Osteooncology and Bone Health
Osteoonyctology and Bone Health

- **Versions 2002–2017:**
  - Bischoff / Böhme / Brunnert / Dall / Diel / Fehm /
  - Fersis / Friedrich/ Friedrichs / Hanf / Huober /
  - Jackisch / Janni / Lux / Maas / Nitz / Oberhoff /
  - Schaller / Scharl / Schütz / Seegenschmiedt /
  - Solomayer / Souchon /Diel / Liedke

- **Version 2018:**
  - Fehm/Solomayer
Bisphosphonates in Metastatic Breast Cancer

- Hypercalcemia
- Reduction of skeletal events (complications)
- Reduction of bone pain
- Increasing bone pain-free survival
- Treatment beyond osseous progression
- Use of bone resorption marker for therapy monitoring
- Bisphosphonates used alone for pain control

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

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 in Metastatic Breast Cancer

- Reduction of hypercalcemia
- Reduction of skeletal complications
- Reduction of bone pain
- Increasing bone pain-free survival
- Treatment beyond progression
  - Progression while on bisphosphonates
- Use of bone resorption markers for therapy monitoring
- Denosumab alone for pain control

<table>
<thead>
<tr>
<th>Oxford</th>
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<tbody>
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<td>4</td>
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<td></td>
<td>5</td>
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</tr>
</tbody>
</table>

Denosumab - Therapy of bone metastases and skeletal related complications:


Statement: Progression under bisphosphonates


Clinical relevance of bone resorption marker:

1. Van Poznak C, Somerfield MR, Barlow WE et al. Role of Bone-Modifying Agents in

**Bisphosphonates for bone pain control:**

Longer-Interval vs Standard Dosing of Zoledronic Acid

1. CALGB 70604 trial: n= 1822 patients with metastatic breast cancer, metastatic prostate cancer, or multiple myeloma, 795 completed the study
   SRE after 2 yrs:
   - 29.5% zoledronic acid every 4 weeks
   - 28.6% zoledronic acid every 12 weeks

2. Optimze-2-trial: n=460 with metastatic breast cancer
   SRE after 1 year:
   - 22.0% zoledronic acid every 4 weeks
   - 23.2% zoledronic acid every 12 weeks

3. Patients eligible for this trial had prior exposure to zoledronate or pamidronate for approx. 1 year or more

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)


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### Bone Modifying Agents for the Therapy of Bone Metastases

<table>
<thead>
<tr>
<th>Agent</th>
<th>LoE</th>
<th>Grade</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clodronate PO 1600 mg daily</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Clodronate IV 1500 mg q3w / q4w</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Pamidronate IV 90 mg q3w / q4w</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Ibandronate IV 6 mg q3w / q4w</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Ibandronate PO 50 mg daily</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Zoledronate IV 4 mg</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Denosumab 120 mg s.c. q4w</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Denosumab 120 mg s.c. q12w</td>
<td>4</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Other dosing or schedules, e.g. derived from adjuvant studies or therapy of osteoporosis</td>
<td>5</td>
<td>D</td>
<td>--</td>
</tr>
</tbody>
</table>
Skeletal Metastases
Treatment with Radionuclids

- Tumor progression after standard treatment of multiple / disseminated metastases and intolerable bone pain (Prerequisite: hot spots in the bone scintigraphy)
  - $^{186}$Rhenium-hydroxyethylidene-diphosphonat
  - $^{153}$Samarium
  - $^{89}$Strontium
  - $^{223}$Radium
  - $^{177}$Lu-EDTMP

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

### Reviews / Overview


$^{186}$Rhenium ($^{186}$Re-HEDP)

**153Samarium (\(^{153}\text{Sm-EDTMP}\))**


**89Strontium (\(^{89}\text{Sr-Chlorid}\))**


**223Ra-dichloride:**


**177Lu (Lutetium)-EDTMP:**


**Metastatic Bone Disease of the Spine**

**Indications for surgery**

**Oxford LoE: 2b**

**GR: C**

**AGO: ++**

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

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**Metastatic Bone Disease: Radiotherapy (RT)**

<table>
<thead>
<tr>
<th>Bone metastases</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>With fracture risk</td>
<td>1a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>With functional impairment</td>
<td>1a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>With bone pain</td>
<td>1a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Single dose RT = fractionated RT</td>
<td>2a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>With neuropathic bone pain</td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Asymptomatic isolated bone metastasis</td>
<td>5</td>
<td>D</td>
<td>+/-</td>
</tr>
<tr>
<td>Reduction of radiation induced pain flare by dexamethasone</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Radiotherapy in combination with hyperthermia</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Limited studies included breast cancer patients!

