A Review of Bone Health Issues in Oncology

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Disclosures

- David Kendler has received research grants, speaking honoraria, and/or consultancies from Amgen, Merck, Astrazenica, Astellis, and Eli Lilly
Objectives:

- Challenging real-life cases in oncology (focus on breast cancer and aromatase inhibitor therapy)
  - Risk assessment
  - Required testing
  - Diet and lifestyle
  - Treatment options
  - Risks and benefits of therapy
Case History: Jean Smith 3 months after Colles fracture

- 67 year old woman
  - She has just returned to you after having Colles fracture from a fall from standing height
  - ER(+) breast cancer age 60 with surgery, radiation, tamoxifen 5 years and now letrazole 2 years
  - Concerned more about breast cancer than osteoporosis and fracture
# Lifetime risk at the age of 50

<table>
<thead>
<tr>
<th>Condition</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporotic fracture(^1,^2)</td>
<td>46-53%</td>
<td>21-22%</td>
</tr>
<tr>
<td>Hip fracture(^2,^3)</td>
<td>15-23%</td>
<td>5-11%</td>
</tr>
<tr>
<td>Radiographic vertebral fracture(^4)</td>
<td>27%</td>
<td>11%</td>
</tr>
<tr>
<td>Clinical vertebral fracture(^2)</td>
<td>15%</td>
<td>8%</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>10-13%</td>
<td></td>
</tr>
<tr>
<td>Prostate cancer</td>
<td></td>
<td>9-11%</td>
</tr>
</tbody>
</table>

NB: variable between countries

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\(^1\) Van Staa TP et al (2001) Bone 29: 517  
“Approximately 50% of people with 1 osteoporotic fracture will have another, with the risk of new fractures rising exponentially with each fracture.”

– International Osteoporosis Foundation
Bone loss and fracture risk associated with cancer therapy

T.A. Guise, The Oncologist 2006

- Normal men: 0.5%
- Late MP women: 1.0%
- Early MP women: 2.0%
- Aromatase inhibitor (AI) therapy: 2.6%
- Bone marrow transplant: 3.3%
- Androgen deprivation therapy: 4.6%
- AI therapy + gonadotropin-releasing hormone agonist: 7.0%
- Ovarian failure secondary to chemotherapy: 7.7%
Breast Cancer Increases Fracture Risk
Results of the WHI observational study

- Prospective cohort study with 5.1 years of follow-up
  - 5,298 breast cancer survivors in WHI study
  - 80,848 reference population with no history of cancer
  - Adjustment for age, weight, and ethnicity
- Women with history of BC had a 31% increased risk of fracture

WHI = Women’s Health Initiative.
Effect of tamoxifen on BMD measured by DXA in pre- versus post-MP women

\( n = 179 \) (Tam 20 mg/d vs placebo 3 yrs; clemoprevention trial of breast cancer)

Powles et al., JCO 1995
Influence of AI on fracture and osteoporosis risk

No head to head studies

Tamoxifene

Anastrozole

Letrozole

Placebo

Exemestane

Tamoxifen e→Exemestane

Fractures %

P < .0001

P < .001

P = .003

P < .001

P = .25

P = 0.001

N = 6,186

Median F/U = 68 months

ATAC

IES

BIG 1-98

MA.17

TEAM

68 months

58 months

76 months

30 months

60 months

Tamoxifene

Anastrozole

Letrozole

Placebo

Exemestane

Tamoxifen e→Exemestane

F/U, follow-up; NS, not significant; ATAC, Arimidex tamoxifen alone or in combination; IES, intergroup exemestane study; BIG 1-98, breast international group 1-98 collaborative group; TEAM, tamoxifen exemestane adjuvant multinational.

