Early breast cancer: adjuvant bisphosphonate treatment beneficial in postmenopausal women

A large meta-analysis of individual patient data from randomised controlled trials including 18,766 women (11,767 of whom were postmenopausal) with early breast cancer found bisphosphonate use for between 2 and 5 years reduced recurrence and mortality in postmenopausal but not premenopausal women. The absolute reduction with bisphosphonate use in postmenopausal women at 10 years was 3.0% for breast cancer recurrence (from 25.8%), 3.4% for distant recurrence (from 21.2%), 2.2% for bone recurrence (from 8.8%) and 3.3% for breast cancer mortality (from 18.0%).

Currently in the UK, no bisphosphonates are licensed specifically to reduce recurrence or mortality in women with breast cancer.

Overview and current advice

Bisphosphonates reduce bone turnover by inhibiting osteoclast maturation and function and are used in many skeletal conditions. When the NICE guideline on early and locally advanced breast cancer was published in 2009, the main role for using bisphosphonates in women with early invasive breast cancer was to prevent treatment-induced osteoporosis. The guideline recommends that bisphosphonates should be offered to women based on their risk of osteoporosis identified by algorithms in 'Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK expert group' (see appendix 2 of the full guideline for details). A decision has recently been taken to update this NICE guideline and details of the update will be available on the guidelines in development webpage in due course.

Bisphosphonates may also have a role in the prevention of metastatic disease, and this was the subject of large randomised controlled trials (RCTs) when the NICE guideline was published. It has been hypothesised that, in bone with high turnover, excess osteoclast activity could be associated with excess production of growth factors which could in turn affect the survival of tumour micrometastases. Using bisphosphonates to reduce osteoclast activity might reduce expression of these factors, thereby preventing the establishment of micrometastatic disease. However, RCTs examining this possible effect have found mixed results. A meta-analysis of individual patient data from RCTs of adjuvant bisphosphonate treatment in early breast cancer has now been published (Early Breast Cancer Trialists’ Collaborative Group 2015) and is summarised in this Medicines Evidence Commentary.
Currently in the UK, no bisphosphonates (alendronic acid, ibandronic acid, pamidronate disodium, risedronate sodium, sodium clodronate or zoledronic acid) are licensed specifically to reduce recurrence or mortality in women with breast cancer. In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using a bisphosphonate outside its authorised indications.

The most common adverse effects of bisphosphonates are gastrointestinal effects (such as nausea, dyspepsia, mild oesophagitis and abdominal pain) and bone, joint or muscle pain. Other less common adverse effects include more serious oesophageal reactions, osteonecrosis of the jaw and atypical stress fractures. See individual summaries of product characteristics and MHRA Drug Safety Update for more information.

**New evidence**

A large meta-analysis of individual patient data published by the Early Breast Cancer Trialists’ Collaborative Group included 18,766 women from 26 RCTs in which women with early breast cancer were randomised to bisphosphonates or a control group with no bisphosphonate use. Mean scheduled treatment duration was 3.4 years and 97% of participants were in trials of 2–5 years treatment. Several bisphosphonates were used, but mainly zoledronic acid (50%), sodium clodronate (27%) and ibandronic acid (16%).

The pre-defined co-primary end points were any recurrence of breast cancer, distant recurrence and breast cancer mortality. Secondary outcomes included all-cause mortality and bone recurrence as the first distant recurrence. Pre-specified primary subgroup investigations included site of first distant recurrence (bone or other site), menopausal status, and class of bisphosphonate.

Median follow-up was 5.6 woman years, during which time 3453 women had a recurrence and 2106 women died. In all 18,766 women, use of bisphosphonates resulted in no statistically significant reduction in recurrence of breast cancer, but statistically significant reductions in distant recurrence (mainly because of a reduction in bone recurrence) and breast cancer mortality (see table below).

In the pre-specified sub-group analyses, there were no benefits of bisphosphonate use in premenopausal women (n=6171). In postmenopausal women there were statistically significant reductions in breast cancer recurrence, distant recurrence, bone recurrence and breast cancer mortality (see table below). The absolute reduction with bisphosphonate use in postmenopausal women at 10 years was 3.0% for breast cancer recurrence, 3.4% for distant recurrence, 2.2% for bone recurrence and 3.3% for breast cancer mortality.
### Table: Key findings in all women and in the subgroup of postmenopausal women

