Adjuvant bisphosphonates: our recommendations

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Mount Vernon Cancer Centre

OPTIMA launch meeting, 27 April 2017
Breast Cancer Metastasis

Tumour cell colonisation of bone

- Tumour cells home to the HSC niche
- Environmental signals maintain tumour cell quiescence

Tumour cell proliferation and metastasis progression

- Escape from quiescence
- Tumour cell proliferation
- Onward Dissemination

Stimulation of bone resorption

Development of bone lesions

Hematopoietic stem cell (HSC)

HSC niche

Tumour cell

Osteoblast

Osteoclast
Bisphosphonates are widely used

- **Osteoporosis**
  - Improve bone mineral density
  - Reduce fracture risk

- **Metastatic breast cancer**
  - Improving QoL
  - Reducing pain
  - Reducing need for palliative radiotherapy
  - Reduce incidence of complications such as spinal cord compression, hypercalcaemia and fractures

- **Well tolerated**
  - Mild toxicity
  - Osteonecrosis of the jaw (1-3%)
Side-effects of bisphosphonates

- Well tolerated
- Mild toxicity
- Osteonecrosis of the jaw (1-3%)
- Renal impairment
- Musculoskeletal symptoms
- Dyspepsia with oral bisphosphonates
Trials of bisphosphonates in early breast cancer in the 1990s (Prospective placebo controlled)

- Diel Trial
  - N=302, bone marrow +ve, clodronate 2yrs
  - YES

- Saarto Trial
  - N=282, node +ve, clodronate 3yrs
  - NO

- Powles trial
  - N=1069, operable, clodronate 2yrs
  - MAYBE

Powles TJ et al JCO 2002; 20: 3219
Diel I et al NEJM 1998; 339: 357
Sakho T et al JCO 2001; 19: 10
ABCSG-12: Pre-menopausal women
Endocrine therapy ± zolendronic acid
84 month follow-up

Gnant M et al NEJM 2009; 360: 679-691
AZURE: Study Design

Accrual September 2003 - February 2006

3,360 Breast Cancer Patients
Stage II/III

<table>
<thead>
<tr>
<th>Countries</th>
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<th>Patients</th>
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</table>

Standard therapy

- 6 doses
- Q3-4 weeks
- 8 doses
- Q 3 months
- 5 doses
- Q 6 months

Zoledronic acid treatment duration 5 years
ITT Analysis: Disease (DFS) and Invasive Disease Free Survival (IDFS)

**DFS**

Adjusted HR 0.94  
95% CI: 0.82-1.06, P=0.298

**IDFS**

Adjusted HR 0.93  
95% CI: 0.82-1.05, P=0.222
AZURE: Invasive DFS by Menopausal Status

Pre, peri and unknown menopausal status

Adjusted HR 1.03
95% CI: 0.89-1.20

Adjusted HR 0.77
95% CI: 0.63-0.96

Menopausal Interaction: $\chi^2_1 = 4.71; P = 0.030$
Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials

*Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)*

*Lancet 2015; 386: 1353–61*
Effect of adjuvant bisphosphonates
Breast Cancer Mortality By Menopausal Status

‡ includes women aged < 45 if unknown
Adjuvant bisphosphonate meta-analysis

• 18,766 women in trials of EBC
• Randomised to bisphosphonate vs control
• 97% were between 2-5 yrs of bisphosphonate therapy

• Benefit only in post-menopausal women
  – 28% reduction in bone recurrence
  – 18% reduction in breast cancer mortality
  – 3.3% absolute gain in breast cancer mortality at 10 years

• No difference seen by bisphosphonate class, treatment schedule, ER status, grade, nodal status or concomitant chemotherapy

EBCTG Lancet 2015; 386: 1353-1361
Benefit of adjuvant bisphosphonates

• Similar to that seen with
  – Taxanes added to anthracycline schedules
  – Aromatase inhibitors vs tamoxifen
SWOG 0307

- **Arm 1:** 3 years of zoledronic acid (ZA, 4 mg IV monthly x 6 then Q3M x 2.5 years)
- **Arm 2:** 3 years of clodronate (1600 mg po daily)
- **Arm 3:** 3 years of ibandronate (50 mg po daily)

- Primary endpoint: DFS
- Secondary endpoints: OS, distribution of sites of first recurrence, adverse events (AEs)

Gralow J et al. ASCO 2015, abs 503
SWOG 0307: DFS

Gralow J et al. ASCO 2015, abs 503
ABCSDG 18 – Study Design

Postmenopausal ER+ breast cancer Adjuvant AI therapy (N = 3425)

Primary endpoint:
Time to first clinical fracture

Secondary endpoints:
Change in BMD at 36 months
Vertebral fractures (new/worsening)

Denosumab 60mg q6m median 7 doses (range 1-16)

Placebo q6m median 7 doses (range 1-16)

Gnant M. et al. ASCO 2015, abs 504
ABCSG 18
Patient Characteristics and Treatment Tolerability

