Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Osteo oncology and Bone Health
Osteoncology and Bone Health

- **Versions 2002–2019:**
  Bischoff / Böhme / Brunnert / Dall / Diel / Fehm / Fersis / Friedrich / Friedrichs / Hanf / Huober / Jackisch / Janni / Kolberg-Liedtke / Lux / Maas / Nitz / Oberhoff / Schaller / Scharl / Schütz / Seegenschmiedt / Solomayer / Souchon

- **Version 2020:**
  Solbach / Solomayer
Metaanalysen and Reviews (metastatic breast cancer)


Results of Phase III trials (metastatic breast cancer)


6. Rosen LS, Gordon DH, Dugan W et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. Cancer 100:36-43, 2004

Clinical relevance of bone resorption marker


Bisphosphonates for bone pain control

Denosumab - Therapy of bone metastases and skeletal related complications


Statement: Progression under bisphosphonates

Clinical relevance of bone resorption marker

Bisphosphonates for bone pain control
<table>
<thead>
<tr>
<th>Study Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. CALGB 70604 trial: n=1822 patients with metastatic breast cancer, metastatic prostate cancer, or multiple myeloma, 795 completed the study</td>
<td>SRE after 2 yrs: 29.5% zoledronic acid every 4 weeks 28.6% zoledronic acid every 12 weeks</td>
</tr>
<tr>
<td>2. Optimise-2-trial: n=460 with metastatic breast cancer</td>
<td>SRE after 1 year: 22.0% zoledronic acid every 4 weeks 23.2% zoledronic acid every 12 weeks</td>
</tr>
</tbody>
</table>


1. Templeton AJ et al. Prevention of symptomatic skeletal events with denosumab administered every 4 weeks versus every 12 weeks: A noninferiority phase III trial (SAKK 96/12, REDUSE). J Clin Oncol 32:5s, 2014 (suppl; abstr TPS5095)


7. Hortobagyi GN, Van Poznak C, Harker WG et al. Continued Treatment Effect of Zoledronic Acid Dosing Every 12 vs 4 Weeks in
Women With Breast Cancer Metastatic to Bone: The OPTIMIZE-2 Randomized Clinical Trial. JAMA Oncol 3(7):906-912, 2017


Skeletal Metastases
Treatment with Radionuclids

| Tumor progression after standard treatment of multiple / disseminated metastases and intolerable bone pain | Oxford |
|---|---|---|---|
| 186Rhenium-hydroxyethylidene-diphosphonat | 1b | B | + |
| 153Samarium | 1b | B | + |
| 89Strontium | 1b | B | + |
| 223Radium | 2b | C | + |
| 177Lu-EDTMP | 2b | C | + |
| 188 Rhenium-HEDP | 1b | B | + |

Cave: the potential benefits should be weighed against the risk of myelosuppression with pancytopenia

Reviews / Overview


186Rhenium (186Re-HEDP)


**153Samarium (153Sm-EDTMP)**

**89Strontium (89Sr-Chlorid)**

**223Ra-dichloride:**

177Lu (Lutetium)-EDTMP


<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decompression surgery, reduction of tumor volume, stabilization surgery (&lt; 24 h) and irradiation of the spine (RT)</td>
<td>2b</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Irradiation of the spine (&lt; 24 h) +/- steroids</td>
<td>3b</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Immediate start of treatment</td>
<td>1c</td>
<td>D</td>
<td>++</td>
</tr>
</tbody>
</table>

Clinical trials have included patients with different tumor entities!


8. Guideline Program Oncology (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive care of oncological patients –


### Metastatic Bone Disease

### Recurrent Bone Pain after RT

<table>
<thead>
<tr>
<th>Recurrent bone pain in pre-irradiated parts of skeleton</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single dose RT *</td>
<td>3b</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Fractionated RT *</td>
<td>3b</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Radionuclide therapy</td>
<td>3b</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Magnetic resonance-guided focused ultrasound</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Radiofrequency ablation</td>
<td>4</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Cryoablation</td>
<td>4</td>
<td>C</td>
<td>+</td>
</tr>
</tbody>
</table>

* Dose and fractionation depending on location, interval from first RT, and dose and fractionation of first radiotherapy.

---

**Recurrent bone pain in pre-irradiated parts of the skeleton**

Magnetic resonance-guided focused ultrasound


Cryoablation / Radiofrequency ablation


Bisphosphonates


**Denosumab**


Bisphosphonates


Denosumab


Recommendations for Prevention of Osteonecrosis of the Jaw (ONJ)

- During bisphosphonate or denosumab treatment, avoid any elective dental procedures involving jaw bone manipulations during treatment with bisphosphonates or denosumab (LoE 2a, recommendation grade A)
- Optimize dental status before start of bisphosphonate or denosumab treatment (LoE 2a, recommendation grade A)
- Inform patients about ONJ risk and educate about early symptom reporting
- In case of high risk for ONJ, use oral bisphosphonate
- Good oral hygiene, limiting of alcohol intake and stopping smoking should be recommended
- In adjuvant bisphosphonate therapy, ONJ was rare (<1%)