Hadji P. et al. BoneKey Reports (2015); 4 (692)
Fracture incidence of postmenopausal healthy and BC women on TAM and AI

Case History: Jean Smith and BMD results

- 67 year old woman with Colles fracture on AI for breast cancer

New information:
- DXA femoral neck T-score = -2.3
Definitions of osteoporosis

» Osteoporosis can be defined clinically and by DXA

– **Clinical definition:** Fragility fracture especially hip or spine

– **Densitometric definition:** T-score $\leq -2.5$ at spine, total hip or femoral neck (or 1/3 radius) in a postmenopausal woman or man over age 50
Fracture Rates, Population BMD Distribution and Number of Fractures

Fracture Rate per 1000 person-years

BMD distribution
Fracture Rate
No of Fractures

Fracture rate per 1000 person-years

BMD T-scores

FRAX Risk Factors

Age (40-90), sex and clinical risk factors

- BMI/DXA
- Prior fragility fracture
- Parental history of hip fracture
- Current tobacco smoking
- Ever long-term use of glucocorticoids (> 3mo and > 5mg/d)
- Rheumatoid arthritis or other secondary causes
- Alcohol intake 3 or more units daily
Case History: Jean Smith and 10 year Absolute Fracture Risk

- 67 year old woman with low bone density (osteopenia), AI for breast cancer
  - Femoral neck T-score = -2.3

New information:

- Risk factors
  - History of Colles fracture, on AI for breast cancer
  - Maternal hip fracture
  - Used Prednisone for 1 year in the past for Polymyalgia Rheumatica
http://www.shef.ac.uk/FRAX/

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: Canada

**Questionnaire:**

1. Age (between 40 and 90 years) or Date of Birth
   
   **Age:** 67
   
   **Date of Birth:** Y: [ ] M: [ ] D: [ ]

2. Sex
   
   [ ] Male
   
   [ ] Female

3. Weight (kg)
   
   60

4. Height (cm)
   
   160

5. Previous Fracture
   
   [ ] No
   
   [ ] Yes

6. Parent Fractured Hip
   
   [ ] No
   
   [ ] Yes

7. Current Smoking
   
   [ ] No
   
   [ ] Yes

8. Glucocorticoids
   
   [ ] No
   
   [ ] Yes

9. Rheumatoid arthritis
   
   [ ] No
   
   [ ] Yes

10. Secondary osteoporosis
    
    [ ] No
    
    [ ] Yes

11. Alcohol 3 or more units/day
    
    [ ] No
    
    [ ] Yes

12. Femoral neck BMD (g/cm²)
    
    T-Score: -2.3

BMI: 23.4

The ten year probability of fracture (%)

with BMD

Major osteoporotic: 43

Hip Fracture: 9.2

If you have a TBS value, click here: Adjust with TBS
FRAX: Jean Smith’s Risk Calculation

<table>
<thead>
<tr>
<th>Condition</th>
<th>Probability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major osteoporotic</td>
<td>43</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>9.2</td>
</tr>
</tbody>
</table>

High risk = 10-year osteoporosis fracture risk over 20% or hip fracture risk over 3%
Case history: Jean Smith Treatment Guidelines

- 67 year old woman with low bone density (osteopenia)
  - Femoral neck T-score = -2.3
  - History of Colles fracture, on AI for breast cancer
  - Maternal hip fracture
  - Used Prednisone for 1 year in the past for Polymyalgia Rheumatica
  - FRAX MOF 43%, HF 9.2%

- Does she meet guidelines criteria for treatment?
North American Menopause Society 2010 Treatment Recommendations

- Postmenopausal women and men over age 50:
  - A hip or vertebral (clinical or morphometric) fracture
  - T-score ≤ -2.5 after excluding secondary causes
  - Low bone mass (-1 to -2.5)
    - 10 year probability of hip fracture ≥ 3%
    - Or of any osteoporosis fracture ≥ 20%
  based on the Canadian-adapted WHO algorithm
Case History: Jean Smith and Calcium/Vit D

- 67 year old woman with low bone density (osteopenia)
  - Femoral neck T-score = -2.3, Colles fracture, on AI for breast cancer, maternal hip fracture, past prednisone for Polymyalgia Rheumatica; FRAX 43/9.2

New information:

- She is taking 1500mg of supplement elemental Ca, 4 dairy servings, and 400IU of Vitamin D daily
Calcium and Vitamin D: OC Guidelines for Women and Men over age 50

Calcium (from diet and supplement)
» 1200 mg/day

Vitamin D
» 800 - 2000 IU/day
» Can use dosing weekly or monthly
» Vitamin D3 better than D2

Jean Smith

67 year old woman with low bone density (osteopenia), Femoral neck T-score = -2.3, Colles fracture, on AI for breast cancer, maternal hip fracture, past prednisone for Polymyalgia Rheumatica; FRAX 43/9.2

taking appropriate Ca and Vitamin D

Does she need any laboratory testing?
Screen for Secondary Etiologies of Osteoporosis

- CBC diff (thalassemia, anemia)
- Ca, PO4 (hyperparathyroidism, malabsorption)
- ALP (Paget’s, liver disease, osteomalacia, fracture)
- eGFR (renal osteodystrophy, renal clearance for BP)
- TSH (hyperthyroidism)
- Maybe SPEP (myeloma)
- Maybe 25 OH Vitamin D after > 3 months on 2000IU/d (Vit D deficiency or insufficiency)
Case History: Jean Smith’s Treatment Options

» 67 year old woman with low bone density (osteopenia), Femoral neck T-score = -2.3, Colles fracture, on AI for breast cancer, maternal hip fracture, past prednisone for Polymyalgia Rheumatica; FRAX 43/9.2 on Ca and Vitamin D

New information:

» No secondary cause of osteoporosis

What medications will reduce her fracture risk?
Treatment Strategies for Osteoporosis

Mild Osteoporosis
Antiresorptive Therapy (Bisphosphonate, estrogen, calcitonin, denosumab or SERM)

Severe Osteoporosis
Bone Anabolic therapy (teriparatide)
Antiresorptive Therapy

Normal bone
Osteoporosis
Osteoporosis Canada Guidelines: Therapy

» First line therapies
  – Alendronate, Risedronate, Zoledronic acid, Estrogen, Raloxifene, Denosumab and Teriparatide

<table>
<thead>
<tr>
<th>Type of Fracture</th>
<th>Antiresorptive Therapy</th>
<th>Bone Formation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bisphosphonates</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alendronate</td>
<td>Risedronate</td>
</tr>
<tr>
<td>Vertebral</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Zoledronic Acid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Denosumab</td>
<td>Raloxifene</td>
</tr>
<tr>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Estrogen** (Hormone Therapy)</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Teriparatide</td>
<td>✓</td>
</tr>
<tr>
<td>Hip</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Non-vertebral†</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Mechanism of Action of Available Osteoporosis Therapies

What are the Key Considerations in Choosing a Therapy?

- **Efficacy**
  - Fracture reduction: hip, vertebral, non vertebral

- **Side effects / intolerance**

- **Adherence (compliance and persistence)**

- **Convenience and preference**

- **Cost and Access**
Effect of 3 Years of Treatment With Denosumab on Fractures in Women With PMO: FREEDOM


- Placebo
  - New vertebral*: 7.2%, $P < 0.0001$
  - Nonvertebral*: 8.0%, $P = 0.0106$
  - Nonvertebral*: 6.5%
  - Hip*: 0.7%

- Denosumab
  - New vertebral*: 2.3%
  - Nonvertebral*: 1.2%

N = 7,808
Effects of Denosumab Treatment on Lumbar Spine BMD and New Vertebral Fractures Through 10 Years

BMD data are LS means and 95% confidence intervals. \( ^aP < 0.05 \) vs FREEDOM baseline. \( ^bP < 0.05 \) vs FREEDOM and Extension baselines. \( ^c \)Percentage change while on denosumab treatment. \( ^d \)Annualized incidence: (2-year incidence) / 2. Lateral radiographs (lumbar and thoracic) were not obtained at years 4, 7, and 9 (years 1, 4, and 6 of the Extension).
Effects of Denosumab Treatment on Total Hip BMD and Nonvertebral Fractures Through 10 Years

BMD data are LS means and 95% confidence intervals. \(^aP < 0.05\) vs FREEDOM baseline. \(^bP < 0.05\) vs FREEDOM and Extension baselines. \(^c\)Percentage change while on denosumab treatment. Percentages for nonvertebral fractures are Kaplan-Meier estimates.
Aromatase inhibitor (AI) therapy has greatly benefitted high risk ER+ breast cancer (BC) patients in reducing recurrence rates. Treatment is usually continued over many years.

