Management of Osteoporosis in Patients with Breast Cancer on Aromatase Inhibitor

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- KKH
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Breast Cancer and Bone Loss

• Patients with breast cancer are at an increase in risk for bone loss
• Gluco-corticoids, chemotherapy, GNRH agonists
• Estrogen deprivation: Aromatase inhibitors/oophrectomy/ovarian ablation.
• As there is an increase in survival of breast cancer patients it is important to ensure bone health for cancer survivors
American Society of Clinical Oncology 2014

- American Society of Clinical Oncology (ASCO) clinical practice guidelines reflect this, recommending that postmenopausal women with early ER-positive breast cancer be offered either Tamoxifen for 10 years, an aromatase inhibitor for 5 years, Tamoxifen initially for 5 years followed by an aromatase inhibitor for up to a further 5 years, or Tamoxifen for 2–3 years followed by an aromatase inhibitor for up to a further 5 years.
Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomized trials

- Advances in adjuvant therapy has been shown to increase breast cancer survival
- Tamoxifen has been the cornerstone of adjuvant therapy for several decades.
- Recently aromatase inhibitors have been shown to reduce recurrence for ER+

- **Early Breast Cancer Trialists' Collaborative Group (EBCTCG):** Meta-analysis
  - Aromatase inhibitors reduce recurrence rates by about 30% (proportionately) compared with tamoxifen.
  - 5 years of an aromatase inhibitor reduces 10-year breast cancer mortality rates by about 15% compared with 5 years of tamoxifen, hence by about 40% (proportionately) compared with no endocrine treatment.

- Lancet 2014
Management of BONE HEALTH in patients on AROMATASE INHIBITORS

Post menopausal Women with Breast Cancer without bone metastasis
Aromatase inhibitors

• Highly potent
• Inhibits conversion of androgens to estrogen in the peripheral tissues (adrenal glands and fats cells)
• Unable to block estrogen production by the ovaries.
• Suppress circulating estrodiol levels to undetectable
• Use predominantly in post menopausal women
• reduction in estrogen levels and up regulation of RANK ligand signal in bone.
Effect of Anastrozole on Bone Mineral Density: 5-Year Results From the Anastrozole, Tamoxifen, Alone or in Combination Trial: Estell et al (UK)

Mean percentage changes in bone mineral density after 1, 2, and 5 years, for patients with data at each time point.

A: Lumbar spine; B: Total Hip
Table 1  Fractures in adjuvant studies with aromatase inhibitors in breast cancer

<table>
<thead>
<tr>
<th>AI study</th>
<th>Number</th>
<th>Duration F/U, months</th>
<th>Fractures (%)</th>
<th></th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aromatase inhibitor</td>
<td>Tamoxifen</td>
<td></td>
</tr>
<tr>
<td>ATAC$^6$</td>
<td>6,241$^a$</td>
<td>68</td>
<td>11.0 (anastrozole)</td>
<td>7.7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BIG 1-98$^{16}$</td>
<td>8,010</td>
<td>35.5</td>
<td>5.8 (letrozole)</td>
<td>4.1</td>
<td>.0006</td>
</tr>
<tr>
<td>IES$^{24}$</td>
<td>4,742</td>
<td>30.6</td>
<td>3.1 (exemestane)</td>
<td>2.3</td>
<td>.08</td>
</tr>
<tr>
<td>ARNO$^{48}$</td>
<td>3,224</td>
<td>28</td>
<td>2.4 (anastrozole)</td>
<td>1.2</td>
<td>NR</td>
</tr>
<tr>
<td>MA.17$^9$</td>
<td>5,187</td>
<td>60</td>
<td>5 (letrozole)</td>
<td>5</td>
<td>.25</td>
</tr>
</tbody>
</table>

$^a$Patients initially randomized: 9,366 (treatment arm, anastrozole+tamoxifen, including 3,125 pts, was suppressed)

NR not reported
Screening

• All patients should have a baseline BMD screen before starting Aromatase Inhibitors
Osteoporosis

• Definition:
• WHO BMD T score < -2.5 SD
• WHO FRAX score: Osteopenia with Hip fracture risk > 3%, major fracture risk >20
• Less than age 50: BMD Z score < 2.0 SD
Decision for specific treatment of postmenopausal women on aromatase inhibitors

- Osteoporosis: BMD < -2.5 SD Universally accepted
- BMD < -2.0 SD: Because of speed of AI induced bone loss
- BMD SD < -1.0 to -2.0
  - FRAX
  - 2 or more risk factors
Bone Related risk factors

- Age > 65
- Previous fragility fractures
- BMI : 20 kg/m$^2$
- Use of gluco-corticosteroids (> 5.0 or 7.5 mg prednisolone daily for 3 months)
- Alcohol abuse ( > 3 standard drinks/ day)
- Smoking
- History of hip fracture in first degree relatives
- Secondary causes of osteoporosis

