<td>15.2%</td>
<td>75% (42 to 89)</td>
<td>9 (5 to 20)</td>
</tr>
</tbody>
</table>

*Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

Commentary
In this "too good to be true" study by Diel and colleagues, clodronate reduced the number of visceral metastases and deaths from breast cancer. Bisphosphonates strengthen the calcium matrix and prevent some skeletal complications from metastatic breast cancer but have no other proven effect (1, 2).

The authors found a reduction from 19% to 8% in visceral metastases and from 13% to 4% in mortality rate. This unexpected finding could be by chance, or it could be some unknown effect on this high-risk patient group with known breast cancer cells in their bone marrow. If the latter is true, then the finding is very important but needs confirmation before it can be accepted. Death and visceral metastases were not end points in the original trial design. Powles and colleagues found no difference in survival or rates of visceral metastases in a much larger study (3).

The presence of breast cancer cells in a bone-marrow aspirate has not yet been widely accepted as a prognostic factor (4). Oncologists are looking for precise reasons to treat with adjuvant therapy, and most patients already have some indication for treatment.

The use of bisphosphonates may depend on cost. Pamidronate for metastatic breast cancer currently costs about U.S. $100 000 to save 1 quality-adjusted life-year (5).

These results cannot be generalised to all patients with breast cancer because it is only 1 study with an unexpected finding—a survival advantage—that does not (yet) make biological sense. Confirmation of the use of bone-marrow aspirate for assessing high risk and subsequent treatment with bisphosphonates to prolong survival is urgently needed. If bisphosphonates prevent metastases at a price society can afford, then confirmation of this landmark study should change practice.

Main results
Analysis was by intention to treat. Patients who received clodronate had a lower incidence of distant metastasis (P = 0.001), bony metastasis (P = 0.003), and visceral metastasis (P = 0.003) than did patients in the control group (Table). Fewer patients died in the clodronate group than in the control group (P = 0.001) (Table).

Conclusion
In patients with primary breast cancer and tumour cells in the bone marrow, oral clodronate, 1600 mg/d for 2 years, reduced the incidence of new bony and visceral metastases in 10 of every 100 women.

References