Living with and beyond cancer

Management of osteoporosis

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Gynecological cancer

Treatment (oophorectomy, chemotherapy, radiation therapy)

Premature ovarian insufficiency / early menopause

- Menopausal symptoms
- Genitourinary symptoms
- Anxiety / depression
- Sexual dysfunction

- Long – term implications on the incidence of chronic conditions
Risk factors related to cancer treatment

**Risk factors for low BMD with POI:***
- Primary amenorrhoea.
- Longer duration of POI.
- >1yr delay in diagnosis.
- Age <20 years at onset of irregular menses.
- Childhood cancer survivors with hypogonadism and:
  - Hypothyroidism AND growth hormone deficiency.
  - Previous treatment with chemotherapy/glucocorticoids (higher cumulative dose).
  - Cranial irradiation.
  - Caucasian ethnicity.

**Initial Bone Health Evaluations**

**General risk factors for low BMD:**
- Non-modifiable
  - Age.
  - Prior fragility fracture.
  - Family history of osteoporosis.
  - Parental history of fracture.
- **Modifiable and lifestyle**
  - Height loss >3cm.
  - Multiple falls.
  - Low physical activity or immobility.
  - Low body weight (body mass index<18 kg/m²).
  - Low muscle mass and strength.
  - Poor balance.
  - Vitamin D insufficiency.
  - Protein or calcium undernutrition.
  - Smoking.
  - Alcohol >2 standard drinks/day.

**Diseases associated with low BMD**
- Rheumatoid arthritis.
- Hyperthyroidism.
- Hyperparathyroidism.
- Chronic kidney disease.
- Coeliac disease or malabsorption.
- Diabetes mellitus.
- Myeloma or MGUS.
- Bone marrow/organ transplant.
- HIV infection.
- Depression.

**Medications associated with low BMD**
- Glucocorticoids.
- Excess thyroid hormone replacement.
- Aromatase inhibitors.

**Blood and urine tests**
- UEC, CMP, LFT, TSH, 25-hydroxy vitamin D.
- Bone turnover markers: not currently recommended for routine use.
- If reduced bone mass is present, also consider the following: serum PTH, coeliac serology, serum electrophoresis and 24-hour urine calcium excretion.

**Imaging**
- **DXA:** Indicated at initial diagnosis for all women with POI, especially if long duration of oestrogen deficiency or other risk factors for osteoporosis. Guidelines suggest the use of Z score <-2 to define low bone mass and T scores <-2.5 to define osteoporosis. ‘Low bone mass’ is the preferred term in this setting rather than osteopenia.²
- Plain imaging: Lateral radiographs of lumbar and thoracic spine or DXA-based Vertebal Fracture Assessment (VFA) should be considered on an individual basis particularly if concerns regarding height loss, back pain, chronic diseases associated with low BMD and current or past glucocorticoid use.

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† FRAX risk calculator is not validated for use in women< 40 years.

Bone mineral density measurement

T-score

\[ \geq -1 \quad : \text{normal BMD} \]

\[ < -1 \text{ and } > -2.5 \quad : \text{osteopenia} \]

\[ \leq -2.5 \quad : \text{osteoporosis} \]

Frax-score is not valid for women < 40 years
Prevention and management of osteoporosis in women with breast cancer

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
Management of Osteoporosis in cancer survivors – General measures

Daily recommended intake

- Calcium (700-1200mg)
- Vitamin D (800 IU)

Treatment of Vitamin D deficiency

<table>
<thead>
<tr>
<th>25OHD concentrations</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-30 ng / ml</td>
<td>1000 – 1400 IU</td>
</tr>
<tr>
<td>&lt; 20 ng/ml</td>
<td>2000 – 5000 IU</td>
</tr>
</tbody>
</table>

Calcium in the prevention of postmenopausal osteoporosis: EMAS clinical guide
Management of Osteoporosis in cancer survivors – Medical therapy

Cancer Treatment (oophorectomy, chemotherapy, radiation therapy)

Premature ovarian insufficiency / early menopause

- HRT indicated (e.g. early stage endometrial cancer)
- HRT not indicated (e.g. breast cancer)

HRT

Non-estrogen based therapy
European guidance for the diagnosis and management of osteoporosis in postmenopausal women

J.A. Kanis, C. Cooper, R. Rizzoli, J.-Y. Reginster on behalf of the Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) and the Committees of Scientific Advisors and National Societies of the International Osteoporosis Foundation (IOF)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on vertebral fracture risk</th>
<th>Effect on non-vertebral fracture risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Osteoporosis</td>
<td>Established osteoporosis&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Alendronate</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Risedronate</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HRT</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td>Denosumab</td>
<td>+</td>
<td>+&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

NA no evidence available, + effective drug

<sup>a</sup> Women with a prior vertebral fracture

<sup>b</sup> In subsets of patients only (post hoc analysis)

<sup>c</sup> Mixed group of patients with or without prevalent vertebral fractures
<table>
<thead>
<tr>
<th>Estrogen dose</th>
<th>Indications</th>
<th>p.o. estrogens</th>
<th>Transdermal 17β estradiol</th>
<th>Tibolone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard dose</td>
<td><strong>Premature ovarian insufficiency</strong></td>
<td>17β-E2 2-4mg or CEE 0.625-1.25mg</td>
<td>50-100μg</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>• Perimenopause</td>
<td>17β-E2 2mg or CEE 0.625mg</td>
<td>50μg</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>• Menopause: poor response to low dose</td>
<td>17β-E2 2mg or CEE 0.625mg</td>
<td>50μg</td>
<td>2.5mg</td>
</tr>
<tr>
<td>Low dose</td>
<td>• Perimenopause</td>
<td>17β-E2 1mg or CEE 0.300-0.450 mg</td>
<td>25-37μg</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>• Menopause</td>
<td>17β-E2 1mg or CEE 0.300-0.450 mg</td>
<td>25-37μg</td>
<td>2.5mg</td>
</tr>
<tr>
<td>Ultra- low dose</td>
<td>• Menopause: starting dose or maintenance dose after initial symptom control with low-dose</td>
<td>17β-E2 0.25-0.5mg</td>
<td>14μg</td>
<td>1.25mg</td>
</tr>
</tbody>
</table>
Effect of hormone replacement therapy on BMD in women with POI

Hormone Replacement Therapy Versus the Combined Oral Contraceptive Pill in Premature Ovarian Failure: A Randomized Controlled Trial of the Effects on Bone Mineral Density

Kiriakova V et al. Maturitas 2019;128:70-80
Anti-osteoporotic agents

Bone Resorption

- HRT
- SERMs
- Bisphosphonates
- Denosumab

Bone Formation

- Teriparatide
- Abaloparatide
- Romosozumab
Bisphosphonates

P.O.

- Alendronate 70mg once/week
- Risedronate 35 mg once/week
  
or 75mg twice/month (1st and 2nd day)
- Ibandronate 150 mg once/month

I.V.

- Ibandronate 3mg IV every 3 months
- Zoledronic acid 5mg IV every 12 months
Breast Cancer Survivors under aromatase inhibitors
Effect of bisphosphonate therapy on BMD

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>Application and dose</th>
<th>Aromatase inhibitors</th>
<th>Duration (months)</th>
<th>BMD change in lumbar spine (from baseline)</th>
<th>BMD change in lumbar spine (compared with placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bisphosphonates trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BATMAN\textsuperscript{a}</td>
<td>303</td>
<td>Orally, 70 mg/week</td>
<td>Anastrozole</td>
<td>36</td>
<td>15.6% (osteoporosis group)\textsuperscript{a}</td>
<td>NA</td>
</tr>
<tr>
<td>ARIBON\textsuperscript{b}</td>
<td>131</td>
<td>Orally, 150 mg/month</td>
<td>Anastrozole</td>
<td>24</td>
<td>3.0%</td>
<td>6.2%</td>
</tr>
<tr>
<td>SABRE\textsuperscript{c}</td>
<td>154</td>
<td>Orally, 35 mg/week</td>
<td>Anastrozole</td>
<td>24</td>
<td>2.2% (moderate risk group)</td>
<td>4.0%</td>
</tr>
<tr>
<td>REBBeCA\textsuperscript{2}</td>
<td>109</td>
<td>Orally, 35 mg/week</td>
<td>Any</td>
<td>24</td>
<td>2.3%</td>
<td>3.9%</td>
</tr>
<tr>
<td>ZO-FAST\textsuperscript{d}</td>
<td>1065</td>
<td>Intravenously, 4 mg every 6 months</td>
<td>Letrozole</td>
<td>60</td>
<td>4.3%</td>
<td>9.7%\textsuperscript{b}</td>
</tr>
<tr>
<td>Z-FAST\textsuperscript{e}</td>
<td>602</td>
<td>Intravenously, 4 mg every 6 months</td>
<td>Letrozole</td>
<td>60</td>
<td>6.2%</td>
<td>8.9%</td>
</tr>
<tr>
<td>E-ZO-FAST\textsuperscript{f}</td>
<td>527</td>
<td>Intravenously, 4 mg every 6 months</td>
<td>Letrozole</td>
<td>12</td>
<td>2.7%</td>
<td>5.4%</td>
</tr>
<tr>
<td><strong>Denosumab trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HALT\textsuperscript{g}</td>
<td>252</td>
<td>Subcutaneously, 60 mg every 6 months</td>
<td>Any</td>
<td>24</td>
<td>4.8%</td>
<td>7.6%</td>
</tr>
<tr>
<td>ABCSG\textsuperscript{12}</td>
<td>3420</td>
<td>Subcutaneously, 60 mg every 6 months</td>
<td>Any</td>
<td>36</td>
<td>7.3%\textsuperscript{d}</td>
<td>10.0%</td>
</tr>
</tbody>
</table>

Only trials with more than 100 participants were selected. BMD change at the lumbar spine was chosen as it was the primary endpoint in most trials. BMD=bone mineral density. NA=not applicable. \*Osteopenic group showed increase of 6.3%. \textsuperscript{b}Comparison with delayed study group (treatment initiated in case of fracture or BMD decrease). \textsuperscript{f}The only trial with fracture data, fracture reduction odds ratio 0.53.