- **3,425** postmenopausal patients on adjuvant AI
  - Median age: 64 years (38-91)
  - Tumor size <2 cm: 72%  
  - Node-negative disease: 71%
  - Grading: G3 19%  
  - Ductal invasive histology: 74%
  - Both ER and PR positive: 83%  
  - HER-2 overexpressing: 6%
  - (Neo)adjuvant Chemotherapy: 25%

- **Adverse and serious adverse events**
  - Mainly associated with known AI profile (Hot flushes, arthralgia, bone pain)
  - No measurable difference between denosumab and placebo in this double-blind trial
  - No case of ONJ despite proactive screening for this condition
  - No case of atypical fracture

Gnant M. et al. ASCO 2015, abs 504
ABCBSG 18 – Risk of Fractures

Median follow-up: - 38 months

Fracture rate somewhat higher than expected (>15% in placebo arm) at 5 years. Does this represent the true rate of fractures? iDMC recommended unblinding.
ABCSG 18 – DFS: ‘time-driven’ ITT Analysis (cross-over patients censored)

![Graph showing disease-free survival and HR comparison between Placebo and Denosumab.]

<table>
<thead>
<tr>
<th>Number of Events / Patients</th>
<th>HR (95% CI) vs Placebo</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Placebo 199 / 1,709</td>
<td>0.807 (0.66 - 0.99)</td>
<td>0.0424</td>
</tr>
<tr>
<td>Denosumab 164 / 1,711</td>
<td></td>
<td>0.0419</td>
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Patients at risk

Placebo: 1709 1661 1616 1562 1424 1269 1066 935 757 675 523 443 279 231 109 69
Denosumab: 1711 1673 1619 1580 1418 1291 1096 976 773 708 543 475 296 250 115 66

*Patients (N=54) who went EoT because of alternate bone-active therapy (BIS, D-Mab) according to the protocol were censored at EoT stratified by hospital type, use of prior aromatase inhibitor, and baseline lumbar spine bone mineral density.

Gnant M. et al, SABCS 2015 S2-02
**D-Care (Denosumab in EBC)**

**ABCSG-18 & D-CARE Trials: Dmab in Adjuvant BC**

**ABCSG-18**
- **Primary Objective:** Compare the effects of Dmab vs placebo on the rate of first clinical fracture in women with nonmetastatic BC receiving NSAI therapy

- **N = 3,400**
  - **Placebo SC q6mo**
  - **Denosumab 60 mg SC every q6mo**
  - **Follow-up without treatment: 96 mo**
  - **Treatment duration: 48 mo**

**D-CARE**
- **Primary objective:** Bone-metastasis–free survival with denosumab vs placebo

- **N = 4,500**
  - **Placebo 120 mg SC monthly x 6 mo, q3mo x 4.5 yr**
  - **Dmab 120 mg SC monthly x 6 mo, q3mo x 4.5 yr**
  - **Treatment duration: 5 yr**

*Abbreviations: ABCSG-18, Austrian Breast and Colorectal Cancer Study Group trial 18; BC, breast cancer; Dmab, denosumab; NSAI, nonsteroidal aromatase inhibitor; R, randomisation; SC, subcutaneous.*

Barriers to the use of bisphosphonates in EBC

• Bisphosphonates are not licensed for treatment of EBC
• Pharma would not be interested in getting a license for a drug whose patent has expired
• Lack of national guidelines
• Not assessed by NICE
• Difficult to deliver 6-monthly treatment

• No funding mechanism in place
• Difficult to engage commissioners
UKBCG survey on use of bisphosphonates in EBC

• 125 oncologists from 56 hospitals responded
• Implementation of adjuvant bisphosphonates
  – 24% YES
  – 59% NO
  – 17% PARTIALLY
• Of those implementing the majority offered zometa 6 monthly for 3 or 5 years
• Funding mainly from Trusts rather than CCGs
• Of those who had not implemented
  – 73% waiting for funding decision
  – 18% waiting for clinical decision
  – 9% waiting for both
National Breast CRG
Benefit of adjuvant bisphosphonates in post-menopausal women

- The National Breast Clinical Reference Group has recommended in their draft guidance that adjuvant bisphosphonates should be considered for all postmenopausal breast cancer patients

- It is recommended that MDT Leads use the guidance to discuss with commissioners how a local adjuvant bisphosphonate service might be commissioned
How breast cancer victims miss out on life-saving pill costing 34p a day

Red tape sees women miss out on breast cancer drug

Lives at risk from funding row over 43p cancer drug

Cancer patients are denied 43p-day drugs

Breast cancer patients 'should be offered cheap bone drug'

Also covered by: Press Association, Daily Express, The Scotsman, itv.co.uk, HuffPost UK, The Independent, Belfast Telegraph
Featured on:
- BBC Radio 4’s Today
- Good Morning Britain
- BBC 5 Live Breakfast
- Victoria Derbyshire
- BBC Breakfast
- Sky News
- ITV Lunchtime News
- 5 News at 5
- BBC News at Ten
Letter to the Editor of The Times - 14th November 2016

Make 43p breast cancer drug available to all, say doctors

Katie Gibbons Health Correspondent

Britain’s most senior breast cancer doctors have called on the health secretary to end confusion which is denying thousands of women a life-changing drug that costs 43p a day.

