Adjuvant bisphosphonates - UK

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Setting/patient population
Prevention of breast cancer spreading to the bone in post-menopausal women with primary breast cancer

Licensed indications
Zoledronic acid was licensed for prevention of bone fractures in adults with advanced cancer by Novartis in 2001 and marketed as Zometa. Novartis then licensed it for osteoporosis in 2005 when it was still patent-protected. As of 2012, after the patent expired, a range of generic manufacturers have licensed it for both uses (only one company has licensed it for both indications; the others have picked one indication only).\(^1\)

Ibandronic acid was licensed to prevent bone fractures in adults with advanced cancer, and for the treatment of tumour-induced hypercalcaemia, by Roche in 1996 and marketed as Bondronat.\(^2\) It is now off-patent.

New indication
A meta-analysis of 26 randomised controlled trials involving nearly 19,000 women around the world with primary breast cancer, more than 11,000 of whom were post-menopausal, concluded that giving a bisphosphonate to post-menopausal women with primary breast cancer could improve the following outcomes:

- Reduced risk of breast cancer spreading to the bones within 10 years by 28% (reduction in absolute risk from 8.8% to 6.6%)
- Reduced risk of breast cancer spreading (to any site, including bone) within 10 years by 18% (reduction in absolute risk from 21.2% to 17.9%).
- Reduced risk of death from breast cancer within 10 years by 18% (reduction in absolute risk from 18.0% to 14.7%)

No benefits or harms were seen in pre-menopausal women.

The benefits of bisphosphonates were similar irrespective of histological type of breast cancer and the use of other treatments such as chemotherapy.\(^3\)

Although the percentage of absolute benefit appears small, the treatment is estimated to save 1,178 lives\(^4\) every year in the UK if given routinely to the entire eligible population (around 35,700).\(^5\)
Current use of bisphosphonates

Bisphosphonates are, in simple terms, drugs that protect the skeleton. They do this by slowing down the breakdown processes that cause bone damage and have been used for many years to treat osteoporosis.

For the last 20 years or so they have also been used to treat people living with cancer that has spread to the bones, which is a common site of metastatic spread in secondary breast cancer. It reduces cancer-induced bone damage and thus prevents fractures.

Examples of bisphosphonates include pamidronate, ibandronic acid, sodium clodronate and zoledronic acid which are all currently used to help prevent the damage caused by breast cancer which has spread to the bone.

Evidence for secondary breast cancer prevention

The meta-analysis combined information from 26 international trials that may have been too small on their own to demonstrate definite benefits, or not designed to be able to detect benefits that only occur in a subset of patients.

Previous studies looking at the use of bisphosphonates in this way were quite varied in their outcomes and/or showed benefits in just subsets of patients. By pooling data as part of a meta-analysis the team were able not only to gain results that provide concrete answers, but also that have the potential to change clinical practice.

The meta-analysis was carried out by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG). This particular study was led by researchers at the University of Oxford and the University of Sheffield within the group and also involved numerous collaborators across the UK and internationally. The EBCTCG, and therefore this meta-analysis, was funded / supported by Cancer Research UK and the UK Medical Research Council.

Clinical consensus

The NHS England Breast Cancer Clinical Reference Group has developed breast cancer service guidance, which is in final draft form. This guidance will recommend that this treatment is offered routinely for postmenopausal women with primary breast cancer, and that both IV (to be delivered in the Oncology Unit) and oral tablet (to be initiated in secondary care but continued in primary care) options are available to patients, and that switching between the two is an option.

The results of the meta-analysis were discussed at a meeting of the UK Breast Cancer Group in November 2015, a forum made up exclusively of breast oncologists. There was unanimous agreement that the data from the paper was sufficient to support implementation and also that there was a moral duty to do so. Some oncologists have started providing the treatment using local funding arrangements; others are attempting to do so, but with many pending funding approval; some have expressed their desire to wait for some kind of national guidance or protocol.

In addition, European consensus guidance was published in the Annals of Oncology in January 2016. The panel recommended that bisphosphonates be offered routinely to postmenopausal women with primary breast cancer.6

Clinical pathway

The NHS England Breast Cancer Clinical Reference Group draft guidance recommends a treatment regime of:

- IV zoledronate/ zoledronic acid (4mgs every 6 months for 3 years)
- Oral ibandronate (50mg daily for 3 years)

It also notes that switching between the IV zoledronate and oral ibandronate is an option.
For IV zoledronate, patients should be treated in the Oncology Units with monitoring and input by Oncology teams. For oral ibandronate, this should be initiated in secondary care but continued in primary care.