Metastatic Bone Disease
Recurrent Bone Pain after RT

Recurrent bone pain in pre-irradiated parts of the skeleton

- Single dose RT *
- Fractionated RT *
- Radionuclid therapy
- Magnetic resonance-guided focused ultrasound
- Radiofrequency ablation
- Cryoablation

Oxford LoE GR AGO
3b C ++
3b C +
3b C +
1b B +
4 C +
4 C +

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


http://leitlinienprogrammonkologie.de/Supportive-Therapie.95.0.html (Zugriff am 18.01.2018)

Magnetic resonance-guided focused ultrasound

Cryoablation / Radiofrequency ablation
Bisphosphonates


Denosumab


Frequent side effects under treatment with BPs and Denosumab

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acute phase-reaction</th>
<th>Kidney Tox.</th>
<th>Upper Gl</th>
<th>Diarrhea</th>
<th>Osteonecrosis of the jaw</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clodronate 1500 i.v.</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Clodronate 1500 p.o.</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Ibandronate 50 mg p.o.</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ibandronate 6 mg i.v.</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Zoledronate 4 mg i.v.</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>q4w oder q12w</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Pamidronate 90 mg i.v.</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Zoledronate 4 mg i.v.</td>
<td>q6m</td>
<td>+</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>0</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Cave: Hypocalcemia under antiresorptive therapy in pts with bone metastases!

Bisphosphonates


Denosumab


Adjuvant Bone Targeted Therapy for Reduction of Bone Metastases and Survival Advantage

<table>
<thead>
<tr>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clodronate (oral)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Postmenopausal patients</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>- Premenopausal patients</td>
<td>1a</td>
<td>B</td>
</tr>
<tr>
<td>Aminobisphosphonate (iv or oral)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Postmenopausal patients</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>- Premenopausal patients</td>
<td>1a</td>
<td>B</td>
</tr>
<tr>
<td>Denosumab (60 mg s.c. q6mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Postmenopausal patients</td>
<td>1b*</td>
<td>B</td>
</tr>
</tbody>
</table>

**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:**
  - Zoledronic acid 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)

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


Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bisphosphonates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Therapy</td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>• Prevention</td>
<td>1b</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td><strong>Denosumab</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Therapy</td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>• Prevention</td>
<td>1b</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td><strong>Hormone replacement therapy</strong></td>
<td>5</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td><strong>Clinical risk assessment for osteoporosis at baseline</strong></td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td><strong>DXA-Scan at baseline in pts with AI or with premature menopause</strong></td>
<td>5</td>
<td>D</td>
<td>+</td>
</tr>
<tr>
<td><strong>Antiresorptive therapy in pts. with reduced bone density</strong></td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td><strong>Repeat DEXA-scan based on risk</strong></td>
<td>5</td>
<td>D</td>
<td>+</td>
</tr>
</tbody>
</table>


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

<table>
<thead>
<tr>
<th>Physical activity</th>
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<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)</td>
<td>4</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Cessation of 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>Antiresorptive therapy after discontinuation of Denosumab</td>
<td>4</td>
<td>C</td>
<td>+/-</td>
</tr>
</tbody>
</table>

* http://www.dv-ostologie.org/dvo_leitlinien/dvo-leitlinie-2014; revised version expected in 2018

** If nutritional supply is insufficient, (in combination with Vit D3 only)


2. German guidelines for the treatment of osteoporosis by the DVO:


1. German guidelines for the treatment of osteoporosis by the DVO:  


**Raloxifene**

**Strontium renalate**

1. German guidelines for the treatment of osteoporosis by the DVO: