What is the Role of Adjuvant Bone Modifying Agents in Breast Cancer?

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DISCLOSURE INFORMATION

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Scientific rationale of adjuvant bone modifying agents

Data from phase III randomized trials and EBCTCG meta-analysis

Clinical Practice Guidelines for adjuvant bone modifying agents
- ASCO/Cancer Care Ontario (2017)
- European Consensus Panel (2016)

Other questions
- Optimal duration
- Best bone modifying agent
Bone Modifying Agents available in the Clinic

**Bisphosphonates**
Inhibit bone resorption by osteoclasts

- Pamidronate (Approved for Paget’s disease, *osteolytic bone metastases of breast cancer and multiple myeloma*, hypercalcemia of malignancy)
- Zoledronate (Approved for *osteoporosis*, Paget’s disease, *cancer related bone complications*, hypercalcemia of malignancy)

**i/v agents**

**Pamidronate**

**Zoledronate**

**Oral agents**

- Clodronate
- Risedronate*
- Ibandronate*
- Alendronate*

*R Approved by US FDA for *osteoporosis*
# Not approved by US FDA for any indications

**RANK Ligand Inhibitors**
Prevents RANK ligand from binding to osteoclasts, thus inhibiting osteoclast activity

- Denosumab (s/c)
  
  Approved by US FDA for *osteoporosis, osteolytic bone metastases of solid tumors and multiple myeloma, giant cell tumor of bone, hypercalcemia of malignancy*
Scientific Rationale of Adjuvant Bone Modifying Agents

Reduce bone metastases by inhibiting tumor-induced osteoclasts

Reduce non-bony metastases by various postulated mechanisms
Adjuvant Bone Modifying Agents in Early Breast Cancer

Current Developmental Status

Bisphosphonates

Denosumab
Adjuvant Bisphosphonates Trials in Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royal Marsden</td>
</tr>
<tr>
<td>NSABP-B34</td>
</tr>
<tr>
<td>ABCSG-12</td>
</tr>
<tr>
<td>AZURE, UK</td>
</tr>
<tr>
<td>GAIN, German</td>
</tr>
<tr>
<td>TEAM IIB</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Bisphosphonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1069</td>
<td>Oral clodronate</td>
</tr>
<tr>
<td>3323</td>
<td>Oral clodronate</td>
</tr>
<tr>
<td>1803</td>
<td>i/v zoledronate</td>
</tr>
<tr>
<td>3400</td>
<td>i/v zoledronate</td>
</tr>
<tr>
<td>3700</td>
<td>Oral ibandronate</td>
</tr>
<tr>
<td>1116</td>
<td>Oral ibandronate</td>
</tr>
</tbody>
</table>

>20 other smaller trials
- Many where primary endpoint is on fracture reduction and/or preservation of bone mineral density with *adjuvant effects being secondary endpoints*

Meta-analysis (EBCTCG, 2015)  
**26 trials; >18,000 patients**
Adjuvant Clodronate in Breast Cancer

Royal Marsden, UK
Primary endpoint: bone mets
N=1069 stage I-III breast cancer
Any menopausal status, any HR status
Postmenopausal 50%, ER+ 46%

R 1:1
PO Clodronate 1600mg/day x 2 years
PO Placebo

NSABP B34
Primary endpoint: DFS
N=3311 stage I-III breast cancer
Any menopausal status, any HR status
Age ≥50: 65%, HR+ 78%

R 1:1
PO Clodronate 1600mg/day x 3 years
PO Placebo

Women ≥50Y
RFS HR 0.75, p=0.045
Bone mets free interval HR 0.62, p=0.027
Non-bone mets free interval HR 0.63, p=0.014
OS HR 0.80, p=0.094

Bone mets free interval improved
5Y HR 0.692, p=0.043
90% vs 86.5%, Δ3.5%

Overall survival improved
10.5Y HR 0.768, p=0.048
(not significant due to multiple analysis)

Clodronate
Placebo
DFS entire cohort not improved
HR 0.91 (95% CI 0.78-1.07) p=0.27

