Postmenopausal Osteoporosis in Women with Breast Cancer
Faculty

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Purpose

Efforts must be made to improve care for women being treated for breast cancer who develop bone loss over time, to include:

• Focus on decreasing diagnosis time and improving management.
• Knowledge of the early signs of bone loss that indicate a need for testing, and competence in evidence-based treatment guidelines.
• Emphasis on personalization of treatment options, particularly for patients with common comorbidities.
Purpose

Bone health raises several complicating factors in postmenopausal women with breast cancer.

• Patients can experience a coinciding dramatic drop in estrogen levels, triggering bone loss.

• Drugs for cancer treatment can cause additional bone loss.

The result of these factors can cause bone loss resulting in osteopenia or osteoporosis, and increased fracture risk.
Outcome Objectives

Upon successful completion of the activity, participants should be able to:

• Review the epidemiology of bone health and osteoporosis risk in postmenopausal women with breast cancer.

• Recognize drug-related bone loss in postmenopausal women treated for breast cancer.

• Use pharmacologic interventions to prevent cancer treatment-induced bone loss.
Introduction

• Osteoporosis (OP) is a skeletal disorder characterized by diminished bone strength, leading to an increased risk of fractures.

• Bone strength is determined by both bone mineral density (BMD) and bone quality.
Introduction

It is commonly known chemotherapy drugs can induce bone loss, including:

- Taxanes
- Doxorubicin
- 5-fluorouracil
- Cyclophosphamide
- Methotrexate
- Cisplatin

In addition, chemotherapy can induce ovarian failure, which can also lead to bone loss.
Introduction

• Cancer treatment-induced bone loss is associated with drugs that reduce serum estrogen levels in women with breast cancer.
• Aromatase inhibitors (AIs) hinder the activity of the aromatase enzyme, causing a drop in serum estradiol.
• Anastrozole, exemestane and letrozole represent the most common AIs used in the treatment of hormone-positive breast cancer, and these AIs consistently reduce BMD.
Introduction

Current literature recommends the use of bisphosphonates and denosumab in postmenopausal women with breast cancer treated with AIs.
Introduction

American Cancer Society/American Society of Clinical Oncology and other authoritative guidelines recommend:

1. DXA BMD screening frequency for women taking AIs and chemotherapy.

2. An awareness of potential adverse effects of bisphosphonates and denosumab, such as osteonecrosis of the jaw and atypical femoral fracture.

3. Preventive practices to minimize these adverse drug effects.
Introduction

Osteoporosis (OP) is a major public health problem:

• Greater than 10 million Americans have OP, an additional 43 million have low bone mass.

• Greater than 2 million OP-related fractures occur each year and more than 70% occur in women.

• Greater than 20% of postmenopausal women have prevalent vertebral fractures.

Vertebral fractures are the hallmark of OP and indicate a high risk of future fractures.
Osteoporosis Diagnosis

• Bone strength consists of BMD and bone quality.
  • When DXA BMD measurements reach a T-score of -2.5, OP criteria are met.
• Lower BMD, higher risk of fracture.
  • Standard deviation drop in BMD at hip increases the risk of fracture 2-3-fold.

Osteoporosis Diagnosis

In addition to WHO bone mineral density criteria, following may also be used to diagnose osteoporosis:

- Low-trauma spine or hip fracture, *regardless* of BMD.
- Osteopenia (T-score between –1 and –2.5) with a fragility fracture of proximal humerus, pelvis or distal forearm.
- Osteopenia and high 10-year fracture probability by use of FRAX® (Fracture Risk Assessment Tool) based on country-specific thresholds.
• Breast cancer is most common female cancer in the U.S. and second highest cause of cancer death in women.
• Breast cancer mortality decreased since the 1970s due to increased screening and improved therapy.
• As the breast-cancer-survivorship population increases, there is growing need to address long-term concerns, including bone health.
Breast Cancer Risk Factors for OP

Cancer escalates fracture risk 5-fold in postmenopausal breast cancer and nearly 20-fold with soft-tissue metastases.

• Chemotherapy drugs can induce bone loss:
  ➢ Taxanes, doxorubicin, 5-fluorouracil, cyclophosphamide, methotrexate, and cisplatin.

• Chemotherapy can induce ovarian failure and a decline in estradiol levels, leading to bone loss.
Breast Cancer Risk Factors for OP

• Bone loss is associated with drugs that reduce serum estrogen levels in women with breast cancer.
• Aromatase inhibitors (AIs) hinder the activity of the aromatase enzyme, causing a drop in serum estradiol level.
• **Anastrozole**, **exemestane**, and **letrozole** represent the most common AIs used in the treatment of hormone-positive breast cancer, and these AIs consistently reduce BMD.
• The result of these factors can cause bone loss, osteopenia or osteoporosis, and increased fracture risk.
Inadequate OP Treatment

Postmenopausal OP is preventable and treatable, but only a small proportion of women at increased risk for fracture are evaluated and treated.

