Actual SFGH Case in 2007

- Very prominent retired VIP UCSF physician admitted after suffering multiple severe spinal and hip fractures after a fall. In fact, the fractures were so severe and unstable, that he was transferred from UCSF to SFGH for special handling by the trauma and neurosurgery services.
- (First time I had ever heard of a transfer going from the university to county hospitals and not the other way around!)
- His past medical history was notable for cardiac disease and prostate cancer.
- His x-rays, in addition to demonstrating multiple severe and unstable hip and spinal fractures showed profound osteopenia.
- Rather than baby sit the patient while in the hospital, the medical service did a more thorough review of his history and discovered:
  - The patient had received many years of lupron therapy for prostate CA
  - Had never received a DXA
  - Had never been offered any osteoporosis prevention or therapy (not even calcium and vitamin D)
  - Patient had gotten “VIP” care from the very best doctors in the system

Osteoporosis (OP) and Prostate Cancer

- High incidence of OP in men with prostate cancer even before ADT (10-25%)
- May be due to advanced age, hypogonadism, and diminished vitamin D
- Risk of OP in androgen deprivation therapy (ADT) patients is markedly increased, and doesn’t depend upon the regimen used

Androgen Deprivation Therapy – Effects on Bone Mineral Density

- In one prospective trial of 62 patients, BMD decreased 7.6% at two years with surgical or chemical castration (+/- antiandrogen therapy)
- Most studies concur in showing declining BMD post Androgen Deprivation Therapy

Comparing Surgical and Chemical Orchietomy, Effects on BMD

- Daniels et al.
- Medical castration is very effective!!
Incidence of First OP fracture after Orchiectomy

Daniels et al.

Incidence of first fracture is 15% at 4 years in castrated patients vs. 1.5% in prostate ca patients without ADT

Rises to 50% vs. 8%

At 9 years!!!!

Fracture Free Survival over Time


Retrospective study of 50,000 patients with prostate cancer 1992-97

Diminishes with increasing dosages of ADT

At 9 years, only 50% patients receiving 9 doses of therapy remained fracture free!

Number of Patients needed to harm to cause a fracture: Synergistic effects of Age and cumulative ADT dose


<table>
<thead>
<tr>
<th>Age</th>
<th>Gonadotropin-releasing Hormone Agonist</th>
<th>Orchiectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4 doses</td>
<td>50-146</td>
<td>50-146</td>
</tr>
<tr>
<td>5-8 doses</td>
<td>50-146</td>
<td>50-146</td>
</tr>
<tr>
<td>9 doses</td>
<td>50-146</td>
<td>50-146</td>
</tr>
<tr>
<td>10-19 years</td>
<td>50-146</td>
<td>50-146</td>
</tr>
<tr>
<td>20-29 years</td>
<td>50-146</td>
<td>50-146</td>
</tr>
<tr>
<td>30-39 years</td>
<td>50-146</td>
<td>50-146</td>
</tr>
<tr>
<td>40-49 years</td>
<td>50-146</td>
<td>50-146</td>
</tr>
<tr>
<td>50-59 years</td>
<td>50-146</td>
<td>50-146</td>
</tr>
<tr>
<td>60-69 years</td>
<td>50-146</td>
<td>50-146</td>
</tr>
<tr>
<td>70-79 years</td>
<td>50-146</td>
<td>50-146</td>
</tr>
<tr>
<td>≥80 years</td>
<td>50-146</td>
<td>50-146</td>
</tr>
</tbody>
</table>

Estimates were calculated on the basis of adjusted rates of fracture five years after diagnosis from a Cox model with any fracture as the outcome. Doses of a gonadotropin-releasing hormone agonist were grouped according to the number of doses received within the 12 months after diagnosis. CI denotes confidence interval.

Treatment of ADT Osteoporosis

- Treatment initiation is recommended for both iatrogenic and naturally occurring hypogonadism in males
- In cases involving Prostate CA – androgen replacement therapy not an option!
- Therefore, recommendations of the American Cancer society and other organizations:
  - Screen patients initiating and continuing ADT therapy
  - Treat with appropriate therapy
**How Good are We with Following the Guidelines: An Assessment of Quality**
*Al Shamsi et al. J Oncol. 2012*