The guidance includes advice as to the monitoring of renal function, calcium and vitamin D as well as dental health, owing to the increased risk of osteonecrosis of the jaw (ONJ). The costs of monitoring are factored into the financial modelling.

**Variable access**

Despite the clinical consensus, a UK-wide survey by the UK Breast Cancer Group in March 2016 showed that access is highly variable, and currently only 24% of respondents are routinely offering it. The survey represented at least 125 breast cancer oncologists across approximately 56 hospitals in the UK. This is estimated to be 50-60% of the total UK population of breast cancer oncologists.

A common theme from the survey is a perceived requirement to wait for, or a desire to have, national endorsement/guidance. What is most concerning is that some oncologists are waiting for a national funding decision, or believe that one is underway – though we’re not aware that any is planned in any of the nations.

**Need for national commissioning guidance**

The survey showed that the vast majority of those trying to implement it were currently experiencing blockages in funding and commissioning (and not for clinical reasons). Indeed the blockage for this indication seems to be that oncologists lack a robust business case to persuade hospital management and/or local commissioners. Although the treatment is cheap (best estimate is about £474 per patient for the whole course when you factor in calcium and renal monitoring and consultant time), there are some up-front costs, and a common complaint is the need for a national appraisal which includes a business case and Financial Impact Assessment, and/or a national commissioning policy.

**Potential savings for the NHS**

The total cost of administering this treatment in the UK to the annual patient population of 35,700 would be £16,917,783. This cost is offset in the short term by savings from no longer needing to take DEXA bone scans in this patient population – a saving of £6,835,122 per annual cohort, and in the long term by around 1,214 fewer women developing secondary breast cancer per annual cohort – a saving of at least £15,172,500. This means that there would be a net saving of at least £5.09m per annual cohort of patients.

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1. European Medicines Agency – zoledronic acid  
2. European Medicines Agency – ibandronic acid  
4. This is based on the impact bisphosphonates had on breast cancer mortality (in post-menopausal women) within 10 years – a reduction in the relative risk of death from breast cancer within 10 years of 18% (reduction in absolute risk from 18.0% to 14.7%). This is a difference of 3.3%.
This is based on the annual average number of breast cancer (ICD10 C50) cases diagnosed in females aged 55 and over in the UK between 2011-2013. Information provided by CRUK, 16 May 2016. The average age for women to reach the menopause in the UK is actually 51, meaning that 35,700 is a modest estimate of the number of women who would be eligible to take bisphosphonates each year. Breast cancer incidence figures were only available in 5 year intervals (50-54; 55-59 and so on), so the more modest estimate has been used.

http://www.nhs.uk/conditions/menopause/Pages/Introduction.aspx


This is based on the impact bisphosphonates had on breast cancer distant recurrence (in post-menopausal women) within 10 years – a reduction in the relative risk of breast cancer spreading (to any site, including bone) within 10 years of 18% (reduction in absolute risk from 21.2% to 17.9%). This is a difference of 3.4% (discrepancy acknowledged – difference presumed to be due to rounding of figures, see appendix of published paper for details).

There is a discrepancy between the number of lives saved (1,178) and the number of secondary breast cancers prevented (1,214). This is because ‘lives saved’ is based on the difference in breast cancer mortality at 10 years between those who received bisphosphonates and those who didn’t, whereas ‘secondary breast cancers prevented’ is based on the difference in distant recurrence at 10 years. Although you might expect the numbers to be more similar, the difference could possibly be explained by a small number of women who died without developing secondary breast cancer.

There is no comprehensive up-to-date estimate of the total cost of a secondary breast cancer patient to the NHS. The best estimate currently available is £12,500 and this, from 2004, is likely to be a gross underestimate. So in reality, the savings are anticipated to be notably higher. Remak, E; Brazil, L (2004): Cost of managing women presenting with stage IV breast cancer in the UK, British Journal of Cancer 91, 77-83.

A lay summary of the financial modelling of adjuvant bisphosphonates has been developed by Breast Cancer Now in collaboration with Professor Rob Coleman. This is based upon cost of treatment and of potential savings outlined in the business case and financial modelling undertaken by South Yorkshire Cancer Strategy Group in February 2016. This modelling is based on zoledronic acid/zoledronate and ibandronic acid/ibandronate only. This is because, although clodronate has been shown to have a similar survival benefit to ibandronic acid, it is more expensive.

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