- Treatment with AI > 6 months
- Chemotherapy induced menopause
- Radiotherapy
- Tamoxifen use in pre-menopausal women
  - (T reduces risk in post menopausal women but increases risk in pre-menopausal women)
Initial Evaluation

- History and Physical Examination
  - Clinical risk factors for fracture
  - Lifestyle factors
- Bone Mineral Density and FRAX analysis at baseline
FRAX

- WHO Fracture Risk Assessment Tool

<table>
<thead>
<tr>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>For the clinical risk factors, a yes or no response is asked for. If the field is left blank, then a &quot;no&quot; response is assumed. See also notes on risk factors.</td>
</tr>
</tbody>
</table>

The risk factors used are the following:

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>The model accepts ages between 40 and 90 years. If ages below or above are entered, the programme will compute probabilities at 40 and 90 year, respectively.</td>
</tr>
<tr>
<td>Sex</td>
<td>Male or female. Enter as appropriate.</td>
</tr>
<tr>
<td>Weight</td>
<td>This should be entered in kg.</td>
</tr>
<tr>
<td>Height</td>
<td>This should be entered in cm.</td>
</tr>
<tr>
<td>Previous fracture</td>
<td>A previous fracture denotes more accurately a previous fracture in adult life occurring spontaneously, or a fracture arising from trauma which, in a healthy individual, would not have resulted in a fracture. Enter yes or no (see also notes on risk factors).</td>
</tr>
<tr>
<td>Parent fractured hip</td>
<td>This enquires for a history of hip fracture in the patient’s mother or father. Enter yes or no.</td>
</tr>
<tr>
<td>Current smoking</td>
<td>Enter yes or no depending on whether the patient currently smokes tobacco (see also notes on risk factors).</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Enter yes if the patient is currently exposed to oral glucocorticoids or has been exposed to oral glucocorticoids for more than 3 months at a dose of prednisolone of 5mg daily or more (or equivalent doses of other glucocorticoids) (see also notes on risk factors).</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Enter yes where the patient has a confirmed diagnosis of rheumatoid arthritis. Otherwise enter no (see also notes on risk factors).</td>
</tr>
<tr>
<td>Secondary osteoporosis</td>
<td>Enter yes if the patient has a risk factor associated with osteoporosis. These include type 1 (insulin dependent) diabetes, hypogonadism and amenorrhoea, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (&lt;45 years), chronic malnutrition, or malabsorption and chronic liver disease.</td>
</tr>
<tr>
<td>Alcohol 3 or more units/day</td>
<td>Enter yes if the patient takes 3 or more units of alcohol daily. A unit of alcohol varies slightly in different countries from 8-10g of alcohol. This is equivalent to a standard glass of beer (285ml), a single measure of spirits (30ml), a medium-sized glass of wine (120ml), or 1 measure of an aperitif (60ml) (see also notes on risk factors).</td>
</tr>
<tr>
<td>Bone mineral density (BMD)</td>
<td>(BMD) Please select the make of DXA scanning equipment used and then enter the actual femoral neck BMD (in g/cm²). Alternatively, enter the T-score based on the NHANES III female reference data. In patients without a BMD test, the field should be left blank (see also notes on risk factors) (provided by Oregon Osteoporosis Center).</td>
</tr>
</tbody>
</table>
Initial Evaluation of patient with low bone mass initiating AI

- Screen for secondary causes of osteoporosis:
  - Ca/ Vitamin D
  - Renal function
  - Thyroid function
  - Liver function tests: Albumin/ total protein/
    Alkaline phosphatase/ Liver enzymes
  - Bone scan evaluations if needed
  - 24 hr urine calcium
Treatment

- Universal Recommendations for all patients
- Adequate calcium and vitamin D in diet
- Smoking cessation/ alcohol moderation
- Fall prevention strategies
- Weight bearing and strength building exercises. Balance exercises
Treatment with specific anti-osteoporotic medications

- Vitamin D
- Suggest keep levels at 30 ng/ml
- Possible lower incidence of Al related arthralgia in patients with Vit D level > 40 ng/ml
Specific treatment of Osteoporosis

• Bisphosphonates:
  • Oral:
    • Risendronate
      – IBIS II trail (Anastrazole and Risendronate) (N= 1410 placebo vs anastrazole)
      – SABRE trail (Anastrazole and Risendronate)(N=234)
    • Alendronate
      – (Hiroaki Inoue et al  N= 92)
    • Ibandronate
      – ARBON trial (N= 25)
Specific therapy for Osteoporosis

- IV Bisphosphonates (Zolendronate 4 mg 6 monthly)
- Largest concentration of data
- Bone substudy of ABCSG-12 trial ($n=401$) over 3 years
- Zometa®-Femara® Adjuvant Synergy Trials
  - (Z-FAST, $N=602$; ZO-FAST, $N=1066$; E-ZO-FAST, $N=527$)
IV Zolendronate