Table 3: Randomised controlled trials to prevent treatment-induced bone loss in women with hormone sensitive breast cancer

### Table 1: Major clinical trials evaluating the use of bisphosphonates or denosumab in women with breast cancer

<table>
<thead>
<tr>
<th>Publication</th>
<th>Study characteristics</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saarto et al., Br J Cancer 2001</td>
<td>61 postmenopausal women with breast cancer with tamoxifen or toremifene, randomized to clodronate (1.6 g daily orally) or placebo</td>
<td>Improvement of both vertebral (+ 1% vs. − 1.7%) and femoral (+2.4% vs. −0.4%) BMD with clodronate at 3 years</td>
</tr>
<tr>
<td>Confavreux et al., Bone 2007</td>
<td>Osteoporotic women treated with anastrozole, Risedronate (35 mg once weekly) SOOPA study</td>
<td>Increase of vertebral BMD (+4.1%)</td>
</tr>
<tr>
<td>Lester et al., Clin Cancer Res 2008</td>
<td>50 women taking anastrozole, Ibandronate ARIBON study</td>
<td>Positive BMD changes (+3% vs. −3.2% at the spine and +0.6% vs. −3.9% at the hip)</td>
</tr>
<tr>
<td>Bruksky et al., Cancer 2012</td>
<td>Postmenopausal women treated with letrozole, 4 mg of zoledronic acid intravenously every 6 months Z-FAST study</td>
<td>Overall difference in vertebral BMD of 6.7% after 3 years in favor of zoledronic acid</td>
</tr>
<tr>
<td>Coleman et al., Ann Oncol 2013</td>
<td>Postmenopausal women treated with letrozole, 4 mg of zoledronic acid intravenously every 6 months ZO-FAST study</td>
<td>Overall difference in vertebral BMD of 9.3% after 3 years in favor of zoledronic acid</td>
</tr>
<tr>
<td>Sestak et al., Lancet Oncol 2014</td>
<td>1410 healthy postmenopausal women at increased risk of breast cancer on anastrozole or placebo, Randomized to risedronate (35 mg once weekly)/placebo IBIS-II Bone substudy</td>
<td>Risedronate counterbalanced the effect of anastrozole-induced bone loss in all subgroups of both osteopenic and osteoporotic women</td>
</tr>
<tr>
<td>Wagner-Johnston et al., Cancer 2015</td>
<td>551 women with T-score &gt; −2 and no fracture history, On treatment with letrozole after having completed therapy with tamoxifen, Randomly allocated to either upfront or delayed zoledronic acid</td>
<td>After 5 years of treatment, a 5% decrease in vertebral BMD in 10.2% of the women in the upfront arm compared with 40.2% in the delayed treatment arm (p &lt; 0.001)</td>
</tr>
<tr>
<td>Gnant et al., Ann Oncol 2015</td>
<td>1803 premenopausal women with estrogen receptor-positive early-stage (I/II) breast cancer, Randomized, open-label, phase III, 4-arm trial, Tamoxifen (20 mg/day orally) and goserelin (3.6 mg subcutaneously every 28 days) vs. anastrozole (1 mg/day orally) and goserelin (3.6 mg subcutaneously every 28 days), both with or without zoledronic acid (4 mg intravenously every 6 months) ABCSG12 trial</td>
<td>Significant bone loss (+0.4% vs. −11.3% BMD) without zoledronic acid at 3 years</td>
</tr>
</tbody>
</table>

Bone health care in women with breast cancer.
Breast Cancer Survivors - Summary for Bisphosphonates

- Overall, bisphosphonates appear to prevent AI-induced bone loss

- Few adverse effects

- Most data on zoledronic acid: 4 mg IV every 3 or 6 months

- Data less robust for oral bisphosphonates

- No fracture data are available: lack of power and short follow-up
Denosumab

**Dosage:** 60mg sc injection, every 6 months

**Fracture:** 5% vs 9.6%

**BMD:** +10% lumbar spine, +6.5% femoral neck

(similar with few previous studies)

*Independent of initial T score*

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*Gnant M et al, Lancet 2015*
Bone anti-resorbing agents as adjuvant cancer therapy

- Suppression of bone remodeling → prevention of bone metastasis and improvement of survival.

### Bisphosphonates

- **Bone recurrence at 10 y**: 7.8% vs 9.0%
- **Distant recurrence at 10 y**: 20.4% vs 21.8%
- **Breast cancer mortality at 10 y**: 16.6% vs 18.4%

*EBCTCG Group, Lancet 2015*

### Denosumab

- **Disease-free survival at 5 years**: 89.2% vs 87.3%
- **Disease-free survival at 8 years**: 80.6% vs 77.5%

*Gnant M et al, Lancet Oncol 2019*
CONCLUSIONS

• BMD measurement and careful evaluation of fracture risk

• Implementation of general measures in all women (calcium and vitamin D supplementation, smoking cessation, moderation of alcohol consumption, exercise)

• HRT in women with POI/early menopause if cancer histology and stage permits.

• Bisphosphonates / denosumab in women at high risk for fracture when estrogen-based therapy is not indicated.