Adjuvant Zoledronate in Breast Cancer

ABCSG-12 (2x2 factorial design)
Primary endpoint DFS
N=1803 stage I-II HR+ breast cancer
Premenopausal on medical ovarian suppression with 4-weekly goserelin
Randomized to tamoxifen vs anastrozole; with or without zoledronate

R 1:1

i/v Zoledronate 4mg x 3 years
6 monthly

No Zoledronate

Median FU 94.4 months (7.9 years)

DFS improved
HR 0.77, 95% CI 0.60-0.99
88.4% vs 85.0%, Δ3.4% (94.4 mths)
p=0.042

OS not significant
HR 0.66, 95% CI 0.43-1.02
p=0.64

Adjuvant Zoledronate in Breast Cancer

AZURE (BIG 01/04)
Primary endpoint DFS
N=3360 stage II-III breast cancer; any menopausal status, any HR status
*Postmenopausal 45%, ER+ 78%*

<table>
<thead>
<tr>
<th>R 1:1</th>
<th>i/v Zoledronate 4mg x 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-4 weekly x 6 months, 3-monthly x 2 years, 6-monthly x 2.5 years</td>
</tr>
<tr>
<td></td>
<td>No Zoledronate</td>
</tr>
</tbody>
</table>

Median FU 84 months (7 years)
ITT population (n=3360)

Menopausal >5 years (n=1041)
Pre-planned subgroup analysis

**DFS not improved**
HR 0.94, p=0.30

IDFS HR 0.93, p=0.22, OS HR 0.93, p=0.37

*Bone metastases as first event HR 0.78, p=0.020*

*Bone metastases at any time, HR 0.81, p=0.022*

**DFS improved**
HR 0.77 (95%CI 0.63-0.96)

**OS not significant**
HR 0.81 (0.63-1.04)
*Coleman et al. Lancet 2014; 15(9): 997-1006*
Adjuvant Ibandronate in Breast Cancer

**GAIN (2x2 factorial design)**

*Primary endpoint DFS*

N=3023 node positive early breast cancer

Any menopausal status, any HR status

Post-menopausal 52%, HR+ 77%

Randomized to ETC vs EC→TX chemo; ibandraonte vs observation

*PO Ibandronate 50mg/day x 2 years*

R 2:1

Observation

**TEAM IIb**

*Primary Endpoint DFS*

N=1116 stage I-III HR+ breast ca

On adjuvant endocrine therapy

Any menopausal status

*PO Ibandronate 50mg/day x 3Y*

R 1:1

Observation

**DFS not improved**

HR 0.945 (0.768-1.161) p=0.589

**OS not improved**

HR 1.040 (0.763-1.419) p=0.803

Median FU 4.6 years

DFS not improved

3Y DFS 94.4% vs 90.8%

HR 0.84, (0.60-1.17)

Bone mets 1.6% vs 4.6%

HR 0.76 (0.43-1.32)

*Von Minckwitz et al. JCO 2013; 31(28): 3531-9; Linn et al. SABCS 2016*
## Adjuvant Bisphosphonates in Breast Cancer
### Summary of Key Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Drug</th>
<th>Primary endpoint</th>
<th>Menopausal/HR status</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royal Marsden</td>
<td>1069</td>
<td>Clodronate</td>
<td>Bone mets</td>
<td>Any</td>
<td>Positive bone mets free survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSABP B34</td>
<td>3311</td>
<td>Clodronate</td>
<td>DFS</td>
<td>Any</td>
<td>Negative for ITT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 years</td>
<td></td>
<td>Positive DFS for women ≥50 years</td>
<td></td>
</tr>
<tr>
<td>ABCSG-12</td>
<td>1800</td>
<td>Zoledronate</td>
<td>DFS</td>
<td>HR+, premenopausal on medical ovarian suppression</td>
<td>Positive DFS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZURE</td>
<td>3400</td>
<td>Zoledronate</td>
<td>DFS</td>
<td>Any</td>
<td>Negative for ITT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 years</td>
<td></td>
<td>Positive DFS for post-menopausal women</td>
<td></td>
</tr>
<tr>
<td>GAIN</td>
<td>3700</td>
<td>Ibandronate</td>
<td>DFS</td>
<td>Any</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEAM IIb</td>
<td>1166</td>
<td>Ibandronate</td>
<td>DFS</td>
<td>HR+, any menopausal status</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 years</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Adjuvant Bisphosphonates in Breast Cancer

**EBCTCG Meta-Analysis**

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)

26 randomized controlled trials, n=18,766

Royal Marsden, NSABP B34, ABCSG-12, AZURE, GAIN studies were included and contributed >13,000 patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopausal status</td>
<td>Post-menopausal 63%</td>
</tr>
<tr>
<td></td>
<td>Pre-menopausal 33%</td>
</tr>
<tr>
<td>HR status</td>
<td>ER positive 73%</td>
</tr>
<tr>
<td></td>
<td>ER negative 19%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Yes: 83%</td>
</tr>
<tr>
<td>Bisphosphonates used</td>
<td>Zoledronate 50%</td>
</tr>
<tr>
<td></td>
<td>Clodronate 27%</td>
</tr>
<tr>
<td></td>
<td>Ibandronate 16%</td>
</tr>
<tr>
<td></td>
<td>Others 7% (pamidronate 5%, risedronate 2%)</td>
</tr>
<tr>
<td>Duration</td>
<td>&gt;2 years: 69%</td>
</tr>
<tr>
<td></td>
<td>2 years: 28%</td>
</tr>
</tbody>
</table>
### Adjuvant Bisphosphonates in Breast Cancer

**EBCTCG Meta-Analysis: Efficacy Data**

<table>
<thead>
<tr>
<th>10 years</th>
<th>All women N=18,766</th>
<th>Post-menopausal women N=11,767</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone recurrence</td>
<td>Δ1.1%, P=0.004 (7.8% vs 9.0%)</td>
<td>Δ2.2%, P=0.0002 (6.6% vs 8.8%)</td>
</tr>
<tr>
<td>Distant recurrence</td>
<td>Δ1.4%, P=0.03 (20.4% vs 21.8%)</td>
<td>Δ3.4%, P=0.0003 (17.9% vs 21.2%)</td>
</tr>
<tr>
<td>Breast cancer mortality</td>
<td>Δ1.7%, P=0.04 (16.6% vs 18.4%)</td>
<td>Δ3.3%, P=0.002 (14.7% vs 18.0%)</td>
</tr>
<tr>
<td>Breast cancer recurrence</td>
<td>Δ3.0%, P=0.002 (22.8% vs 25.8%)</td>
<td>Δ2.3%, P=0.005 (21.1% vs 23.5%)</td>
</tr>
<tr>
<td>All cause mortality</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No improvement in pre-menopausal patients

**Accompanying Editorial:**

“...absolute reduction in risk of breast cancer death at 10 years of 3.3% in post-menopausal women is similar to the benefit seen with anthracyclines versus non-anthracyclines polychemotherapy...”

Why is Adjuvant Bisphosphonates Effective only in Post-menopausal Women?

Hypothesis:
Post-menopausal (low estrogen) state results in increase bone turnover
- excess production of growth factors from bone
- favor survival of disseminated tumor cells or micrometastases within the bone marrow microenvironment
Adjuvant Bisphosphonates in Breast Cancer

Toxicities

Generally well tolerated

Acute phase reaction (fever, myalgia, fatigue) from intravenous bisphosphonates

Rare side effects:
- Jaw osteonecrosis, esophagitis, atypical fractures
- Overall incidence of jaw osteonecrosis <0.5% in adjuvant trials
  - Slightly higher with i/v zoledronate compared to oral agents

Consider for postmenopausal breast cancer patients
- Natural or induced menopause
- Weigh potential benefits and risks for the individual patient
  (majority of patients in the EBCTCG meta-analysis were of sufficient risk to receive chemotherapy)

Zoledronate and clodronate are the recommended agents
- Zoledronate 4mg every 6 months for 3-5 years OR Clodronate 1600mg daily for 2-3 years
- Different durations may be considered but not >5 years for zoledronate or >3 years for clodronate (no data)

Should be started soon after primary cancer treatment
- Did not specify when but mentioned ‘within 6 months of completing chemotherapy’
- Some concerns of overlapping toxicities between chemotherapy and bisphosphonates