AIs reduce circulating estradiol; even low levels of estradiol in postmenopausal women are important for bone health

- All clinical trials of AI show decreases in bone density (BMD)
- Clinical fractures in patients on AI are increased to a greater degree than one would expect from the modest declines in BMD
- Different fracture locations are seen in patients on AI as compared with PMO (hip and ankle v. spine and wrist)
- BC clinical trials collected fracture by adverse event reporting; dedicated fracture trials show 5-year clinical fracture incidence of 18%, double the rate reported in BC trials
CTIBL Breast Cancer

» Risk calculators (FRAX) do not capture the excess fracture risk from AIs

» Many treatment algorithms for patients on AI recommend antiresorptive therapy if BMD T-score < -2; or < -1.5 if another risk factor is present

» Potential therapies for CTIBL include oral and iv bisphosphonates, and denosumab

» Clinical trials of ZOL suggest superior protection from bone loss when ZOL is given before AI initiation; no antifracture efficacy has been demonstrated. For CTIBL, ZOL 4mg iv 6-monthly was used.

» Smaller clinical trials of oral bisphosphonates (ALN, IBN and RIS) have shown BMD effectiveness in preventing CTIBL but no fracture data
Upfront Zoledronic Acid Increases BMD in Spine/ and Hip: ZO-FAST Study (no fracture efficacy)

DeBoer R. et al. SABCS 2010 San Antonio
AI: Effect of Denosumab on Lumbar Spine Bone Mineral Density

ABCSG18 AI Fracture Risk with Dmab v. PBO

3425 breast cancer patients on aromatase inhibitor randomized to demand or placebo.
Breast cancer DFS and antiresorptive therapies

» Metastatic BC has likely spread before surgical resection

» Antiresorptive therapy benefits to BC DFS may be due to changes in the bone environment making it unfavourable to breast cancer cells

» Meta-analysis of BP studies indicates likely BC DFS benefit of BP is restricted to PMP women
Stages of BC bone metastases

A) Tumour cell colonisation of bone
- Tumour cells home to the HSC niche
- Environmental signals maintain tumour cell quiescence

B) Tumour cell proliferation and bone metastasis progression
- Escape from quiescence
- Tumour cell proliferation
- Stimulation of bone resorption

Development of bone lesions
- Tumour cell
- Hematopoietic stem cell (HSC)
- Osteoblast
- Osteoclast

Breast cancer recurrence by menopausal status: Meta-analysis of BP studies

Breast cancer mortality by menopausal status: Meta-analysis of BP studies

Breast cancer on AI Disease Free Survival: Dmab v. PBO. ABCSG18

**ITT Analysis**

<table>
<thead>
<tr>
<th>Number of Events / Patients</th>
<th>HR (95% CI) vs Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>203 / 1,709</td>
<td>0.816 (0.66 - 1.00)</td>
</tr>
<tr>
<td>Denosumab</td>
<td>167 / 1,711</td>
<td>0.0510 Log-rank</td>
</tr>
</tbody>
</table>

**With Cross-over Patients Censored**

<table>
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<th>HR (95% CI) vs Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>199 / 1,709</td>
<td>0.807 (0.66 - 0.99)</td>
</tr>
<tr>
<td>Denosumab</td>
<td>164 / 1,711</td>
<td>0.0419 Log-rank</td>
</tr>
</tbody>
</table>
Case History: Jean Smith and Long Term Treatment Issues after 5 yr on ALN, now off AI

67 year old woman with low bone density (osteopenia), FN T-score = -2.3, Colles fracture, on AI for breast cancer, maternal hip fracture, prednisone for Polymyalgia Rheumatica, FRAX 43/9.2, taking Ca and Vitamin D, no secondary cause of osteoporosis, on alendronate for 5 years.

New information:

– Off AI

– Follow-up 5 years later shows FN DXA increased 5%. Now, FN T-score = -1.9
Mean Percent Change (± SE) in Total Spine BMD From Original FIT Baseline

- P<0.001 ALN/ALN vs ALN/PBO
- ALN/Placebo
- ALN/ALN (Pooled 5 mg and 10 mg groups)

Continuing or Stopping Alendronate After 5 Years (FLEX): Clinical Vertebral Fractures

<table>
<thead>
<tr>
<th></th>
<th>Stopped alendronate (placebo)</th>
<th>Continued alendronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with clinical vertebral fracture (%)</td>
<td>5.3</td>
<td>2.4</td>
</tr>
</tbody>
</table>

RR: 0.45
95% CI: 0.24 – 0.85

How long should antiresorptive therapy be continued?