• Fewer than 1 in 4 women age ≥ 67 years with an OP-related fracture undergoes BMD measurement or begins OP treatment.

• Even among women with fractures, lack of treatment is common.
Nonpharmacologic Therapy

• Lifestyle modifications may improve musculoskeletal integrity and balance, preserve bone strength, and prevent future fractures.

• Adequate intake of calcium and vitamin D is important:
  • Daily supplementation with vitamin-D3 at a dose of 1,000 to 2,000 IU is typically needed to maintain an optimal serum 25(OH)D level.
  • For adults age ≥ 50 years, the recommended calcium intake (dietary plus supplements if necessary) is 1,200 mg/day.
Nonpharmacologic Therapy

• Regular, weight-bearing, resistance exercise.
• Balance-improving exercises to minimize falls.
• Avoiding tobacco and excessive use of alcohol.
• Address personal and eliminate environmental risk factors for falling.
2020 AACE PMO Guidelines
Pharmacologic OP Therapy

Several agents are approved by the U.S. FDA for prevention and/or treatment of postmenopausal OP. Full prescribing drug information should be reviewed before recommending any specific agent.
# Pharmacologic OP Therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prevention</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raloxifene (Evista)</td>
<td>60 mg PO daily</td>
<td>60 mg PO daily</td>
</tr>
<tr>
<td>Alendronate (Fosamax)</td>
<td>5 mg PO daily</td>
<td>10 mg PO daily</td>
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<tr>
<td></td>
<td>35 mg PO weekly</td>
<td>70 mg PO weekly</td>
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<tr>
<td>Risedronate (Actonel, Atelvia)</td>
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<td>5 mg PO daily</td>
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<tr>
<td></td>
<td>35 mg PO weekly</td>
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<tr>
<td></td>
<td>150 mg PO monthly</td>
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</tr>
<tr>
<td>Ibandronate (Boniva)</td>
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<td></td>
<td>150 mg PO monthly</td>
<td>150 mg PO monthly</td>
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<tr>
<td>Zoledronic acid (Reclast)</td>
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<td>5 mg IV once yearly</td>
</tr>
<tr>
<td>Denosumab (Prolia)</td>
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<td>Teriparatide (Forteo)</td>
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<tr>
<td>Abaloparatide (Tymlos)</td>
<td>-</td>
<td>80 mcg SQ daily</td>
</tr>
<tr>
<td>Romosozumab (Evenity)</td>
<td>-</td>
<td>210 mg SQ monthly</td>
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Pharmacologic OP Therapy

There is concern regarding the use of osteoanabolic agents in women with a history of breast cancer, regardless of radiation history, since the risk of breast cancer recurrence persists through the lifespan and there are theoretical risks for promoting the growth of occult, disseminated breast cancer cells, particularly within bone.
Pharmacologic OP Therapy

Current literature recommends the use of bisphosphonates, including zoledronic acid (ZA) and denosumab in postmenopausal women with breast cancer treated with AIs.

- ZA, studies: Z-FAST trial, ZO-FAST study, and N03CC (Alliance) trial
- Denosumab study: the ABCSG-18 trial

There are no randomized trials comparing bisphosphonates with denosumab for the prevention of bone loss and fracture in women taking AIs.
**Z-FAST Trial**

**Study:** 602 postmenopausal women with early, hormone receptor-positive breast cancer receiving adjuvant letrozole randomized to receive upfront or delayed-start ZA (4 mg intravenously every 6 months) for 5 years.

- **Primary endpoint:** change in lumbar spine BMD at month 12
- **Secondary endpoints:** changes in BMD and bone turnover markers at 2, 3, and 5 years, fracture incidence at 3 years and time to disease recurrence
Final 5-year L-spine and Total Hip BMD Results

Z-FAST Trial – Spine / Hip BMD

Z-FAST Trial

**Outcome:** Upfront ZA was the preferred treatment strategy vs. delayed administration, in postmenopausal women with early breast cancer receiving letrozole for 5 years.

- Significantly and progressively increased BMD
- Long-term coadministration of letrozole and ZA was well-tolerated
ZO-FAST Study

**Study:** 1065 postmenopausal women receiving adjuvant letrozole (2.5 mg/day for 5 year) were randomly assigned to immediate ZA 4 mg every 6 months for 5 years, or delayed ZA (initiated for fracture or on-study BMD decrease).

