Osteo-oncology and Bone Health
Osteo-oncology and Bone Health

- **Versions 2002-2014:** Bischoff / Böhme / Brunnert / Dall / Diel / Fehm / Fersis / Friedrich / Friedrichs / Huober / Jackisch / Janni / Lux / Maas / Nitz / Oberhoff / Schaller / Scharl / Schütz / Seegenschmiedt / Solomayer / Souchon

- **Version 2015:** Fehm / Hanf
Bisphosphonates in Breast Cancer

- Hypercalcemia
- Reduction of skeletal events (complications)
- Reduction of bone pain
- Treatment beyond progression of bone met‘s
- In combination with neoadjuvant chemotherapy
- Prevention of bone metastases/ survival advantage
  - Adjuvant in postmenopausal patients
  - Advanced breast cancer
- Prevention of breast cancer with oral BPs
  (in women receiving BP for low BMD)

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a A ++</td>
<td></td>
</tr>
<tr>
<td>1a A ++</td>
<td></td>
</tr>
<tr>
<td>1a A ++</td>
<td></td>
</tr>
<tr>
<td>5 D ++</td>
<td></td>
</tr>
<tr>
<td>2b C +/-</td>
<td></td>
</tr>
<tr>
<td>1a A +</td>
<td></td>
</tr>
<tr>
<td>2b C +/-</td>
<td></td>
</tr>
<tr>
<td>2b C +/-</td>
<td></td>
</tr>
</tbody>
</table>
Denosumab in Breast Cancer

- Reduction of hypercalcemia 1a A ++
- Reduction of skeletal complications 1a A ++
- Reduction of bone pain 1a A ++
  - Increasing bone pain-free survival 1b A ++
- Treatment beyond progression 5 D +
  - Progression under bisphosphonates 4 C +/-
## Bone Modifying Agents for the Therapy of Bone Metastases

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Grade</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clodronate PO</td>
<td>1600 mg daily</td>
<td>1a</td>
<td>A ++</td>
</tr>
<tr>
<td>Clodronate IV</td>
<td>1500 mg q3w / q4w</td>
<td>1a</td>
<td>A ++</td>
</tr>
<tr>
<td>Pamidronate IV</td>
<td>90 mg q3w / q4w</td>
<td>1a</td>
<td>A ++</td>
</tr>
<tr>
<td>Ibandronate IV</td>
<td>6 mg q3w / q4w</td>
<td>1a</td>
<td>A ++</td>
</tr>
<tr>
<td>Ibandronate PO</td>
<td>50 mg daily</td>
<td>1a</td>
<td>A ++</td>
</tr>
<tr>
<td>Zoledronate IV</td>
<td>4 mg q4w</td>
<td>1a</td>
<td>A ++</td>
</tr>
<tr>
<td>Zoledronate IV</td>
<td>4 mg q12w*</td>
<td>1b²</td>
<td>B +</td>
</tr>
<tr>
<td>Denosumab s.c.</td>
<td>120 mg q4w</td>
<td>1a</td>
<td>A ++</td>
</tr>
<tr>
<td>Other dosing or schedules</td>
<td>derived from adjuvant</td>
<td>5</td>
<td>D - -</td>
</tr>
<tr>
<td></td>
<td>studies or therapy of</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>osteoporosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*for patients after zoledronate iv 4 mg q4w for 1 year or longer
Tumor progression after standard treatment of multiple / disseminated metastases and intolerable bone pain (prerequisite: hot spots in the bone scintigraphy)

- \(^{186}\text{Rhenium-hydroxyethylidene-diphosphonat}\)  
- \(^{153}\text{Samarium}\)  
- \(^{89}\text{Strontium}\)  
- \(^{223}\text{Radium}\)

Cave: Myelosuppression with risks of pancytopenia has to balance potential benefits.
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

Oxford LoE: 2b  GR: C  AGO: ++
Bone Metastases
Acute Spinal Cord Compression / Paraplegia

- Decompression surgery, reduction of tumor volume, stabilisation surgery (< 24 h) and irradiation of the spine (RT)
  - Oxford / AGO LoE / GR
  - 2b C ++

- Irradiation of the spine (< 24 h) +/- steroids
  - 3b C ++

- Immediate start of treatment
  - 1c D ++

Clinical trials have included patients with different tumor entities!
Surgery for Bone Metastases
Technical Aspects

Spine and limbs

Oxford LoE: 3b  GR: C  AGO: +

- Marrow splints
- Plate osteosynthesis
- Compound osteosynthesis (replacement by PMMA and osteosynthesis)
- Vertebral replacement by titanspacer
- Tumor-Endoprosthesis
- Vertebroplasty / Kyphoplasty +/- thermoablation of the tumor
- Kypho-IORT (in studies only)*
- Resection of involved bone in oligometastatic disease (sternum, ribs, vertebrectomy and replacement with spondylodesis)