9. https://www.onkosupport.de/asors/content/e4126/e1743/e1861/e1862/e4628/LaufzettelAGSMOFarbefinal.pdf
Adjuvant Bone Targeted Therapy for Improvement of Prognosis

<table>
<thead>
<tr>
<th>Clodronate (oral)</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal patients</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Premenopausal patients</td>
<td>1a</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aminobisphosphonate (iv or oral)</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal patients</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Premenopausal patients</td>
<td>1a</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Denosumab (6 x 120 mg/3–4w + 14 x 120 mg/3m)</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal patients Stage II and III</td>
<td>1b</td>
<td>B</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Denosumab (60 mg s.c. q6m)</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal patients undergoing AI therapy</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Clodronate

Adjuvant Aminobisphosphonates

Denosumab


Guidelines

Dosage of Adjuvant Bisphosphonates for Improvement of Survival

- Non-Aminobisphosphonates:
  - Clodronat po 1600 mg/d (Bonefos / Clodronic acid)
  - Clodronat po 1040 mg/d (Ostac / Clodronic acid)

- Aminobisphosphonates:
  - Zoledronat iv 4 mg/6 m (Zometa / Zoledronic acid)
  - Ibandronat po 50 mg/d (Bontronat / Ibandronic acid)
  - Pamidronat po (orally not available in most countries)
  - Risedronat po 35 mg/w (Actonel / Risedronic acid)
  - Alendronat po 70 mg/w (Fosamax / Alendronic acid)
  - Optimal duration yet to be defined; in adjuvant studies duration of BP treatment varied from 2–5 years

Aminobisphosphonates include:
Zoledronic acid (65 %), oral ibandronate (24 %), oral pamidronate (8 %), oral risendronate (2 %), oral alendronate (1 %) (data from EBCTCG metaanalysis)


Bisphosphonates


Denosumab


Risk of osteoporosis and tamoxifen (fracture risk)

**Bisphosphonates**


Denosumab


Tamoxifen


7. Pineda-Moncusí M, Garcia-Giralt N, Diez-Perez A et al. Increased Fracture Risk in Women Treated With Aromatase Inhibitors
Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis

Further recommendations (based on DVO-guidelines for treatment, diagnosis and prevention of osteoporosis)*

<table>
<thead>
<tr>
<th>Physical activity</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Avoiding immobilisation</td>
<td>4</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Calcium (1000–1500 mg/d)**</td>
<td>4</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Vitamine D3 suppl. (800–2000 U/d or 20,000 U/w)</td>
<td>4</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Stop smoking, reduction of alcohol</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Avoiding BMI &lt; 20 mg/m²</td>
<td>3b</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Bisphosphonates after discontinuation of Denosumab (time-limited)</td>
<td>3c</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Drugs approved for osteoporosis treatment in adults (see next slide)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* http://www.dv-osteologie.org/dvo_leitlinien/dvo-leitlinie-2014; revised version expected in 2018
** If nutritional supply is insufficient, (in combination with Vit D3 only)


<table>
<thead>
<tr>
<th>Effect of Denosumab Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FREEDOM / FREEDOM Extension Trial</strong></td>
</tr>
<tr>
<td>N=1001, ≥ 2 dose of Denosumab or placebo, follow up ≤ 7 months after discontinuation treatment</td>
</tr>
<tr>
<td>Vertebral fracture rate per 100 participant year:</td>
</tr>
<tr>
<td>1.2 during denosumab therapy</td>
</tr>
<tr>
<td>7.1 after denosumab therapy</td>
</tr>
<tr>
<td>8.5 placebo</td>
</tr>
<tr>
<td>Non vertebral fracture rate per 100 participant year:</td>
</tr>
<tr>
<td>2.8 after denosumab vs. 3.8 placebo (n.s.)</td>
</tr>
<tr>
<td><strong>Multiple vertebral fracture (% of all vertebral fractures):</strong></td>
</tr>
<tr>
<td>60.7% after denosumab therapy vs. 38.7% placebo; p=0.049</td>
</tr>
</tbody>
</table>

Cummings SR et al. J Bone Miner Res 2017

**Medical Treatment of Osteoporosis**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate 70 mg po/w*</td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Denosumab 60 mg sc/6m*</td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Ibandronate 150 mg po/m*</td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Ibandronate 3 mg iv/3 m</td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Parathyroid hormone (1-84) 100 µg sc/d</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Raloxifene 60 mg po/d (improves spine only)</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Risedronate 35 mg po/w*</td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Strontium ranelate 2 g po/d**</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Teriparatide (1-34) 20 µg sc/d</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Zoledronate 5 mg iv/12 m*</td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
</tbody>
</table>

* Drugs tested in clinical studies with breast cancer patients and tumor therapy-induced osteoporosis
** Elevated risk of myocardial infarction. Substance restricted to postmenopausal pts. with severe osteoporosis and high fracture risk.


**Raloxifen**


**Strontium renalate**