Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Osteo oncology and Bone Health
Osteoconology and Bone Health

- **Versions 2002–2020:**
  Bischoff / Böhme / Brunnert / Dall / Diel / Fehm /
  Fersis / Friedrich / Friedrichs / Hanf / Huober /
  Jackisch / Janni / Kolberg-Liedtke / Lux / Maas / Nitz / Oberhoff /
  Schaller / Scharl / Schütz / Seegenschmiedt / Solbach / Solomayer /
  Souchon

- **Version 2021:**
  Banys-Paluchowski / Kolberg-Liedtke
Bisphosphonates in Metastatic Breast Cancer

- Therapy of hypercalcemia
- Reduction of skeletal events / complications
- Reduction of bone pain
- Increasing bone pain-free survival
- Treatment beyond osseous progression
- Use of bone resorption markers for therapy monitoring
- Bisphosphonates alone for pain control

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>1a</td>
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<td>A</td>
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</tr>
<tr>
<td></td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>D</td>
<td>-</td>
</tr>
</tbody>
</table>

Meta-analyses and Reviews (metastatic breast cancer)

Results of Phase III trials (metastatic breast cancer)
3. Body JJ, Diel IJ, Lichinitser M et al. Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with with
metastatic bone disease; results from two randomized, placebo-controlled phase III studies. Br J Cancer 90:1133-1137, 2004


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


Progression under bisphosphonates


**Clinical relevance of bone resorption marker**

**Bisphosphonates for bone pain control**
**Randomized trials – Zoledronic acid:**

**Randomized trials – Other bone-targeted agents**
3. Lipton A, Steger GG, Figueroa J et al. Randomized Active-Controlled Phase II Study of Denosumab Efficacy and Safety in Patients With

**Non-randomized studies:**

**Systematic reviews:**
Reviews / Guidelines:

Zoledronic acid:
1. Himelstein AL, Foster JC, Khatcheressian JL et al. Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in
Patients With Bone Metastases: A Randomized Clinical Trial. JAMA 317(1):48-58, 2017


Pamidronate:

Denosumab & bisphosphonates:

Denosumab:

Sequential therapy with different BTAs:
Skeletal Metastases
Treatment with Radionuclids

- Tumor progression after standard treatment of multiple / disseminated metastases and intolerable bone pain
  - $^{186}$Rhenium-hydroxyethylidene-diphosphonat
  - $^{153}$Samarium
  - $^{153}$Strontium
  - $^{223}$Radium
  - $^{177}$Lu-EDTMP
  - $^{188}$Rhenium-HEDP

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

Reviews / Overview

$^{186}$Rhenium ($^{186}$Re-HEDP)
153Samarium (153Sm-EDTMP)

89Strontium (89Sr-Chlorid)

223Ra-dichloride:

177Lu (Lutetium)-EDTMP
Metastatic Bone Disease of the Spine

Indications for surgery

- Spinal cord compression
  - With progressive neurological symptoms
  - With pathological fractures
- Instability of the spine
- Lesions in pre-irradiated parts of the spine


Bone Metastases Acute Spinal Cord Compression / Paraplegia

Recommendations and Clinical Practice Guidelines:


Reviews:

Operative therapy:

Radiation therapy: Randomized studies:
Radiation therapy: Non-randomized studies:


Steroids: Systematic review:

Military Leadership and Organizational Behavior

Military Leadership and Organizational Behavior


8. Chow E, Meyer RM, Ding K et al. Dexamethasone in the prophylaxis of radiation-induced pain flare after palliative radiotherapy for


## Recurrent Bone Pain in pre-irradiated parts of the skeleton

<table>
<thead>
<tr>
<th>Treatment</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


