Bone health in breast cancer patients

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Bone health in breast cancer patients

- Bone health and breast cancer therapy
- Adjuvant use of bone stabilizing agents
- Treatment guidelines in MBC
- Open questions
- YOUR Questions

Thanks to Prof. Peyman Hadji (Frankfurt) and Prof. Ralf Schmidmaier (Munich) for generously sharing their slides on short notice.
Age and Estrogen dependent Change of BMD and BT

POSTMENOPAUSAL
↓ Estradiol
↓ Inh A, Inh B, ↑ FSH
↑ Act, BMP tone

Abbreviations: Act, activin; BMP, bone morphogenetic protein; FSH, follicle-stimulating hormone; Inh, Inhibin.
Breast Cancer Increases Fracture Risk
Results of the WHI observational study

- Prospective cohort study with 5.1 years of follow-up\(^1\)
- 5,298 breast cancer survivors in WHI study
- 80,848 reference population with no history of cancer
- Adjustment for age, weight, and ethnicity
- Women with history of BC had a 31% increased risk of fracture

WHI = Women’s Health Initiative.
# Tolerability of AI in DATA, IDEAL, and NSABP B-42

<table>
<thead>
<tr>
<th></th>
<th>DATA</th>
<th>IDEAL</th>
<th>NSABP-42</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1,660</td>
<td>1,824</td>
<td>3,923</td>
</tr>
<tr>
<td>Drug</td>
<td>Anastrozole</td>
<td>Letrozole</td>
<td>Letrozole</td>
</tr>
<tr>
<td>Comparison</td>
<td>3 years vs. 6 years</td>
<td>2.5 years vs. 5 years</td>
<td>5 years</td>
</tr>
<tr>
<td>AEs overall, per cent</td>
<td>~75 %</td>
<td>70 %</td>
<td>-</td>
</tr>
<tr>
<td>AEs recorded</td>
<td>e.g. Arthralgia 52% vs. 58%</td>
<td>1,591 vs. 1,843 (+16%)</td>
<td>-</td>
</tr>
<tr>
<td>≥CTC grade 3</td>
<td>~12%</td>
<td>~10%</td>
<td>-</td>
</tr>
<tr>
<td>Arthralgia/Myalgia</td>
<td></td>
<td>Arthralgia, Hot flushes, osteoporosis</td>
<td>-</td>
</tr>
<tr>
<td>Bone fractures</td>
<td>7.4% vs. 9.8%</td>
<td>?</td>
<td>5.4% vs. 4.8% @ 7 years</td>
</tr>
<tr>
<td>Osteopenia /-porosis</td>
<td>16% vs. 21%</td>
<td>10%</td>
<td>-</td>
</tr>
</tbody>
</table>
Fracture incidence of postmenopausal healthy and BC women on TAM and AI

ESMO clinical practice guideline: Bone health in cancer patients

- Clinicians treating cancer patients need to be aware of:
  - Treatments to reduce skeletal morbidity in metastatic disease
  - Strategies to minimise cancer treatment-induced skeletal damage

- ESMO guidelines “provide a framework for maintaining bone health in patients with cancer”

Influence of Risedronate (OAW) on BMD in women with ER/PR pos Breast Cancer on AI Treatment

Mean ± SE percent change in bone mineral density in spine, total hip,
#p<0.05, ##p<0.01 for comparison between RIS (solid line) and placebo (dashed line) groups using linear mixed
*p<0.05, **p<0.01 change from baseline using paired t test.

Prevention of therapy-induced osteoporosis

- n=252, luminal EBC, adjuvant AI, -1.0 > T > -2.5

Ellis et al, JCO 2008
Prevention of therapy-induced osteoporosis

- ABCSG-18: n=3420, luminal EBC, adjuvant AI

<table>
<thead>
<tr>
<th>Oestrogen receptor status</th>
<th>Placebo every 6 months (n=1709)</th>
<th>Denosumab 60 mg every 6 months (n=1711)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>16 (~1%)</td>
<td>20 (1%)</td>
</tr>
<tr>
<td>Positive</td>
<td>1693 (99%)</td>
<td>1691 (99%)</td>
</tr>
</tbody>
</table>