<table>
<thead>
<tr>
<th>Task 2: Evaluations screening strategies, prevention measures, and pharmacological treatment of osteoporosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient with BMI at baseline visit</td>
</tr>
<tr>
<td>Patient with BMI at any followup visit</td>
</tr>
<tr>
<td>Vitamin D supplementation during followup</td>
</tr>
<tr>
<td>Calcium supplementation during followup</td>
</tr>
<tr>
<td>Bisphosphonate use during followup</td>
</tr>
<tr>
<td>Calcitonin use during followup</td>
</tr>
</tbody>
</table>

Either a repeat BMI or treatment with a bisphosphonate during followup: 28.4% (42/148)

- Canadian retrospective cohort study
- 149 patients with non-metastatic prostate cancer who received at least one dose ADT
- 2008-2009 Tertiary care center

**Evidence Supporting Bisphosphonate in ADT**
*Neto et al. Prost Cancer and Prost Diseases (2012) 15, 36-44*

- Meta-analysis of 15 studies with 2,634 patients
- Multiple different agents included

**Fracture Reduction**
- All fracture risk reduction \(0.80\) \((0.69, 0.94)\)
- \(Z=2.8\) \(p=0.005\)
- NNT (14-166) depending upon agent at type of fracture

**Reduction in Osteoporosis**
- Risk reduction \(0.39\) \((0.28, 0.55)\)
- NNT (2.49-3.06) depending upon agent studied
Donosumab increases BMD up to 36 months

*Smith et al. NEJM 2009; 361 (8)*

Androgen Deprivation Therapy

**Take Home Points**

- ADT is very bad for the bones
  - RAPID, Dramatic loss in BMD
  - BMD and Fx incidence worse with advancing age and cumulative ADT dose
  - Surgical or chemical castration the same
  - Close monitoring of BMD (at least 1-2 years)
  - Bisphosphonates recommended, especially in lower BMD individuals
  - Denosumab: FDA approved to increase bone mass in patients receiving ADT

Donosumab lowers rate of vert. fractures at 12, 24, and 36 months

*Smith et al. NEJM 2009; 361 (8)*

Aromatase Inhibitors

**Breast Cancer and Osteoporosis**

- Chemotherapy causes gonadal ablation, premature menopause and premature osteoporosis
- May be possible direct anti-metabolic effects of chemotherapy on bone
- Increasing use of Aromatase inhibitors

  - Use of 3rd generation non-steroidal: anastrozole and letrozole cause 96-99% aromatase inhibition – very effective
  - Used more widely for metastatic or high risk disease because of superiority vs. tamoxifen
Comparing AI’s to Tamoxifen: Different effects on Fracture Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Median follow-up (months)</th>
<th>Fracture incidence (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC [18]</td>
<td>6364</td>
<td>48</td>
<td>11.0</td>
<td>0.000</td>
</tr>
<tr>
<td>BIG 1-98 [16]</td>
<td>8010</td>
<td>26</td>
<td>5.7</td>
<td>0.000</td>
</tr>
<tr>
<td>BIG [18]</td>
<td>6720</td>
<td>36</td>
<td>7.0</td>
<td>0.000</td>
</tr>
<tr>
<td>ANDIG (ARMS II) [15]</td>
<td>3260</td>
<td>36</td>
<td>2.0</td>
<td>0.000</td>
</tr>
<tr>
<td>MA.07 [12]</td>
<td>3847</td>
<td>36</td>
<td>5.1</td>
<td>0.000</td>
</tr>
</tbody>
</table>

REBBeCa: Risedronate Effect on Bone Loss in Breast Cancer


- Randomized double blinded placebo controlled trial
- 12 months follow up with 12 month extension
- 87 newly post-menopausal women after chemotherapy for breast cancer
- Risedronate weekly vs. placebo
- Primary outcome: changes in hip and spine BMD

Patient Characteristics

<table>
<thead>
<tr>
<th>Bone mineral density (mg/dl)</th>
<th>0.1 ± 0.047</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of adult fracture (n, %)</td>
<td>7/38 (18.9, 33.9)</td>
</tr>
<tr>
<td>Breast cancer treatment (n, %)</td>
<td>27/68 (40.3, 48.6)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>30/68 (44.1, 44.1)</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>31/68 (45.6, 45.6)</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>32/68 (47.0, 47.0)</td>
</tr>
<tr>
<td>Aromatase inhibitor</td>
<td>30/68 (44.1, 44.1)</td>
</tr>
</tbody>
</table>

Fewer than 20% of patients were taking an aromatase inhibitor.
Use of Bisphosphonates to Prevent Bone Loss in Breast Cancer Treated with AI’s
Greenspan et al. J Clinical Oncology June 2008