- Z-FAST (post-menopausal women with early ER + breast cancer. Analysis at mth 36)
- Up-front group: Administer together with AI
- Delayed group: Administer after BMD < -2.0 SD
- Only 25% of patients in delayed group required treatment
- Women receiving upfront treatment continued to gain BMD after 36 months (BMD 6.7% vs 5.2% p < 0.001)
- Trend to reduced fracture in upfront group, but no statistically significant. (5.7% vs 6.3% p = 0.002)
The effect of anastrozole on bone mineral density during the first 5 years of adjuvant treatment in postmenopausal women with early breast cancer

Hiroaki Inoue et al

BMD changes of lumbar spine according to upfront, delayed or without Bis. In patients treated with upfront Bis (bold line; n = 19), 5.4% BMD increase from baseline was noted at the lumbar spine whereas in those without Bis (thin line; n = 21) BMD decreased by 4.3% from baseline within 24 months (p < 0.0001).
Denosumab

- Ellis et al: (N=125)
- ER+ post menopausal women with T score -2.5 SD, Tx with Ca and Vit D
- Randomised into placebo or Denosumab
- Lumbar spine BMD increased 5.5% and 7.7% at 12 mths and 24 mths vs placebo
  - J Clinical Oncology 2008

- Not many RCTs and small numbers
Osteoporosis Treatments NOT recommended for AI induced Bone loss

• Estrogen therapy: Contra-indicated in patients with ER +breast cancer

• SERMS: Raloxifene. Not recommended as Tamoxifen has been shown to reduce effectiveness of aromatase inhibitors (? increase in AI metabolism).

• Recombinant human PTH: Not recommended as radiation is a risk factor for osteogenic sarcoma (possible effect of human PTH)
Cancer patients at increased risk for bone loss and fracture because of therapy or age

History & physical examination, BMD screening, FRAX analysis

Lifestyle modifications, calcium and vitamin D supplementation

T score > −1.0
T score between −1.0 and −1.5
T score between −1.5 and −2.0
T score < −2.0 or FRAX 10-year fracture risk >20% for major fracture or > 3% for hip fracture

Check 25(OH) D level

Consider pharmacologic therapy
Strongly consider treatment with pharmacologic therapy

Repeat DXA every 2 years

*The high-risk groups of patients include those who have had any type of fragility fracture (eg, distal radius fracture, hip fractures, any compression fracture) and patients who are receiving aromatase inhibitors, androgen deprivation, or glucocorticoids.
*See section on "Fracture Risk" (page 5-2) for details on FRAX analysis.
*See section on "Management of Bone Health in Patients With Cancer: Nonpharmacologic Components" (page 5-7) for information on lifestyle modifications and calcium and vitamin D supplementation.
*See section on "Management of Bone Health in Patients With Cancer: Nonpharmacologic Components" (page 5-8) for information on correcting vitamin D deficiency.

In selected cases, longer or shorter intervals may be considered. If a major change in patient risk factors or a major intervention occurs, repeating DXA scan at 1 year is reasonable.

Figure 1 Algorithm for the management of bone health in cancer patients in the United States.
Abbreviations: BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; FRAX, Fracture Risk Assessment tool.
European Society for Clinical and Economical Aspects of Osteoporosis and Osteoarthritis (ESCO)

Fig. 1 Algorithm describing the suggested approach to patients with breast cancer treated with AIs
Summary

• Patient with breast cancer are at increase risk of bone loss
• Aromatase inhibitors accelerate bone loss
• Screening BMD recommended before initiation of AI
• Universal tx for all
• Specific Tx: BMD < -2.0 SD T score (post menopausal)
• BMD -1.0 to 2.0 SD with 2 or more risk factors/FRAX
Treatment options

• IV Zolendronate supported by RCTs.
• Only 25% of delayed patients required treatment, so upfront treatment unlikely necessary.
• Oral bisphosphonates: IBIS II trail
  – likely better patient acceptance, but concern about insufficient data and possibility of reduced compliance.
• SC Denosumab not many studies.
  – Maybe for patients intolerant of bisphosphonates.
• No RCT comparing bisphosphonates to Denosumab
Patient with breast cancer initiating or receiving AI therapy

- T-score ≥ -2.0
  - No additional risk factors
    - Calcium and vitamin D supplements
      - Monitor risk status and BMD every 1 to 2 years*

- Any 2 of the following risk factors:
  - T-score < -1.5
  - Age > 65 years
  - Low BMI (< 20 kg/m²)
  - Family history of hip fracture
  - Personal history of fragility fracture after age 50
  - Oral corticosteroid use of > 6 months
  - Smoking (current and history of)
    - Bisphosphonate therapy, plus calcium and vitamin D supplements (zoledronic acid 4 mg/6 months)
      - Monitor BMD every 2 years

- T-score < -2.0