*Study participation recommended
Metastatic Bone Disease: Radiotherapy (RT)

Bone metastases

- With fracture risk
- With functional impairment
- With bone pain
  - Single dose RT = fractionated RT
- With neuropathic bone pain
- Asymptomatic isolated bone metastases

Only few studies included breast cancer patients!
Recurrent bone pain in pre-irradiated parts of the skeleton

- Single dose RT*  
  3b  C  ++

- Fractionated RT*  
  3b  C  +

- Radionuclid therapy  
  3b  C  +

- Magnetic resonance-guided focused ultrasound  
  1b  B  +

* Dosing and fractionation depending on location, interval from first RT, and dose and fractionation of first radiotherapy.
Side-Effects and Toxicity – Bisphosphonates (BP) and Denosumab (Db)

- Renal function deterioration due to IV-aminobisphosphonates
- Osteonecrosis of the jaw (ONJ) mostly under IV-BP and denosumab therapy (1.3% / 1.8%)
  - Association with (simultaneous) anti-angiogenic therapies
- Severe hypocalcemia (Dmab>BPs)
- Acute Phase Reaction* (IV Amino-BPs, Db) 10-30%
- Gastrointestinal side effects (oral BPs) 2-10%
- Atypical femur fractures
  - absolute risk of 11 per 10,000 person years of BP use

In adjuvant bisphosphonate therapy, major side effects were rarely observed (except APR*).
Recommendations for Precautions to Prevent ONJ*

Oxford LoE: 4  GR: C  AGO: +

- During bisphosphonate or denosumab treatment, avoid any elective dental procedures, which involve jaw bone manipulations – if interventions are inevitable, prophylactic antibiotics are recommended (LoE 2b)

- Optimize dental status before start of bisphosphonate or denosumab treatment, if feasible (LoE 2b)

- 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

*Osteonecrosis of the jaw
Adjuvant Bisphosphonates for Reduction of Bone Metastases and Survival Advantage

- Clodronate (oral)
  - Postmenopausal patients
  - Premenopausal patients

- Aminobisphosphonates (iv or oral)
  - Postmenopausal patients
  - Premenopausal patients

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

www.ago-online.de
Dosage of Adjuvant Bisphosphonates for Improvement of Survival

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

- **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 residronate (2%), Oral alendronate (1%) (data from EBCTCG-metaanalysis)
Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis

<table>
<thead>
<tr>
<th>Therapy and Prevention</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td>1b B ++</td>
</tr>
<tr>
<td></td>
<td>1b A +</td>
</tr>
<tr>
<td>Denosumab</td>
<td>1b B ++</td>
</tr>
<tr>
<td></td>
<td>1b A +</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>5 D -</td>
</tr>
<tr>
<td>Regular BMD-measurement recommended (Intervals depending on previous T-values)</td>
<td>2b B +</td>
</tr>
</tbody>
</table>
Further recommendations (based on DVO-guidelines for treatment, diagnosis and prevention of osteoporosis)*

- Physical activity
- Avoiding immobilisation
- Calcium (1000–1500 mg/d)**
- Vitamine D3 suppl. (800–2000 U/d)
- Cessation of smoking, reduction of alcohol
- Avoiding BMI < 20 mg/m²
- Drugs approved for the treatment of osteoporosis in adults (see next slide)

| Oxford / AGO LoE / GR | 4 | C | ++ | 4 | C | ++ | 4 | C | ++ | 4 | C | ++ | 2b | B | ++ | 3b | C | ++ |


**if nutritional supply is insufficient, (in combination with Vit D3 only)
## Medical Treatment of Osteoporosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Strength</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>70 mg po/w*</td>
<td>++</td>
<td>1b B</td>
</tr>
<tr>
<td>Denosumab</td>
<td>60 mg sc/6m*</td>
<td>++</td>
<td>1b B</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>150 mg po/m*</td>
<td>++</td>
<td>1b B</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>3 mg iv/3m</td>
<td>+</td>
<td>1b B</td>
</tr>
<tr>
<td>Parathyroid hormone (1-84) 100 µg sc/d</td>
<td></td>
<td>+</td>
<td>1b B</td>
</tr>
<tr>
<td>Raloxifene 60 mg po/d (improves spine only)</td>
<td></td>
<td>+/-</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>Risedronate</td>
<td>35 mg po/w*</td>
<td>++</td>
<td>1b B</td>
</tr>
<tr>
<td>Strontium ranelate 2 g po/d **</td>
<td></td>
<td>+</td>
<td>1b B</td>
</tr>
<tr>
<td>Teriparatide (1-34) 20 µg sc/d</td>
<td></td>
<td>+</td>
<td>1b B</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>5 mg iv/12 m*</td>
<td>++</td>
<td>1b B</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 pats. with severe osteoporosis and high risk of fractures**
TABELLE 4.2.: INDIKATION FÜR EINE MEDIKAMENTÖSE OSTEOPOROSETHERAPIE NACH RISIKOPROFIL in Abhängigkeit von Geschlecht, Lebensalter, DXA-Knochendichte und weiteren Risikofaktoren.

