Prevention of Bone Fragility in Cancer Survivors

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Fred Hutchinson Cancer Center Survivorship Program
5th CME course
Outline: bone health in cancer survivors

1) Appreciate risk factors for osteoporotic fracture relevant to cancer survivors and when to screen
2) Discuss adjuvant data on reduction of bone recurrence in postmenopausal breast cancer with antiresorptive agents
3) Outline current indications, dosing and administration of currently available bone protective agents used in patients with cancer
4) Describe the adverse effects and safety considerations of approved bone protective agents
Osteoporosis is characterized by:
- low bone mass
- structural deterioration of bone tissue
- susceptibility to fragility fractures
  - commonly: spine, hip & wrist

Silent until a fracture occurs hence screening bone density rec for:
- Women ≥ 65, men ≥ 70
  - Younger if risk factors

Previous fracture, glucocorticoid therapy, parental history of hip fracture, low body weight, current smoking, ↑ EtOH, rheumatoid arthritis, “secondary osteoporosis” =
- hypogonadism or premature menopause (<45 years), DM-1, chronic malnutrition or malabsorption, chronic liver disease
3-D Micro CT: loss of horizontal trabeculae in osteoporosis

52 year old Female

84 year old Female (with vertebral fracture)

Bone density is a major determinant of fracture risk
The more negative the T score, the higher the risk

A fragility fracture of the hip or spine makes the clinical diagnosis of osteoporosis and warrants treatment
Fragility fracture = a fracture after fall from standing height or without trauma

# Mechanisms of bone loss / fragility in cancer

| Drugs: opiates, steroids, alkylating agents | hypogonadism |
| Solid tumors: Breast, Endometrial, Ovarian Prostate | Hypogonadism “+/- secondary hyperparathyroid |
| Various | Weight loss, cachexia |
| Myeloma spectrum disorders | OB inhibition, rarely osteomalacia |
| Leukemia (ALL, CML) | Steroids, ? TKIs |
| Lymphoma | steroids |
| Stem cell transplant | Steroids / GVHD, malabsorption, immunosuppressives, chemo |
| Neuroendocrine cancer (ANY) | Ectopic ACTH, Cushing’s |

1. De Maddalena C et al, Pain Physician 2012
2. Drake MT JBMR 2014
5. Pundole X et al, Bone Marrow Transplant. 2017
Drugs that may ↑ fracture risk

- Glucocorticoids (PO + high dose inhaled)
- Excessive thyroid replacement
- Proton pump inhibitors
- Anticonvulsants
- Long-term heparin use
- GnRH agonists (Lupron): prostate cancer
- aromatase inhibitors
- Thiazolidinediones
- Sedative hypnotics (FALL risk)
- Furosemide: falls ± calciuresis
- Opiates (cause hypogonadism)
DXA at the 1 year mark can be justified based on potential large amounts of bone loss with cancer therapies

Bone Loss at One Year (%)

Naturally occurring bone loss

Bone loss in patients on cancer therapies

0.5
1.0
2.0
2.6
3.3
4.6
7.0
7.7

0
1
2
3
4
5
6
7
8
9
10

Normal Men
Postmenopausal Women > 55 Years
Menopausal Women < 55 years
AI Therapy in Postmenopausal Women
Bone Marrow Transplant
ADT/GnRH agonist
AI Therapy + GnRH Agonist in Premenopausal Women
Premature Menopause Due to Chemotherapy

Abbreviations: ADT: androgen deprivation therapy; AI: aromatase inhibitor; GnRH: gonadotropin-releasing hormone

5 years on aromatase inhibitor versus tamoxifen: ↑ bone loss & fractures

- Mean baseline age = 64  n= 108

<table>
<thead>
<tr>
<th></th>
<th>anastrozole</th>
<th>tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar Spine</td>
<td>6.1% loss</td>
<td>2.8% gain</td>
</tr>
<tr>
<td>Hip</td>
<td>7.2% loss</td>
<td>0.7% gain</td>
</tr>
<tr>
<td>Fracture incidence</td>
<td><strong>11%</strong></td>
<td>7.7%</td>
</tr>
</tbody>
</table>

Eastell et al. Effect of Anastrozole on Bone Mineral Density: 5-Year Results From the Anastrozole, Tamoxifen, Alone or in Combination Trial.  *J Clin Oncol* 2008
After AI stopped at 5 yr mark:
1) BMD recovery year 6-7
2) ↓ fractures

Median Change in BMD, %
prior Rx:
Anastrozole
Tamoxifen

Lumbar spine BMD % change
- Yr 6: +2.35
- Yr 7: +4.02

Total hip BMD % change
- Yr 6: +0.71
- Yr 7: +0.50

Risk factors for osteoporotic fracture and the FRAX calculator
A higher number of fractures occur in women with osteopenia than with osteoporosis

*The World Health Organization defines osteoporosis as a T-score ≤ –2.5
†Peripheral devices used to measure T-score
Prior fracture at any site increases risk of future fracture at all other sites

<table>
<thead>
<tr>
<th>Prior Fracture</th>
<th>Relative Risk of Future Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wrist</td>
</tr>
<tr>
<td>Wrist</td>
<td>3.3</td>
</tr>
<tr>
<td>Vertebral</td>
<td>1.4</td>
</tr>
<tr>
<td>Hip</td>
<td>NA</td>
</tr>
</tbody>
</table>

Fragility fracture = without trauma or after fall from standing height

NA = not available.
Age Independently Predicts Hip Fracture Risk

At any given T-score, older age = higher fracture risk

T-score= standard deviations below healthy young normal bone density

FRAX Online WHO Fracture Risk Calculator: For Use in Osteopenia (T score -1.1 to -2.4)

If BMD is known, this is a “dummy button”

10-year fracture probability

Treat if:
> 20% or
> 3%

Steroids: ≥ 5 mg prednisone per day for ≥ 3 months
NCCN bone health task force: lower treatment threshold in cancer patients, use clinical judgment

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

Gralow et al JNCCN 2013
Fracture Risk Increases at Low Doses of Daily Corticosteroids

Fractures occur at relatively higher bone density values with steroid therapy

Relative risk of fracture compared with control

- Hip fracture
- Vertebral fracture

Prednisone 10 mg = Dexamethasone 1.5 mg

For all patients on steroid ≥ 7.5 mg/day, anticipated duration ≥ three months: start calcium, vitamin D, and drug therapy

Multiple uses of antiresorptives (bisphosphonates and denosumab) in cancer

Non-metastatic: Osteoporosis doses

- Prevent bone loss, fractures
  - ADT\(^1\), aromatase inhibitor\(^2\)
- 2015: adjuvant effect in breast cancer\(^3,4\)

4. EBCTCG, Lancet 2015
Meta analysis of 38 trials of adjuvant bisphosphonate vs placebo in breast CA

<table>
<thead>
<tr>
<th></th>
<th># trials</th>
<th># patients</th>
<th>Trials received</th>
<th>Patients received</th>
<th>% received</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any clodronate regimen</td>
<td>7</td>
<td>5167</td>
<td>5</td>
<td>5053</td>
<td>98%</td>
</tr>
<tr>
<td>Any amino-bisphosphonate</td>
<td>31</td>
<td>16860</td>
<td>21</td>
<td>13713</td>
<td>81%</td>
</tr>
<tr>
<td>Total, all regimens</td>
<td>38</td>
<td>22027</td>
<td>26</td>
<td>18766</td>
<td>85%</td>
</tr>
</tbody>
</table>

- treatment duration: 2–5 years (mean 3.4 years)
- median follow up 5.6 woman-years

EBCTCG. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials, Lancet 2015
In postmenopausal: mortality benefit similar to adjuvant chemotherapy, regardless of ER status

<table>
<thead>
<tr>
<th></th>
<th>Absolute benefit</th>
<th>Follow up Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td>3.1%</td>
<td>10 years</td>
</tr>
<tr>
<td>Anthracyclins over CMF</td>
<td>3%</td>
<td>5 years</td>
</tr>
<tr>
<td>Taxanes + anthracyclines</td>
<td>3.2%</td>
<td>8 years</td>
</tr>
</tbody>
</table>

‡ includes women aged < 45 if unknown

“postmenopausal” definition: natural or induced by GnRH agonist

EBCTCG, Lancet 2015
3.3% mortality benefit (= to adjuvant chemo) in postmenopausal was driven by less bone recurrence over yrs 0-4

<table>
<thead>
<tr>
<th>11,767 postmenopausal women</th>
<th>Bone recurrence %</th>
<th>Breast cancer mortality %</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>placebo</td>
<td>bisphos</td>
</tr>
<tr>
<td>5 years</td>
<td>5.4</td>
<td>3.6</td>
</tr>
<tr>
<td>10 years</td>
<td>8.8</td>
<td>6.6</td>
</tr>
<tr>
<td></td>
<td>RR= 0.72 (0.6-0.86)</td>
<td>2p=0.0002</td>
</tr>
</tbody>
</table>

No difference in non-breast cancer mortality  \( RR = 0.99 (0.82 \text{--} 1.19) \)

\( RR = 0.99, \ 95\% \ CI \ 0.82\text{--}1.19; \ 2p=0.91 \)
Zoledronic acid: most commonly studied, dosing frequency available in US

- clodronate daily
- zoledronic acid 4mg every 6 mo
- ibandronate 50mg daily
- oral pamidronate
- risedronate

EBCTCG. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials, Lancet 2015
Adjuvant denosumab in breast CA

primary endpoint = time to 1st clinical fracture

• Prospective, randomized, double-blind, placebo-controlled
• Mean age = 64 (38-91); 45% subjects with normal BMD

Postmenopausal early HR+ breast cancer receiving adjuvant AI*

Denosumab 60 mg SC Q6M
(n = 1711)

Placebo SC Q6M
(n = 1709)

*EXCLUSIONS: history IV bisphosphonate, oral bisph x 3 years (or if less, off x 1 year), SERMS, Cushing’s disease, Paget’s disease, hyper / hypocalcemia, hyperprolactinemia, or other active metabolic bone disease.

• Secondary endpoints: Δ BMD, vertebral fractures, cancer free survival, bone met free survival, overall survival

1. Denosumab reduced fracture risk vs placebo
2. BMD may underestimate fracture risk in aromatase inhibitor treated patients

- Zero case of osteonecrosis of the jaw and atypical femur fracture
- Median doses / time on study: 7 doses / 38 months.
- Patients treated until the prespecified # of 247 first clinical fractures reached
FRAX 10 yr risk for 64 yo Caucasian with osteopenia ~ double that of other ethnicities hence ABCSG-18 population was higher risk for fractures

<table>
<thead>
<tr>
<th></th>
<th>FRAX major osteoporotic fracture</th>
<th>FRAX hip fracture risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Caucasian</td>
<td>11%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Austria</td>
<td>9.8%</td>
<td>2.3%</td>
</tr>
<tr>
<td>US Black</td>
<td>4.8%</td>
<td>0.7%</td>
</tr>
<tr>
<td>US Latino</td>
<td>6.0%</td>
<td>0.9%</td>
</tr>
<tr>
<td>US Asian</td>
<td>5.9%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

99% Austrian or Swedish patients in ABCSG-18
Denosumab 60mg q6 months improves Disease-Free Survival in breast CA

"Double benefit" (fracture / cancer outcome) may help patients make decision to start antiresorptive drug therapy

*All subjects had recently initiated adjuvant aromatase inhibitors
- Median doses of DMAb = 7 [IQR 4-10]

Not FDA approved adjuvant therapy. Gnant et al, Lancet Oncol. 2019
2015: Converging data for better survival (adjuvant) in postmenopausal breast CA

+ Gamma delta T cells

↓ CD11b+ macrophages infiltrating tumors

↓ MMP-9

↓ VEGF

bisphosphonates
denosumab

↓ turnover

Less recurrence & improved survival

Affect on bone microenvironment is common denominator, arguing against other mechanisms
In contrast to ABCSG-18, the D-CARE study of DMAb 120mg fails to show adjuvant benefit