- **Primary end point:** change in lumbar spine BMD at 12 months
- **Secondary end points:** Lumbar spine and total hip BMD at subsequent follow-up, disease-free survival (DFS), and overall survival.
**ZO-FAST Study – Spine BMD**

Changes in BMD vs baseline

(A) in the Intention-to-treat population at 12, 36, and 60 months (P-values are for each timepoint versus baseline) and (B) by menopausal status at 60 months/early discontinuation.

BMD, bone mineral density; LS, lumbar spine; PMW, postmenopausal women.

ZO-FAST Study

Outcome: Immediate ZA in postmenopausal women receiving letrozole preserved BMD and was associated with improved DFS compared with letrozole alone.
N03CC Alliance Trial

Study: 551 postmenopausal women with BC completing tamoxifen and undergoing daily letrozole treatment were randomized to upfront or delayed ZA (4 mg IV every 6 months).

• In the delayed arm, ZA was initiated for post-baseline BMD T-score < -2.0 or fracture.
N03CC Alliance Trial – Spine BMD

5-year RCT of immediate vs. delayed* zoledronic acid (4 mg IV every 6 mos) for the prevention of bone loss in 551 postmenopausal women with breast cancer starting letrozole after tamoxifen:

*In the delayed arm, ZA was initiated for post-baseline bone mineral density (BMD) T-score < -2.0 or fracture

CL. 5-year follow-up of a randomized controlled trial of immediate versus delayed zoledronic acid for the prevention of bone loss in postmenopausal women with breast cancer starting letrozole after tamoxifen: N03CC (Alliance) trial. Cancer. 2015 Aug 1;121(15):2537-43.
N03CC (Alliance) Trial – Hip BMD

5-year RCT of immediate vs delayed* zoledronic acid (4 mg IV every 6 mos) for the prevention of bone loss in 551 postmenopausal women with breast cancer starting letrozole after tamoxifen:

*In the delayed arm, ZA was initiated for post-baseline bone mineral density (BMD) T-score < -2.0 or fracture

CL. 5-year follow-up of a randomized controlled trial of immediate versus delayed zoledronic acid for the prevention of bone loss in postmenopausal women with breast cancer starting letrozole after tamoxifen: N03CC (Alliance) trial. Cancer. 2015 Aug 1;121(15):2537-43.
N03CC (Alliance) Trial

Outcome: Immediate treatment with ZA prevented bone loss compared with delayed treatment in postmenopausal women on letrozole. Differences were maintained at 5 years.
ABCSPG-18 trial

Study: 3420 postmenopausal women with early hormone receptor-positive breast cancer receiving treatment with AIs were randomly assigned in a 1:1 ratio to receive either denosumab 60 mg or placebo administered subcutaneously every 6 months in 58 trial centers in Austria and Sweden.

Primary endpoint: time from randomization to first clinical fracture, analyzed by intention to treat.
ABCSDG-18 trial

Outcome: Adjuvant denosumab 60 mg twice per year reduced the risk of clinical fractures in postmenopausal women with breast cancer receiving AIs.

No additional toxicity was noted with denosumab.
“Anticancer Effects” of OP Therapy

• For patients at high risk of spine fracture but not at risk for hip or non-vertebral fractures, raloxifene which has the additional benefit of reducing breast cancer risk, may be appropriate.

• Current literature shows that the use of adjuvant zoledronic acid (EBCTCG study), but not denosumab (D-CARE trial), in postmenopausal women with early breast cancer reduces the risk of bone metastases and dying with breast cancer.
EBCTCG Study

Study: A large meta-analysis of 36 RCTs of adjuvant bisphosphonate therapy in women with breast cancer

Outcome: Adjuvant bisphosphonates reduced the rate of breast cancer recurrence in bone and improved breast cancer survival in postmenopausal women.
D-CARE Trial

Study: 4509 women with early-stage breast cancer randomly assigned to receive denosumab (n=2256) or placebo (n=2253) for a total of 5 years.

Outcome:

• **Primary endpoint:** Bone metastasis-free survival was not significantly different between the groups.

• Denosumab did not improve disease-related outcomes for women with stage II or III breast cancer despite preclinical evidence suggesting RANKL inhibition might delay bone metastasis or disease recurrence.
Adverse Effects of OP Therapy

- Similar to postmenopausal OP in women without breast cancer, safety concerns of antiresorptive therapy include osteonecrosis of the jaw (ONJ) and atypical femur fractures (AFF).
- Clinicians should also be aware that post-denosumab “rebound” in bone turnover has been linked to an increased risk of compound vertebral fractures.
Screening, Monitoring, and Management Guidelines for OP

• Several groups published recommendations for evaluation of fracture risk and management of low bone density in women initiating AIs.