<table>
<thead>
<tr>
<th>Lebensalter in Jahren</th>
<th>T-Score (Nur anwendbar auf DXA-Werte. Die Wirksamkeit einer medikamentösen Therapie ist für periphere Frakturen bei einem T-Score &gt; -2,0 nicht sicher belegt.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-2,0 bis -2,5</td>
</tr>
<tr>
<td>Frau</td>
<td>Mann²</td>
</tr>
<tr>
<td>50-60</td>
<td>60-70</td>
</tr>
<tr>
<td>60-65</td>
<td>70-75</td>
</tr>
<tr>
<td>65-70</td>
<td>75-80</td>
</tr>
<tr>
<td>70-75</td>
<td>80-85</td>
</tr>
<tr>
<td>&gt;75</td>
<td>&gt;85</td>
</tr>
</tbody>
</table>

¹ Alternative Risikomodellierungen können bei Bedarf vergleichend zu Rate gezogen werden (siehe Langfassung).
² bei Verwendung eines männlichen Referenzkollektivs für die T-Scores

Therapieindikation auch schon bei um 1,0 höherem T-Score³,⁴, wenn:
- Glukokortikoide oral ≥ 2,5 mg und < 7,5 mg Prednisolonäquivalent tgl. (außer bei rheumatoider Arthritis +0,5)
- Diabetes mellitus Typ 1
- ≥ 3 niedrigtraumatische Frakturen in den letzten 10 Jahren im Einzelfall (mit Ausnahme von Finger-, Zehen-, Schädel- und Knöchelfrakturen)
Osteo-oncology and Bone Health (2/19)

No further information

No references
Bisphosphonates in Breast Cancer (3/19)

No further information

References:

First three statements:

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 2004; 100:36-43

Statement: In combination with neoadjuvant chemotherapy


Statement: Prevention of bone metastases/survival advantage


Statement: Bisphosphonates - Prevention of breast cancer


**Denosumab in Breast Cancer (4/19)**

*No further information*

**References:**

*Denosumab - Therapy of bone metastases and skeletal related complications:*


**Statement: Progression under bisphosphonates**

Bone modifying Agents for the Therapy of Bone Metastases (5/19)

No further information

References:

2. Hortobagyi GN et al. Efficacy and safety of continued zoledronic acid every 4 weeks versus every 12 weeks in women with bone metastases from breast cancer: Results of the OPTIMIZE-2 trial. J Clin Oncol 32:5s, 2014 (suppl; abstr LBA9500).
**Skeletal Metastasis Treatment with Radionuclids (6/19)**

*No further information*

**References:**

**Reviews / Overview**


**186**Rhenium (**186**Re-HEDP)


_{153}Samarium (^{153}Sm-EDTMP)_


_{89}Strontium (^{89}Sr-Chlorid)_


_{223}Ra-dichloride:

Metastatic Bone Disease of the Spine – Indication for surgery (7/19)

Further information:

References:

Bone Metastases Acute Spinal Cord Compression / Paraplegia (8/19)

Further information:

References:

Surgery for Bone Metastases (9/19)

Further information:

References:

Metastatic Bone Disease: Radiotherapy (10/19)

Further information:

References:

Metastatic Bone Disease Recurrent Bone Pain (11/19)

Further information:

References:

Recurrent bone pain in pre-irradiated parts of the skeleton

Magnetic resonance-guided focused ultrasound


TED-voting of the AGO-group (n=17): ++ n=1; + n=14; +/- n=2
Side-Effects and Toxicity – Bisphosphonates (BP) and Denosumab (Db) (12/19)

Further information:

References

Bisphosphonates

**Denosumab**

Recommendations for Precautions to Prevent ONJ (13/19)

Further information

References:

Adjuvant Bisphosphonates for Reduction of Bone Metastases and Survival Advantage (14/19)

No further information

References:

Clodronate:


**Adjuvant Aminobisphosphonates**

Dosage of Adjuvant Bisphosphonates for Improvement of Survival (15/19)

No further information

References:

Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis (16/19)

No further information

References:

Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis (17/19)

No further information

References:


Medical Treatment of Osteoporosis (18/19)

No further information

References:

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

Raloxifene


TED-voting of the AGO-group (n=28): ++ n=0; + n=9; +/- n=18; - n=1

Strontium renalate

TED-voting of the AGO-group (n=25): ++ n=1; + n=15; +/- n=9
Guidelines of the DVO (19/19)

No further information

References:

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