(Continued from previous column)

![Graph showing risk of fracture over time]

Risk of fracture (%)

- Fractures (n)/patients (n)
- Hazard ratio vs placebo
- p value

Gnant et al, Lancet 2015
Prevention of therapy-induced bone loss

Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO, IMS, and SIOG

Peyman Hadji\textsuperscript{a,+,1,2,3}, Matti S. Aapro\textsuperscript{b,7}, Jean-Jacques Body\textsuperscript{e,1}, Michael Gnant\textsuperscript{d,4}, Maria Luisa Brandi\textsuperscript{e,1,5}, Jean Yves Reginster\textsuperscript{f,5}, M. Carola Zillikens\textsuperscript{g,3}, Claus-C. Glüer\textsuperscript{h,1,3}, Tobie de Villiers\textsuperscript{i,1,6}, Rod Baber\textsuperscript{j,6}, G. David Roodman\textsuperscript{k,2}, Cyrus Cooper\textsuperscript{l,1}, Bente Langdahl\textsuperscript{m,3}, Santiago Palacios\textsuperscript{n,6}, John Kanis\textsuperscript{o,1}, Nasser Al-Daghri\textsuperscript{p,5}, Xavier Nogues\textsuperscript{q,5}, Erik Fink Eriksen\textsuperscript{r,3}, Andreas Kurth\textsuperscript{s,4}, Rene Rizzoli\textsuperscript{t,1,5}, Robert E. Coleman\textsuperscript{u,2,4}
Prevention of therapy-induced bone loss

Patient with cancer receiving endocrine treatment known to accelerate bone loss (AI, GnRH and TAM in premenopausal women)

- T-score > -2.0 and no additional risk factors
  - Exercise
  - Calcium and vitamin D if necessary
  - Monitor risk and BMD at 1–2 year intervals

- Any 2 of the following risk factors:
  - Age > 65 years
  - T-score < -1.5
  - Smoking (current or history)
  - BMI < 20
  - Family history of hip fracture
  - Personal history of fragility fracture > 50 years
  - Oral glucocorticoid use for > 6 months

- T-score < -2.0
  - Exercise
  - Calcium and vitamin D
  - Denosumab or Bisphosphonate therapy (zoledronic acid, alendronate, risedronate, ibandronate)
  - Monitor BMD every 2 years
  - Check compliance with oral therapy

Hadji et al, 2017
Bone-directed therapy in breast cancer patients

Coleman et al, ESMO clinical practice guideline bone health in cancer patients (2014)
Bone metastases in animal models

✓ CK+ HER2+ tumor cells could be detected in the bone marrow already in the stage of atypical ductal hyperplasia. This spread is thus not a late event in tumor progression.
Disseminated tumor cells in the bone marrow of patients with EBC

- DTCs can already be detected in 30-40% of patients at time of primary diagnosis
- Presence of DTCs is associated with poor outcome
- Systemic chemotherapy cannot eliminate all DTCs

Zoledronic acid in EBC patients with DTCs

Figure 4: Proportion of patients with DTC-positive bone marrow at 12 and 24 months after diagnosis.

- Control group: 27% at 12 months, 12% at 24 months
- ZOL group: 16% at 12 months, 0% at 24 months

Statistical significance:
- p = 0.106, 12 months
- p = 0.032, 24 months

Banys et al, BMC Cancer 2013
Optimal time to start zoledronic acid in EBC: ZO-FAST

For the ITT population, the disease-free survival was compared between IM-zoledronic acid 4 mg (42 events) and D-zoledronic acid 4 mg (62 events).

HR = 0.66; log-rank P-value = 0.0375

EBCTCG meta-analysis for adjuvant bisphosphonates

11,767 women

RR 0.82 (95% CI 0.73–0.93)
Log rank 2p=0.002
10-year gain 3.3% (95% CI 0.8 to 5.7)
Recommendaions of European Experts (2016): Bisphosphonates in EBC

questionnaire to all members of the writing committee to identify areas of consensus. The panel recommended that bisphosphonates should be considered as part of routine clinical practice for the prevention of CTIBL in all patients with a T score of ≤-2.0 or ≥2 clinical risk factors for fracture. Compelling evidence from a meta-analysis of trial data of >18,000 patients supports clinically significant benefits of bisphosphonates on the development of bone metastases and breast cancer mortality in post-menopausal women or those receiving ovarian suppression therapy. Therefore, the panel recommends that bisphosphonates (either intravenous zoledronic acid or oral clodronate) are considered as part of the adjuvant breast cancer treatment in this population and the potential benefits and risks discussed with relevant patients.

across all risk groups. There was consensus that a lack of regulatory approval for bisphosphonates in this setting should not preclude their use, with the majority indicating they could administer adjuvant bisphosphonates in their health care system as an off-label treatment based on a locally or nationally defined protocol or treatment guideline. The Panel was in agreement that either daily
Bisphosphonates in EBC: Who benefits?

- **Age ≥55**
  - **No**
    - **Natural amenorrhea for ≥ 12 months**
      - Prescribe a BP
  - **Yes**
    - **Prescribe a BP**

- **Menstrual period within past 12 months**
  - **Adjuvant treatment plan includes GnRH analogue**
    - **Yes**
      - Prescribe a BP for the duration of GnRH analogue.
    - **No**
      - Assess fracture risk and use BPs according to CTIBL guidelines. Counsel patient that BPs do not affect survival outcomes when used in this context.
Bone stabilizing agents in EBC: Denosumab

Study Goals ABCSG-18

To investigate the effect of adjuvant denosumab 60mg/Q6M in postmenopausal breast cancer patients receiving AI regarding:

- Bone health: (Gnant et al. Lancet 2015; 386: 433-43)
  - Clinical Fractures
  - Bone Mineral Density (BMD)
  - Vertebral Fractures (clinical and morphometric)

- Outcomes:
  - Disease-free survival
  - Bone metastases-free survival
  - Overall survival

- Safety
Bone stabilizing agents in EBC: Denosumab

**ABCSD-18 Sensitivity Analysis DFS (cross-over censored*)**

- **Placebo**: 199 / 1,709
- **Denosumab**: 164 / 1,711

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

*D 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.

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Bone stabilizing agents in EBC: Denosumab
Bone health in cancer patients: ESMO guidelines

clinical practice guidelines

Bone health in cancer patients: ESMO Clinical Practice Guidelines†

R. Coleman¹, J. J. Body², M. Aapro³, P. Hadji⁴ & J. Herrstedt⁵ on behalf of the ESMO Guidelines Working Group*
# Bone health in cancer patients: ESMO guidelines

## Table 3. Summary of anti-resorptive agent efficacy and regulatory approval in cancer patients

<table>
<thead>
<tr>
<th>Indications</th>
<th>Regulatory approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevention of skeletal-related events</strong></td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid 4 mg i.v. every 3–4 weeks [30–35]</td>
<td>All solid tumours and multiple myeloma&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Denosumab 120 mg s.c. every 4 weeks [36–38]</td>
<td>All solid tumours&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pamidronate 90 mg i.v. every 3–4 weeks [30, 31, 39]</td>
<td>Breast cancer and multiple myeloma&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Clodronate 1600 mg p.o. daily [40, 41]</td>
<td>Osteolytic lesions&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ibhandronate 50 mg p.o. daily [42,43]</td>
<td>Breast cancer&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ibhandronate 6 mg i.v. monthly [44]</td>
<td>Breast cancer&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Prevention of breast cancer metastases</strong></td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid 4 mg i.v. 6 monthly [45, 46]</td>
<td>None</td>
</tr>
<tr>
<td>Zoledronic acid 4 mg i.v. monthly × 6 then 3–6 monthly [47]</td>
<td>None</td>
</tr>
<tr>
<td>Clodronate 1600 mg daily [48,49]</td>
<td>None</td>
</tr>
<tr>
<td><strong>Prevention of prostate cancer metastases</strong></td>
<td></td>
</tr>
<tr>
<td>Denosumab 120 mg s.c. monthly [50]</td>
<td>None</td>
</tr>
<tr>
<td><strong>Prevention of treatment induced bone loss</strong></td>
<td></td>
</tr>
<tr>
<td>Denosumab 60 mg s.c. 6 monthly [51, 52]</td>
<td>None</td>
</tr>
<tr>
<td>Zoledronic acid 4 mg i.v. 6 monthly [46]</td>
<td>None</td>
</tr>
<tr>
<td>Alendronate 70 mg p.o. weekly [53]</td>
<td>None</td>
</tr>
<tr>
<td>Risedronate 35 mg p.o. weekly [54]</td>
<td>None</td>
</tr>
<tr>
<td>Ibhandronate 150 mg p.o. monthly [55]</td>
<td>None</td>
</tr>
<tr>
<td>Pamidronate 90 mg i.v. every 3 months [56]</td>
<td>None</td>
</tr>
</tbody>
</table>