The pills, which are routinely used to treat osteoporosis, could extend the life of up to 27,000 women with late-stage breast cancer and prevent one in ten deaths.

Confusion over which health body is responsible for commissioning the drugs means that three quarters of oncologists cannot prescribe them, according to a recent survey.

Now 41 breast cancer experts have urged Jeremy Hunt to make the commissioning of bisphosphonates a national priority to prevent the death of more than a thousand women eligible for the treatment each year.

It is the responsibility of clinical commissioning groups (CCGs) to decide whether to pay for the drugs, which experts say will lead to a postcode lottery as many are unaware of the guidance.

In a letter to The Times they have urged Mr Hunt to clarify who is responsible for prescribing bisphosphonates, which research shows could cut the risk of dying from breast cancer within ten years of surgery by almost a fifth.

“While commonly used to treat osteoporosis and advanced cancer, significant evidence published in July 2015 demonstrated their potential in post-menopausal breast cancer patients to reduce the risk of the disease spreading and becoming incurable,” they write.

“Adopting them routinely in this way wouldn’t just save hundreds of lives each year, it would offer the NHS a long-term cost saving.”

Analysis published in The Lancet showed they could reduce the risk of breast cancer spreading to the bone and prevent it from becoming incurable.

Breast Cancer Now estimates that 27,000 women are potentially missing out on treatment. If the drug were routinely available to all eligible postmenopausal women, the charity believes that 1480 patients a year could be saved.

Mir Rosenblatt, of Breast Cancer Now, said: “The health secretary has said on many occasions that he wants cancer treatment in this country to be the best in Europe, and this issue represents an important bureaucratic barrier to that promise.

“We, alongside leading clinicians and patients, now call on the health secretary to step in to give clarity and ensure that all postmenopausal women diagnosed with breast cancer are able to access these effective and cheap drugs.”

The charity wrote to NHS England in March to demand clarity on funding and a clear policy on making the drug available. They were told that NHS England Specialised Services believed commissioning responsibility sat locally with CCGs.

Breast cancer is the most common cancer in the UK and kills 11,500 a year.

Letters, page 32
Summary of adjuvant bisphosphonates financial modelling
Developed by Breast Cancer Now in collaboration with Professor Rob Coleman
Cost of treatment and of potential savings taken from business case and financial modelling by South Yorkshire Cancer Strategy Group, Feb 2016
A Patient population
B Pathway scenarios
C Cost-savings elsewhere
D Total cost versus total savings
E Cost savings and lives saved per UK nation

Key points for England (29,600 post-menopausal women)
- C = Saving of cost of investigations needed without bisphosphonates approx £6m (per annual cohort)
- D= Saving of cost of having secondary breast cancer due to reduction of 1006 pts/yr @ estimate cost of £12500 (2004 and likely underestimate with new higher cost drugs) = £12,580,000
- Cost of bisphophonates approx £14m
- Total saving = £14 -£6 -£12,580,000 = approx £4 m savings per annual cohort i.e £ 400k year 1 , £800k year 2 to £4m by year 10.
OPTIMA recommendations for adjuvant bisphosphonates

• A recent meta-analysis has demonstrated a survival benefit for women with EBC receiving adjuvant bisphosphonates. The benefit is seen in postmenopausal women and those who become postmenopausal as a result of their treatment. The metaanalysis does not demonstrate superiority of one agent over another or an optimal duration of therapy.

• In the OPTIMA trial, all patients are eligible for treatment with bisphosphonates as they are either postmenopausal or if they were premenopausal at diagnosis they will have received ovarian suppression.

• It is recommended that patients in the OPTIMA trial receive a bisphosphonate (oral or iv) for 3-5 years.
Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline

Sukhbinder Dhesy-Thind, Glenn G. Fletcher, Phillip S. Blanchette, Mark J. Clemons, Melissa S. Dillmon, Elizabeth S. Frank, Sonal Gandhi, Rasna Gupta, Mihaela Mates, Beverly Moy, Ted Vandenberg, and Catherine H. Van Poznak

DOI: 10.1200/JCO.2016.70.7257 Journal of Clinical Oncology – published online before print March 6, 2017
ASCO/CCA guidelines

• Zolendronic acid 4mg iv every 6 months for 3-5 years or clodronate oral 1,600mg daily for 2-3 years be considered as adjuvant therapy for postmenopausal patients with breast cancer who are deemed candidates for adjuvant systemic therapy

• Further research comparing different agents, doses, dosing intervals, duration is required

• Data on denosumab is promising but insufficient
Conclusions

• Meta-analysis shows a benefit in survival from the use of adjuvant bisphosphonates in the treatment of EBC
  – If adopted in the UK it would lead to 1000 breast cancer deaths being avoided
• Evidence for denosumab is weaker but a large prospective RCT has completed
• Denosumab is more convenient to administer but more expensive acquisition cost
• Bisphosphonates are not licensed for use in EBC, and pharma will not apply for license. Wide variation exists in the adoption of this policy
• In OPTIMA you can adopt your current policy in expectation that adjuvant bisphosphonates will be increasingly used