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>ABCSG -18</th>
<th>D-CARE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal ER/PR+ (100%) HER2+ or - All on adjuvant non-steroidal Aromatase inhibitors (AI)</td>
<td></td>
<td>Pre or postmenopausal (% not presented) HR+ or – (75%) HER2+ or – Not all on adjuvant AIs</td>
</tr>
</tbody>
</table>

| Dose and Schedule | 60mg SC q6m | 120mg SC q3-4w for 1st 6 doses 120mg SC q3m for next 54m |

| Patients demography | 71% Node negative 6% HER2+ 75% No chemo | 95% Node positive 20% HER2+ 4% No chemo |

| Primary endpoint | Time to first clinical fracture | Bone metastasis-free survival |

| Secondary endpoint | DFS | DFS/OS |

| Results primary endpoint | Benefit for denosumab (HR 0.50) | No benefit for denosumab |

| Results secondary endpoint | Benefit for denosumab (HR 0.82) | No benefit for denosumab |

| Osteonecrosis of Jaw | None | 5%

POSTmenopausal breast cancer algorithm for use of bone modifying agents to protect bone mineral density and/or achieve adjuvant benefit

Enough risk to justify incremental adjuvant Rx?*

Osteoporosis or Fx of spine/hip

- High FRAX?
  - NO: Any
  - YES: Any FDA approved therapy (DMAb 2nd line)

- Osteopenia
  - NO: Osteopenia
  - YES: Zol acid or denosumab

Al planned

- Osteopenia / porosis
  - NO (e.g. ER-): Zol acid
  - YES: Zol acid or denosumab

*All drug options may be appropriate for conditions with low risk of systemic recurrence (DCIS, T1mi, high risk prevention)
Treatments for osteoporosis: FDA approval requires ↓ spine fractures

**Antiresorptives**
- Bisphosphonates: IV & PO
- SERMs: raloxifene, tamox
- Calcitonin
- Estrogen (HRT)
- Denosumab

**Anabolics**
- Teriparatide, abaloparatide
- Romosozumab (sclerostin mAb)

**Antiresorptive** = ANTI-CATABOLIC = inhibitor of osteoclast activity

**Anabolic** = stimulates OSTEOBLAST activity
Calcium and vitamin D are important in cancer patients with bone loss

• When using potent antiresorptives (zol acid and densoumab), essential to get enough calcium and vitamin D to prevent hypocalcemia
• Calcium goal: 1200mg from food plus pills
  – Caution if calcium nephrolithiasis
• Vitamin D : check 25-OHD level
  – Goal 25-OHD level = 30 ng/mL
  – 2022 NEJM randomized trial\(^1\) found no effect of 2000 IU vitamin D in healthy subjects
  • Vast majority did not have osteoporosis
  • Vast majority had normal 25-OHD level to start with

1. LeBoff MS et al, NEJM 2022
Specific FDA approval for zoledronic acid and denosumab for “endocrine therapy” in cancer

<table>
<thead>
<tr>
<th>CANCER RELATED</th>
<th>Zoledronic Acid</th>
<th>Denosumab 120mg monthly</th>
<th>Zoledronic Acid 5mg yearly</th>
<th>Denosumab 60mg every 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine-therapy induced osteoporosis / osteopenia</td>
<td>√ 4mg q6 months</td>
<td>-</td>
<td>-</td>
<td>√</td>
</tr>
<tr>
<td>OSTEOPOROSIS</td>
<td>Postmenopausal osteoporosis (PMO)</td>
<td>-</td>
<td>-</td>
<td>√</td>
</tr>
<tr>
<td>Prevention of PMO (osteopenia)</td>
<td>-</td>
<td>-</td>
<td>√</td>
<td>-</td>
</tr>
<tr>
<td>Men</td>
<td>-</td>
<td>-</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Glucocorticoid therapy</td>
<td>-</td>
<td>-</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

1. aromatase inhibitors or androgen deprivation therapy
Concerns with use of PTH analogues in CA survivors of solid tumors that can go to bone

- For CA patients with severe osteoporosis, what about anabolic drugs like teriparatide (rPTH) and abaloparatide (rPTHrp)?
  - Contraindicated if history of XRT
  - Would avoid unless:
    1) in remission ~ 10 yrs
    2) benefit > theoretical risks (activating dormant cancer cells\(^1,2\))

- 2019 romosozumab (mAb sclerostin) FDA approval
  - No data in cancer patients
  - Attractive since ↑bone formation & ↓bone resorption

1. Farooki et al [Letter], NEJM 2007
**RESIDUAL antiresorptive effect in BONE after stoppage?**

- Denosumab 60mg or 120mg should not be held for > 6 months due to concerns about “rebound” ↑ in bone resorption
- “Chase” DMAb with bisphosphonate for 1-2 years to (mostly) block rebound bone loss
All Postmenopausal Women
1) Lifestyle and Nutritional Optimization for Bone Health Especially Calcium and Vitamin D
2) Determine the 10-year Fracture Risk According to Country-Specific Guidelines

Low-Moderate Risk

Low Risk
- Reassess fracture risk in 2-4 yrs

Moderate Risk
- OR
- (2.1) Bisphosphonates
  - (2.1) Reassess fracture risk in 3-5 yrs
  - (2.2) Reassess fracture risk in 5-10 yrs
- (2.2) (5 yrs for oral, 3 yrs for IV)

High-Very High Risk

High Risk
- OR
- (3.1) Denosumab
  - (3.1) Reassess fracture risk in 5-10 yrs
- (3.2) Reassess fracture risk in 5-10 yrs

(4.1) Teriparatide or Abaloparatide
- For 2 yrs

(8.1) Calcium + Vitamin D
- as adjunct therapy

Low-Moderate Risk
- (2.2) Consider a drug holiday
  - (11.1) Reassess fracture risk every 2-4 yrs
  - (2.2) If bone loss or patient becomes high risk, consider restarting therapy

High Risk
- (2.2) Continue therapy or switch to another therapy

Intolerant to or inappropriate for above therapies

Low-Moderate Risk
- Chase with bisphosphonates and then stopping for a drug holiday
  - (11.1) Reassess fracture risk every 1-3 yrs
  - If bone loss, fracture occurs, or patient becomes high risk, consider restarting therapy

High Risk
- (3.2) Continue therapy or switch to another therapy

Age <60 or <10 yrs past menopause
- Low VTE risk

No Vasomotor Symptoms
- High Breast Cancer Risk
  - (5.1) SERM (raloxifene, bazedoxifene)

With Vasomotor Symptoms
  - (6.1 + 6.2) HT (no uterus, Estrogen; with uterus, Estrogen + Progestin) or Tibolone

Age >60

Consider (in order):
1) SERM (5.1)
2) HT/Tibolone (6.1+6.2)
3) Calcitriol (7.1)
4) Calcium + Vitamin D (8.2)

Eastell et al JCEM 2019
Case: 27-year-old female hematologic malignancy survivor, hx of XRT
- Complains of hot flashes

- Premature menopause due to chemotherapy
- Bone density scan shows osteopenia
  - No history of fractures
- Adequate calcium, vitamin D intake
- What is the most physiologic drug for bone health?

A) alendronate, a weekly oral bisphosphonate
B) Raloxifene
C) Hormone replacement therapy (estradiol + progesterone)
D) Denosumab (subcutaneous injection every 6 months)
E) Zoledronic acid (yearly intravenous infusion)
F) Teriparatide (SC daily x 2 years)
Case Summary: 27-year-old female hematologic malignancy survivor

- If possible given underlying malignancy, age and history: replace gonadal steroid
  - represents the most physiologic option for a patient with premature menopause

- Give hormone replacement therapy (HRT) or oral contraceptive pill (OCP) until ~ age 50
  - In patients with an intact uterus, unopposed estrogen should never be given
  - HRT or OCP not appropriate for patients at high risk for DVT

- Since the patient was having hot flashes, raloxifene (a Selective Estrogen Receptor Modulator not best choice
  - SERMs can cause hot flashes
  - If no hot flashes, could use this drug up until ~ age 65
Oral bisphosphonates: safe and effective method to decrease osteoclast activity

- Cannot give if esophageal stricture
- GERD is not a contraindication
- Do not cause abdominal pain, etc
- Must be taken on empty stomach, first thing in AM (do not lay down supine), with regular water
  – mineral water, coffee, vitamins will block absorption