» Sustained efficacy
» Sustained safety
» Resolution of effect (ROE)
  – Incorporation of BP in bone long-term
  – With ALN and ZOL long resolution of effect
  – With all others, short ROE

» Continue treatment as long as patient remains at risk
  – If, after 5 yr on ALN OR ZOL, BMD T-score < -2.5 or prevalent hip/spine fracture: NO DRUG HOLIDAY
Chalk Stick Fracture
Atypical (Subtrochanteric) Fractures With Antiresorptive Therapy

ASBMR Task Force Definition¹:

Major Features*

» Subtrochanteric

» Minimal trauma

» Transverse configuration

» Non-comminuted

» Complete fractures through both cortices (may be associated with a medial spike)

» Beaking

*4/5 Major features required to define atypical femoral fracture.


Atypical (Subtrochanteric) Fractures With Antiresorptive Therapy

**ASBMR Task Force Definition**:  

**Minor Features**

- Increase in cortical thickness
- Prodromal symptoms
- Bilateral fractures
- Delayed healing
- Comorbid conditions
- Use of pharmaceutical agents (e.g., BPs, GCs, proton pump inhibitors)

*None of the Minor Features are required but have been sometimes associated with these fractures.*

Hip fractures cause a high rate of morbidity and mortality\textsuperscript{2,3}

Incidence of subtrochanteric fracture very low
ONJ: Clinical Description

» Exposed bone in maxillofacial area that occurs in association with dental surgery or occurs spontaneously, with no evidence of healing*

Working Diagnosis of ONJ

» No evidence of healing after 8 weeks of appropriate evaluation and dental care

» No evidence of metastatic disease in the jaw or osteoradionecrosis

Khosla ASBMR task force JBMR 2007;22(10):1479-91
Relative Risk/Benefit

<table>
<thead>
<tr>
<th>Event</th>
<th>Incidence per 100,000 person years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bis-ONJ</td>
<td>1.03</td>
</tr>
<tr>
<td>Bis-AFF (8 yr)</td>
<td>78</td>
</tr>
<tr>
<td>Bis-AFF (2 yr)</td>
<td>2</td>
</tr>
<tr>
<td>Murder</td>
<td>1.62</td>
</tr>
<tr>
<td>Fatal MVA</td>
<td>8.4</td>
</tr>
<tr>
<td>Hip fracture at 85 y</td>
<td>3000</td>
</tr>
</tbody>
</table>

1. Transportation Canada. 2007 Casualty Rates.
Guidelines for cancer treatment-induced bone loss
IOF 2013 algorithm for managing bone health on AI

Women Starting Aromatase Inhibitor for Breast Cancer

General Measures: regular physical activity
vitamin D ≥ 800 IU/day or 10’000 IU/week
calcium intake ≥ 1000 mg/day
smoking cessation

Initial Assessment: DXA, FRAX, Ca, PTH, 25-OHD, (BTM)

Premenopausal with Ovarian Suppression
- T-Score < - 1.0
- ≥ 1 Vertebral Fr.
- Prevalent Fragility Fr.

Postmenopausal
- T-Score < - 2.5
- T-Score < - 1.5 & ≥ 1 CRF
- T-Score < - 1.0 & ≥ 2 CRF
- FRAX ≥ 3% for Hip Fr.

Antiresorptive Therapy:
(AI Treatment Duration)
- Zoledronic Acid
- Oral bisphosphonates (compliance!)
- Denosumab

Postmenopausal
- Prevalent Fragility Fr.
- Age ≥ 75 Yrs

ESMO 2014 algorithm for managing bone health during cancer treatment

Patient with cancer receiving chronic endocrine treatment known to accelerate bone loss

- T-score > -2.0 and no additional risk factors
  - Exercise
  - Calcium and vitamin D
  - Monitor risk and BMD at 1–2 year intervals

- Any 2 of the following risk factors:
  - Age >65 years
  - T-score < -1.5
  - Smoking (current or history)
  - BMI < 20
  - Family history of hip fracture
  - Personal history of fragility fracture >50 years
  - Oral glucocorticoid use for > 6 months

- T-score < -2.0
  - Exercise
  - Calcium and vitamin D
  - Bisphosphonate therapy (zoledronic acid, alendronate, risedronate, ibandronate) and Denosumab
  - Monitor BMD every 2 years
  - Check compliance with oral therapy