<sup>a</sup>European approval.  
<sup>b</sup>United States.  

i.v., intravenous; s.c., subcutaneous; p.o., per os (by mouth).
Bone health in breast cancer | Prof. Harbeck

Bone health in cancer patients: ESMO guidelines

Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

*bisphosphonates*. Prophylactic use of bisphosphonates, although not formally approved in most countries, may be discussed in women with a low-oestrogen status (undergoing ovarian suppression or postmenopausal), as prolongation of DFS and breast cancer specific survival was demonstrated in these populations [I, B] [105, 138, 139]. In patients with treatment-related bone loss, bisphosphonates decrease the risk of skeletal complications [I, A] [140, 141].
Bone health in EBC: EMA approvals for denosumab

The claimed indication for Prolia was:

“The treatment of osteoporosis in postmenopausal women at increased risk of fractures. Prolia significantly reduces the risk of vertebral, non vertebral and hip fractures. The treatment of bone loss associated with hormone ablation in men with prostate cancer and in women with breast cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures.”

The approved indication and posology are the following:

“Treatment of osteoporosis in postmenopausal women at increased risk of fractures. Prolia significantly reduces the risk of vertebral, non vertebral and hip fractures. Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures.”
Bone health in breast cancer | Prof. Harbeck

Bone health in EBC: EMA approvals for denosumab

reasonable. In this small study, a significant gain in lumbar spine was demonstrated in the denosumab-treated group, of the same magnitude that had been demonstrated in larger denosumab studies in other indications and therefore it was considered reasonable by the CHMP to extrapolate to fracture results from these studies. The female HALT population would be considered by definition as postmenopausal. Treatment with an aromatase inhibitor is a clear risk factor in this group of patients and the applicant has demonstrated an effect of denosumab also in this sub-population. Hence, the indication valid for postmenopausal osteoporosis (“Postmenopausal women at increased risk of fractures”) is also valid for women treated with aromatase inhibitors for non-metastatic breast cancer. A separate indication for the female HALT population was thus considered not to be necessary by the CHMP.
Bone modifying agents in breast cancer

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-Third, 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

RELATED GUIDELINES


- ASCO-CCO Clinical Practice Guideline focused update on the role of bone-modifying agents in metastatic breast cancer. [in progress, expected completion in 2017]
So, Where are we exactly?
Bone health in breast cancer patients

✓ Bone health is an important issue in breast cancer patients due to natural changes and treatment induced bone loss (TIBL)

✓ Next to exercise, calcium and vitamin D, bone modifying agents (e.g. bisphosphonates, denosumab) are effective in reducing TIBL

✓ Adjuvant use of bone modifying agents (e.g. bisphosphonates, denosumab) is effective in reducing recurrences and thus prolonging DFS in postmenopausal patients.

✓ Body of evidence larger for adjuvant use of bisphosphonates with improvement of OS demonstrated in EBCTCG metaanalysis. Effective in postmenopausal patients irrespective of tumor biology, type of bisphosphonate. ABCSG 12 also demonstrated efficacy in premenopausal patients with ovarian suppression.
EVIDENCE-BASED, PATIENT-ORIENTED BREAST CANCER THERAPY

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