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<thead>
<tr>
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<th>All women (n=18,766)</th>
<th>Postmenopausal women (n=11,767)</th>
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<tbody>
<tr>
<td></td>
<td>Rate ratio (95% CI)</td>
<td>10-year risk with bisphosphonate versus control</td>
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<td><strong>Recurrence of breast cancer</strong></td>
<td>0.94 (0.87 to 1.01) 2p=0.08, NS</td>
<td>24.9% vs. 25.9% absolute 10-year gain 1.1% (95% CI −0.7 to 2.9)</td>
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<td><strong>Distant recurrence</strong></td>
<td>0.92 (0.85 to 0.99) 2p=0.03</td>
<td>20.4% vs. 21.8% absolute 10-year gain 1.4% (95% CI −0.3 to 3.1)</td>
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<td><strong>Bone recurrence</strong></td>
<td>0.83 (0.73 to 0.94) 2p=0.004</td>
<td>7.8% vs. 9.0% absolute 10-year gain 1.1% (95% CI −0.1 to 2.3)</td>
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<td><strong>Breast cancer mortality</strong></td>
<td>0.91 (0.83 to 0.99) 2p=0.04</td>
<td>16.6% vs. 18.4% absolute 10-year gain 1.7% (95% CI 0.0 to 3.5%)</td>
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Abbreviations: CI, confidence interval; NS, not significant; p, p value; SE, standard error

Bisphosphonate use had no effect on distant recurrence other than bone recurrence or on locoregional recurrence or on contralateral breast cancer in all women or in the postmenopausal subgroup.

The benefits of non-aminobisphosphonates (sodium clodronate) and aminobisphosphonates (zoledronic acid and ibandronic acid) appeared similar. There was no apparent benefit with the non-aminobisphosphonate pamidronate but the number of women taking this bisphosphonate was low (n=953). The number of women taking risedronate sodium (n=398) was also low and insufficient to assess its efficacy and no women received alendronic acid in the studies included. For bone recurrence, the benefits appeared to be similar in trials of low-intensity bisphosphonate schedules (such as 6-monthly intravenous zoledronic acid) and higher-intensity schedules (such as monthly intravenous zoledronic acid, daily oral ibandronic acid or daily oral sodium clodronate). Similar reductions with bisphosphonates in the presence or absence of chemotherapy were also seen, suggesting any benefits are additive to chemotherapy and vice versa.

Use of bisphosphonates was associated with a statistically significant reduction in fractures in women for whom this information was available (n=13,341). Fracture was reported in 6.3% of women in the bisphosphonate group and 7.3% of women in the control group; rate ratio 0.85, 95% CI 0.75 to 0.97, 2p=0.02.

### Commentary

**Commentary provided by Professor Chris Holcombe, Consultant Oncoplastic Breast Surgeon Royal Liverpool University Hospital and Deputy Chair of the National Breast Cancer Clinical Reference Group**
This meta-analysis looked at patient level data for nearly 19,000 women, with a median follow up of 5.6 woman-years. There was definite benefit only in postmenopausal women (nearly 12,000 women), with highly significant reductions in breast cancer recurrence, distant recurrence (bone or otherwise), bone recurrence and breast cancer mortality. The absolute gain from treatment at 10 years was a 3.3% reduction in breast cancer mortality, suggesting perhaps 200 of approximately 6800 postmenopausal deaths from breast cancer annually could be prevented. Reductions in bone recurrence and breast cancer mortality were seen across all breast cancer types, and there was no increase in non-breast cancer mortality.

There is now clear evidence that bisphosphonates given as adjuvant therapy to postmenopausal women who have had breast cancer results in an 18% relative reduction in breast cancer deaths compared with no bisphosphonate use. Treatment with bisphosphonates is relatively easy to give and inexpensive, and they have an established long-term safety record. Bisphosphonates also reduce the risk of fractures and improve bone health in this group of women, most of whom are taking aromatase inhibitors which may cause a reduction in bone mineral density with a possible consequent increased risk of fracture.

Adjuvant bisphosphonate treatment would seem to provide an achievable gain in improving breast cancer mortality, particularly because most women with breast cancer are postmenopausal. The commentary accompanying this meta-analysis recommended that its publication should lead to widespread adoption of bisphosphonates for the adjuvant therapy of early-stage breast cancer in postmenopausal women. The type of bisphosphonate required, as well as the dosing interval and duration of therapy, remains somewhat unclear and no bisphosphonates are licensed specifically for this use. However, draft guidance from the National Breast Cancer Clinical Reference Group is now recommending that intravenous zoledronic acid 4 mg every 6 months for 5 years should be offered to postmenopausal women with early breast cancer.

There is a small incidence of osteonecrosis of the jaw with bisphosphonate treatment (an uncommon adverse reaction occurring in between 1 in 1000 and 1 in 100 people), so good dental health is important. Renal function should also be monitored, and people should be adequately supplemented with calcium and vitamin D.

Study sponsorship

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References


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