Favus MJ, NEJM 2010
Bisphosphonate holiday results in significantly more clinical spine fractures

• 10 years of alendronate VS 5 years on → 5 years off
  — lower risk of clinically recognized vertebral fractures with 10 years on drug

<table>
<thead>
<tr>
<th></th>
<th>Spine Fractures (%)</th>
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</thead>
<tbody>
<tr>
<td>Stopped after 5 years</td>
<td>5.3%</td>
</tr>
<tr>
<td>Stayed on for 10 years</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

RR, 0.45; 95% CI: 0.24-0.85

# Selected Adverse Effects of Oral / IV Bisphosphonates and Denosumab

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Oral bisphosphonates</th>
<th>Zoledronic acid</th>
<th>Denosumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagitis</td>
<td>possible</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Acute phase reactions</td>
<td>Weekly – no</td>
<td>Common after first dose</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>Monthly - possible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>no</td>
<td>↑ risk if: vitamin D deficient, if renal insufficiency, if blastic mets</td>
<td></td>
</tr>
<tr>
<td>Acute renal insufficiency</td>
<td>No risk.</td>
<td>Can occur</td>
<td>No risk</td>
</tr>
<tr>
<td></td>
<td>“Not recommended” if GFR &lt; 35</td>
<td>Contraindicated GFR &lt; 35</td>
<td></td>
</tr>
<tr>
<td>Atypical (iatrogenic) femur fracture</td>
<td>Can occur – likely related to duration of use</td>
<td>After 5 years of alendronate: 1 / 5,000</td>
<td></td>
</tr>
<tr>
<td>“Rebound” spine fractures</td>
<td>No</td>
<td>Yes - case reports</td>
<td></td>
</tr>
<tr>
<td>Osteonecrosis of the jaw</td>
<td>1/10,000 – 100,000</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>3 year RCT (n= 8000) of yearly zol acid 5mg: 1 case in placebo and 1 case in drug group</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>6 monthly DMAb 60mg: after 5 years (n=1457), 3 cases of ONJ</td>
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<td></td>
</tr>
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</table>

Atypical (iatrogenic) Femur Fracture: Often Bilateral

Images courtesy of Fergus McKiernan, MD
Atypical Femur Fracture: Underappreciated in Context of long term use of bisphosphonate or denosumab in cancer settings

- May present with a prodrome of dull or aching anterior thigh or groin pain
- Often bilateral
- Higher risk in Asian Americans

- Imaging early in clinical course consistent with "stress reaction" along lateral femur
  - May be confused with metastatic disease

- Stop drug and refer to orthopedist given potential for progression
  - Early imaging changes $\rightarrow$ complete fracture

FRAX 10-year probability of major osteoporotic fracture for untreated 72 year-old woman with FN T-score = -3.0 is 25%

Fearing Drugs’ Rare Side Effects, Millions Take Their Chances With Osteoporosis

But doc, I am the one patient who gets every side effect

- For such patients, I encourage them to take a “course” of bisphosphonate drug therapy for ~3 years
  - A “test dose” of zol acid 1-2mg can be offered
- Atypical femur fracture (AFF) and ONJ related to duration of use
  - Drug holiday appears to cause reduction in risk of AFF
- Further discussions based on their bone density response and whether they are still taking cancer therapy with adverse bone effects
  - Denosumab should usually be chased with bisphosphonate to block rebound bone loss
Summary

- Drug therapy to protect BMD & lower fracture risk if:
  - osteoporotic BMD, or if clinical osteoporosis (hip or vertebral fracture)\(^1\)
  - FRAX risk calculation
    - > 3% for hip fracture, or, > 20% for any major fracture
  - chronic aromatase inhibitor or ADT
- Hormone replacement is most physiologic option for young survivors of non-estrogen dependent cancer with premature menopause
- Caution with PTH analogues in survivors of bone tropic cancers
- Consider bisphosphonate holiday depending on residual fracture risk
  - after IV bisphosphonate x 3 yrs or oral bisph 3-5 yrs
  - after aromatase inhibitor, GnRH analogue, or chronic steroid is stopped
- Stop denosumab with caution and bisphosphate “chaser”-- an evolving area

“Bone” appetite!

Comments and questions