### Side-Effects and Toxicity: Bisphosphonates (BP) and Denosumab (Dmab)

<table>
<thead>
<tr>
<th>Side-Effect</th>
<th>LoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal function deterioration due to IV-aminobisphosphonates</td>
<td>1b</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw (ONJ) mostly under IV-BP and Dmab therapy (1.4 – 2.8% /1.3 – 3.2%)</td>
<td>1b</td>
</tr>
<tr>
<td>Association with (simultaneous) anti-angiogenic therapies</td>
<td>3b</td>
</tr>
<tr>
<td>Severe hypocalcemia (Dmab &gt; BPs)</td>
<td>1b</td>
</tr>
<tr>
<td>Acute Phase Reaction (IV Amino-BPs, Dmab) 10–30 %</td>
<td>1b</td>
</tr>
<tr>
<td>Gastrointestinal side effects (oral BPs) 2–10 %</td>
<td>1b</td>
</tr>
<tr>
<td>Atypical femur fractures (absolute risk of 11 per 10,000 person years of BP use)</td>
<td>2b</td>
</tr>
<tr>
<td>Extremely rare: Uveitis / Scleritis under BP treatment</td>
<td>4</td>
</tr>
</tbody>
</table>

### References

**Denosumab**


**Sequential therapy**

**Bisphosphonates**


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**Table: Frequent side effects under treatment with BPs / Denosumab**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acute phase reaction</th>
<th>Kidney Tox.</th>
<th>Upper GI</th>
<th>Diarrhea</th>
<th>ONJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clodronate 1500 IV</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Clodronate 1600 PO</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Ibandronate 50 mg PO</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ibandronate 6 mg IV</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Zoledronate 4 mg IV</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Pamidronate 90 mg IV</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Zoledronate 4 mg IV q6m</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Denosumab 120 mg SC q4w</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

Cave: Hypocalcaemia under antiresorptive therapy in pts with bone metastases!
Denosumab


## Recommendations for Prevention of Osteonecrosis of the Jaw (ONJ)

<table>
<thead>
<tr>
<th>Oxford LoE: 2a</th>
<th>GR: A</th>
<th>AGO: ++</th>
</tr>
</thead>
<tbody>
<tr>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimize dental status before start of bisphosphonate or denosumab treatment (LoE 2a, recommendation grade A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inform patients about ONJ risk and educate about early symptom reporting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In case of high risk for ONJ, use oral bisphosphonate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good oral hygiene, limiting of alcohol intake and stopping smoking should be recommended</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In adjuvant bisphosphonate therapy, ONJ was rare (&lt;1%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASORS Evaluation
https://www.onkosupport.de/asors/content/e412b/e1743/e1861/e1862/e4628/LaufferteiNSMFOrbefinal.pdf

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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>Adjuvant</th>
<th>Bone Targeted Therapy</th>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clodronate (oral)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal patients</td>
<td>1a</td>
<td>A</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal patients</td>
<td>1a</td>
<td>B</td>
<td>+/-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminobisphosphonate (IV or oral)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal patients</td>
<td>1a</td>
<td>A</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal patients</td>
<td>1a</td>
<td>B</td>
<td>+/-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denosumab (6 x 120 mg/3–4w + 14 x 120 mg/3m)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal patients Stage II and III</td>
<td>1b</td>
<td>B</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denosumab (60 mg SC q6m)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal patients undergoing AI therapy</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Clodronate**


**Adjuvant Aminobisphosphonates**


**Denosumab**


**Guidelines**

Dosage of Adjuvant Bisphosphonates for Improvement of Survival

- **Non-Aminobisphosphonates:**
  - Clodronate PO 1600 mg/d (Bonefos / Clodronic acid)
  - Clodronate PO 1040 mg/d (Ostac / Clodronic acid)

- **Aminobisphosphonates:**
  - Zoledronate IV 4 mg/6 m (Zometa / Zoledronic acid)
  - Ibandronate PO 50 mg/d (Bondronat / Ibandronic acid)
  - Pamidronate PO (orally not available in most countries)
  - Risedronate PO 35 mg/w (Actonel / Risedronic acid)
  - Alendronate 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 risedronate (2%), oral alendronate (1%) (data from EBCTCG meta-analysis)

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# 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/12m*</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**