• Guidelines for evaluating bone density were developed from guidelines for screening, monitoring and treatment of OP in postmenopausal women.

• Women with highest risk of fracture are most likely to benefit from drug therapy; therefore, selection of women based on fracture risk as determined by a combination of BMD and clinical risk factors is desirable.
American Cancer Society / American Society of Clinical Oncology Guideline recommends primary care clinicians refer postmenopausal breast cancer survivors for a baseline dual-energy x-ray absorptiometry (DXA) scan and repeat BMD testing every two years for women who are taking an aromatase inhibitor and for women who have chemotherapy-induced premature menopause.
ASCO Guideline

The American Society of Clinical Oncology (ASCO):

• BMD testing for all postmenopausal women taking an AI, including those in whom an AI has been recommended but not yet initiated.

• Patients with non-metastatic cancer who are prescribed a drug that causes bone loss, or whose baseline or subsequent BMD is near the threshold of treatment using FRAX® should be offered BMD testing every 2 years, or more frequently if deemed medically necessary, based on the results of BMD testing and expected bone loss.
Joint Position Statement

Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG:

• Risk factors (RFs) that increase fracture risk in women with breast cancer in addition to AI therapy include, 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 > 6 months, rheumatoid arthritis and smoking.

• In patients initiating AI treatment, fracture risk should be assessed, and bone-directed therapy should be given to all patients with a T-score < -2.0, with a T-score of < -1.5 with one additional RF, or with ≥ 2 RFs (without BMD) for the duration of AI treatment.

• Patients with T-score > -1.5 and no RFs should be managed based on BMD loss during the first year and the local guidelines for postmenopausal OP.
Joint Position Statement

• FRAX® can be used to select patients for OP treatment, although FRAX® is not designed to estimate fracture risk in women with breast cancer and may underestimate AI fracture risk.

• This consensus guideline recommends ticking the "rheumatoid arthritis" box in FRAX® to allow for the fracture effect of starting AIs as it appears that the fracture risk in women taking AIs is equivalent to that seen in rheumatoid arthritis.

• Because bisphosphonates decrease incidence of bone cancer recurrence and breast cancer specific mortality, adjuvant bisphosphonates are recommended for all postmenopausal women at significant risk of disease recurrence.

• Check treatment compliance regularly.

• Obtain DXA BMD after 12 to 24 months of treatment.
ESMO Guideline

In at-risk patients, an assessment of clinical risk factors and measurement of BMD by DXA is recommended.
Figure 1 Algorithm for use of bone-targeted treatments for bone metastases and myeloma bone disease.
ESMO Guideline

1. Therapy with AIs and ovarian suppression therapy/oophorectomy for breast cancer, and androgen deprivation therapy (ADT) for prostate cancer, is recommended.

2. Use of the lowest T-score from spine or hip sites recommended. If patients have an annual 10% decrease in BMD (or 4% to 5% in patients with osteopenia at baseline) using the same DXA machine, secondary causes of bone loss such as vitamin-D deficiency should be evaluated and antiresorptive therapy initiated.
3. Denosumab as first-line treatment followed by bisphosphonates (combined treatment duration for up to 5 years).

4. Every 6-month intravenous zoledronate, weekly oral alendronate or risedronate, or monthly oral ibandronate for the duration of endocrine treatment for up to 5 years.

5. Although ONJ is a very rare event with treatment doses of antiresorptive drugs, regular dental care and attention to oral health is advisable.
Antiresorptive therapy is recommended in women receiving an AI with either a DXA BMD T-score of less than -2.0 or with two risk factors for fracture.
Summary

Cancer alone escalates the risk of fracture, with the incidence increasing about 5-fold for postmenopausal women with breast cancer and nearly 20-fold for those who have developed soft-tissue metastases.

With improved screening methods and treatments, the breast-cancer-survivorship population continues to increase, with a growing need to address long-term care concerns, including bone health.
This learning activity can improve competence and skill in identifying osteoporosis and bone loss in patients being treated with breast cancer to provide appropriate treatment for patients. Increasing the skill level of a wide range of clinicians in the management of bone loss and osteoporosis in women receiving treatment for breast cancer will lead to improvement in patient’s long-term health.
References

Slide 11: Osteoporosis to Prevent Fractures: Screening


References


References


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Resources


Resources