Limited data to recommend other bisphosphonates or denosumab
- Some experts suggested denosumab as an alternative if unable to tolerate bisphosphonates
  (ABCSG-18; unpublished in 2017)
## Adjuvant Bisphosphonates in Breast Cancer

### European Consensus Panel

<table>
<thead>
<tr>
<th>Bisphosphonates recommendations</th>
<th>Premenopausal women on adjuvant ovarian suppression</th>
<th>Post-menopausal women at intermediate or high risk of recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong> I, A</td>
<td>Prevent cancer therapy induced bone loss and metastases</td>
<td>Prevent metastases irrespective or fracture risk</td>
</tr>
<tr>
<td><strong>Duration</strong> II, A</td>
<td><strong>Not exceed duration of ovarian suppression</strong> unless indicated for low T score (3-5 years)</td>
<td>3-5 years and only continued after 5 years if indicated by fracture risk</td>
</tr>
<tr>
<td><strong>Agent/dose/schedule</strong> I, A</td>
<td><strong>Zoledronate</strong> (4mg IV Q6 months) or <strong>Clodronate</strong> (1600mg PO daily)</td>
<td>At start of adjuvant therapy</td>
</tr>
</tbody>
</table>
## Adjuvant Bisphosphonates in Breast Cancer

### European Consensus Panel

<table>
<thead>
<tr>
<th>Consensus Statements</th>
<th>% panel members that agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Should be considered in post-menopausal women</td>
<td>92%</td>
</tr>
<tr>
<td>Should be considered in pre-menopausal women receiving ovarian suppression</td>
<td>92%</td>
</tr>
<tr>
<td>Should <em>not</em> be considered in pre-menopausal women</td>
<td>87%</td>
</tr>
<tr>
<td>Should be considered even though there is no regulatory approval for their use in this setting</td>
<td>75%</td>
</tr>
<tr>
<td>Should be considered in women with ER negative early breast cancer</td>
<td>62% (21% disagree, 17% neutral/abstain)</td>
</tr>
</tbody>
</table>
Dental clearance and preventive dentistry
Monitor bone mineral density
Monitor calcium and creatinine
Calcium and Vitamin D supplements, as appropriate

**Dental procedures required during adjuvant bisphosphonates?**
- No clear guidelines
- Some experts suggest holding bisphosphonates for 2 months prior to dental procedures and resuming when wound is healed

*Dhesy-Thind et al. JCO 2017; 35: 2062-81*
## Adjuvant Bisphosphonates in Breast Cancer

### Zoledronate versus Clodronate

<table>
<thead>
<tr>
<th>Administration, Logistics</th>
<th>Clodronate</th>
<th>Zoledronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Oral</td>
<td>i/v every 6 months</td>
</tr>
<tr>
<td>More convenient</td>
<td>More convenient</td>
<td>Less convenient</td>
</tr>
<tr>
<td>Preferred by patients</td>
<td>Preferred by patients</td>
<td>(patient has to travel to a medical facility; takes up nursing/pharmacy time)</td>
</tr>
<tr>
<td>(SWOG S0307 showed 73% patients would prefer oral versus intravenous formulation if efficacy is similar)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compliance</th>
<th>Non-compliance rate as high as 50% beyond 2 years</th>
<th>Compliance likely better</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Toxicities</th>
<th>More GI toxicities</th>
<th>More acute phase reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slightly less jaw osteonecrosis (~0.5%)</td>
<td>Slightly more jaw osteonecrosis (~1%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Cost/availability</th>
<th>£1800 per year in UK</th>
<th>£50 per year in UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not available in the USA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Dhesy-Thind et al. JCO 2017; 35: 2062-81*
SUCCESS Trial; 2x2 factorial design

**Primary endpoint: DFS**

N=3754 high risk early breast cancer

Randomized to FEC→docetaxel vs FEC→docetaxel/gemcitabine;
2 years vs 5 years zoledronate

<table>
<thead>
<tr>
<th>Median FU 3 years</th>
<th>2Y zoledronate</th>
<th>5Y zoledronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>~90%</td>
<td>~90%, p=0.827</td>
</tr>
<tr>
<td>OS</td>
<td>~95%</td>
<td>~95%, p=0.713</td>
</tr>
<tr>
<td>Bone recurrence</td>
<td>28 events</td>
<td>25 events</td>
</tr>
<tr>
<td>All grade AEs</td>
<td>27.2%</td>
<td>46.2%</td>
</tr>
<tr>
<td>G3,4 AEs</td>
<td>5.1%</td>
<td>7.6%</td>
</tr>
</tbody>
</table>