- Since publication of trial, standard of care has shifted away from tamoxifen and towards aromatase inhibitors
- 12 month extension of REBBeCa to 24 months (roughly 10% drop out in both arms)
- Use of AI’s increased from less than 20% to 44% in second year
  - Allowed for subgroup analysis of patients on AI’s

Z-Fast: Zoledronic Acid and AI’s
Brufsky et al. J Clinical Oncology 2007

- Open label, randomized, unblinded study
- Patients receiving letrozole received either A. upfront or B. delayed Z.A. (if their t-score dropped <2.0)

Fig 2. Mean (SEM) percent change in bone mineral density of the lumbar spine and the total hip at months 6 and 12 in women with early-stage breast cancer administered upfront or delayed zoledronate

Zo-Fast (not to be confused with Z-fast)
Bundred et al. Cancer July 2008

Nearly identically designed study looking at BMD in 931 patients
Donosumab and Bone Mass in Patients on Aromatase Inhibitor Therapy

- 2008 Randomized double blinded placebo controlled trial
- N=125 placebo; N=127 60 mg Donosumab q 6m.
- All women with low bone mass but not osteoporosis
- Stratified by duration of AI therapy (<= 6 months)
- Follow up at 12 and 24 months

Statistically significant increases in BMD at 12 (5.5%) and 24 (7.6%) months

Not affected by duration of AI use

FDA approval of Donosumab to increase bone mass in breast cancer patients receiving adjuvant AI therapy

Diabetic therapy: Thiazolidinediones (Glitizones)

- Peroxisome proliferator-activated receptor-γ protein agonist
- Ppar-γ helps regulate bone formation
- Decreased IGF-1 expression
  - Decreased bone formation
- Decreased osteoblastogenesis
- Promote osteoclast differentiation through increased Rank-L

Percentage change from baseline (± 95% CI) in bone mineral density (BMD) at the (A) total hip, (B) femoral neck, (C) trochanter, (D) one-third radius, and (E) total body.

- Statistically significant increases in BMD at 12 (5.5%) and 24 (7.6%) months
- Not affected by duration of AI use
- FDA approval of Donosumab to increase bone mass in breast cancer patients receiving adjuvant AI therapy
Glitazones: Effects on BMD

- Schwartz AV, Sellmeyer DE, et al. 2006
  - Observational: Health, aging, and body composition
  - Postmenopausal women with 0.61% bone loss/yr

- Glintborg et al. 2008
  - Prospective trial in women with PCOD
  - 16 week follow up: -1.1% BMD spine; -1.4% femoral neck

- Grey et al. 2007
  - Prospective trial of BMD in postmenopausal women
  - 14 week follow up with decline BMD Hip -1.9%

Glitazones: Effect on Fracture Risk

- ADOPT Trial
  - 1840 women, 2511 Men
  - Compared rosiglitazone, metformin, and glyburide
  - Follow up 4 years
  - Vertebral fractures not assessed

  - Cumulative fracture risk no different in men

  - Women, 2X cumulative Fx rate (seen in pre and post-menopausal women):
    - Rosiglitazone 15%
    - Metformin 7.3%
    - Glyburide 7.7%

UK General Practice Research Database (GPRD)


- Observational study of older individuals

- TZD therapy and its duration are associated with sig increase in nonvertebral fractures

  - hip/femur OR= 4.54
  - humerus OR=2.12
  - Forearm OR=2.90

And the Evidence Keeps Growing…

- Jones SG. Am J Manag Care 2009, 15:491–496.
  - Claims database
  - TZD doubles risk limb fracture in women

  - Meta-analyses of 10 trials (n=13,715) and two observational studies (n=31,789)
  - TZD double fracture risk in women/ not men
More Evidence!

  - Retrospective (N=84,339)
  - Men and women at increased risk of fracture
  - Fracture risk increases with cumulative exposure


  Medicare beneficiaries over 65
  - Compared TZD, sulfonylureas and metformin
  - TZD monotherapy is associated with increased risk of peripheral fractures regardless of sex and type

What to do?

- Meager data: No randomized trials of anti-resorptive agents (eg. bisphosphonates)

- Avoid use of TZD in patients at high risk for fracture

- Use lower doses of TZD or in combination
  - TZD-metformin combinations exist
  - Or incretins (some evidence that they promote bone formation)