**No difference in efficacy but follow-up is short**
Other Questions

**Best Bisphosphonates?**

**SWOG S0307 Trial**

**Primary endpoint: DFS**

N=6097 Stage I-III breast cancer

Any menopausal status; any HR status

78% ER+

<table>
<thead>
<tr>
<th>Treatment</th>
<th>5Y DFS</th>
<th>5Y OS</th>
<th>G3,4 AE</th>
<th>Jaw ON</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO Clodronate 1600mg/day x 3 years</td>
<td>87.6%</td>
<td>92.4%</td>
<td>8.3%</td>
<td>0.36%</td>
</tr>
<tr>
<td>PO Ibandronate 50mg/day x 3 years</td>
<td>87.4%</td>
<td>92.9%</td>
<td>10.5%</td>
<td>0.77%</td>
</tr>
<tr>
<td>i/v Zoledronate x 3 years</td>
<td>88.3%</td>
<td>92.6%</td>
<td>8.8%</td>
<td>1.26%</td>
</tr>
</tbody>
</table>

**No difference in efficacy between 3 bisphosphonates**

**Some difference in toxicity profile**

Gralow et al, JNCI October 2019
Adjuvant Denosumab

Very **potent inhibitor of osteoclast activity**
As effective, if not more effective, than bisphosphonates
(in reducing osteoporotic fractures, treating hypercalcemia of malignancy,
and in reducing skeletal events in metastatic cancers)

**Advantages over i/v zoledronate**
- Subcutaneous injection
- Less acute phase reaction
- No dose adjustments required up to creatinine clearance 30ml/minute
Is denosumab a viable alternative in patients unable to tolerate bisphosphonates?

**ABCSG-18 (Published)**
- **Primary endpoint:** clinical fractures
- **Secondary endpoint:** DFS
- **N=3425 early HR+ breast cancer**
- **Post-menopausal, on adjuvant AI**

<table>
<thead>
<tr>
<th>R 1:1</th>
<th>s/c Denosumab 60mg during AI</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 monthly</td>
<td></td>
</tr>
</tbody>
</table>

**D-CARE (Unpublished)**
- **Primary endpoint:** Bone mets free survival
- **N=4509 early breast cancers**
- **Any menopausal, any HR status**
- **77% ER+**

<table>
<thead>
<tr>
<th>R 2:1</th>
<th>s/c Denosumab 120mg up to 5 years</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>monthly x 6 then 3 monthly up to 5 years</td>
<td></td>
</tr>
</tbody>
</table>

- **Median FU: 73 months**
  - **DFS HR 0.82, p=0.026**
  - **5Y DFS: 89.2% vs 87.3%, Δ1.9%**
  - **8Y DFS: 80.6% vs 77.5%, Δ3.1%**

- **Median FU: 67 months**
  - **No improvement in DFS or OS**
  - **DFS HR 1.04, p=0.57**
  - **OS HR 1.03**

*Gnant et al. Lancet Oncol Feb 2019; Coleman et al. Proc ASCO 2017*
Adjuvant Bone Modifying Agents in Early Breast Cancer

### PRE-/PERI-MENOPAUSAL

<table>
<thead>
<tr>
<th>HR negative</th>
<th>HR positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ovarian suppression not planned</td>
</tr>
</tbody>
</table>

### POST-MENOPAUSAL

Any HR status

---

**ADJUVANT BONE MODIFYING AGENTS **

**NOT INDICATED**

**Adjuvant Bone Modifying Agents may be considered**

<table>
<thead>
<tr>
<th>Risk of Cancer Recurrence</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone Receptor Status</td>
<td>Low</td>
<td>Positive/High</td>
</tr>
<tr>
<td>Clinical Fracture Risk</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Risk of Treatment Toxicities</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>

**LOW BENEFIT: RISK RATIO OF ADJUVANT BONE MODIFYING AGENTS**

**HIGH**