Bone health in Breast Cancer: Optimizing Care

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Overview

• Understanding Bone Structure & Biology
• Bone Health (general)
• Preventing Osteoporotic Fractures in Early Breast Cancer
• Adjuvant Bisphosphonates in Early Breast Cancer
• Bone Health with Bone Metastases
Structure of Normal Bone

**Matrix**
(magnified)
collagen fibres
and other
substances,
which make
bone resilient

**Mineral**
mainly calcium
and phosphate,
which makes
bone rigid

**Cells**
osteoblasts
and osteoclasts,
which renew
and repair bone

The structure
of normal bone

This diagram shows a
cross-section through
part of the thigh bone
(femur).
Background on Bone Biology

Bone is a living tissue which is constantly renewing via a balance of resorption of old bone (via Osteoclasts) and deposition of new bone (via Osteoblasts).

Adapted from Novert's Pharmaceuticals
Abnormal Bone Remodeling
Leads to Osteoporosis

Osteoclastic bone resorption OUTWEIGHS Osteoblastic new bone formation

Loss of estrogen or testosterone increases ratio of resorption to formation
RANK Ligand

1. Tumour cells produce factors that stimulate osteoblasts to secrete RANKL.
2. Osteoblasts and other bone cells increase expression of RANKL.
3. Over-expression of RANKL drives increased formation, function and survival of osteoclasts, leading to excessive bone resorption.
4. Bone resorption releases growth factors from the bone matrix that may perpetuate tumour activity.
Disruption to this balance can result in weak or brittle bones
More prone to fractures with little to no trauma or stress
Associated with increased morbidity and mortality
Bisphosphonates

- Inhibit osteoclast action
  - Inhibit bone breakdown
  - Prevent bone damage
  - Improve bone density and strength

RANKL Inhibitor - Denosumab
Why bone health needs attention in Early Stage Breast Cancer?

- Most Women with breast cancer are postmenopausal and, therefore, at increased risk for osteoporosis.

- Growing incidence of bone complications in cancer survivors
  - Evolution of antineoplastic therapy including chemotherapy and hormonal therapy
  - Aging population

- Tremendous quality-of-life and functional implications

- Finally, bone is the most common site of metastasis in breast cancer.
Risk Factors of Osteoporosis

- Female
- Advanced Age
- White and Asian Ethnicity
- Family History of Osteoporosis
- Small Frame
- Decreased Estrogen Levels
- Decreased Testosterone Levels
- Increased Thyroid Hormones
- Increased Parathyroid Hormones
- Increased Adrenal Hormones
- Steroid Use
# Osteoporosis Risk Factors: Cancer Therapy Related

## Risk Factors Among Patients With Cancer

- Radiation treatment
- Chemotherapy (induces Menopause)
- Androgen-deprivation therapy (Men with Prostate Cancer)
- Aromatase inhibitor therapy (decreased estrogen)
- Ovarian Suppression
  - GnRh Agonists (Zoladex, Lupron)
  - Oophorectomy
- Other therapies that decrease estrogen or testosterone production

Lifestyle Risk Factors – Osteoporosis

### Risk Factors Among Patients With Cancer

- Low Calcium Intake
- Smoking
- Sedentary Lifestyle
- Excessive Alcohol
- Eating Disorders or Poor Dietary Habits
Predictors of Fracture Risk

- BMD (DXA), femoral neck T-score
  - Serial monitoring should be done on the same equipment with the same reference standards at the same site
- Age
- Drugs – Aromatase inhibitors, ovarian suppression
- History/presence of vertebral fracture
  - Best predictor of a subsequent fracture is an existing one
- Risk of falls
- Vitamin D/ Calcium levels
Preventing Osteoporotic Fractures in Early Breast Cancer
Bone Loss – watch closely!

- Naturally Occurring Bone Loss
  - Normal Men
  - Postmenopausal Women
  - AI Therapy in Postmenopausal Women
  - ADT
  - AI Therapy + GnRH Agonist in Premenopausal Women
  - Premature Menopause Secondary to Chemotherapy

Steroidal and Nonsteroidal AIs Increase Fracture Risk Compared With Tamoxifen

Bone Health

- Bone Density Scans—What You Need to Know
- Risk Factors for Bone Loss and Fractures
- The Latest Medicines, Vitamins, and Supplements
- The Top Ten Facts You Must Know about Bone Health

DEXA
Exercise
Vitamin D
Calcium
Osteoporosis management
What do I do for my patients for bone health?

- Vigorous activities
- Moderate activities
- Light activities
- DEXA scans
- Vitamin D supplements
- Calcium supplements
Treatments to Prevent Bone Loss

• Exercise
• Adequate Calcium Intake (at least 1300 mg/day)
• Adequate Vitamin D Levels (at least 800 IU/day)
• Low Caffeine
• Quit Smoking
• Maintain Healthy Weight
• Tamoxifen
• Raloxifene
• Bisphosphonates
Exercise

Why Exercise?

• Bone is a living tissue that responds to exercise by becoming stronger.

• Regular exercise generally achieve greater peak bone mass (maximum bone density and strength) than those who do not.

• Maintains muscle strength, coordination, and balance - helps to prevent falls and related fractures.
Exercise

What are the best Bone Building Exercises?

• Weight-bearing and Resistance - work against gravity
  • Weight bearing –
    - 30 minutes a day, 3 or 4 times a week.
    - walking, hiking, jogging, climbing stairs, tennis, and dancing.
  • Resistance exercises – 2 or 3 times a week
    - activities that use muscular strength to improve muscle mass and strengthen bone.
    - include weight lifting with free weights or resistance bands.
• Non weight-bearing exercises, include swimming and bicycling.
  - build and maintain strong muscles and have excellent cardiovascular benefits,
  - not the best way to exercise your bones.
Exercise

Design your own Work-out

• Check with your doctor before you begin a regular exercise program
• Perform extension (backward-bending) exercises.
• Target areas most prone to fractures
• Exercise needs to be continued to maintain benefits
• Resistance levels should be increased
• Increase the weights slowly
• Balance exercises
Recommended Calcium and Vitamin D Intake

• Essential mineral for maintaining bone health and reducing fracture risk
• Assess calcium and vitamin D levels
• A proper diet is important to maintain bone strength.
• Dietary Sources of calcium –
  - dairy products, green, leafy vegetables, tofu, shellfish and almonds.
  - orange juice, bread and cereal are fortified with calcium.
• Calcium supplements achieve the recommended amount
  Calcium carbonate
  – Efficient absorption requires stomach acid
  Calcium citrate
  – Useful for patients on proton pump inhibitors
Vitamin D

• Fat-soluble vitamin

• Sources
  – Foods
    • Naturally found in very few foods
    • Added to many foods on the market
  – Supplements
  – Sunlight
Food Sources of Vitamin D

3 oz smoked salmon = 583 IU

3 oz light tuna, canned in oil = 229 IU

1 large, whole egg = 29 IU
Foods Fortified with Vitamin D

8 oz skim milk = 115 IU

8 oz orange juice = 100 IU

1 cup Cheerios = 40 IU

½ cup yogurt = 40 IU
Dietary Supplements

- Calcium
  - Carbonate or citrate
  - Dose dependent absorption
  - Two doses per day

- Vitamin D
  - D₂ or D₃
  - D₃ is best
Calcium Supplementation

• Foods affect calcium absorption/retention
  – Reduced absorption: high oxalic acid or phytic acid content
  – Increased excretion: high sodium, protein, caffeine
  – Reduced excretion: fruits and vegetables

Daily Recommended Intakes

– 9-18 years = 1300 mg
– 19-50 years = 1000 mg
– 51 years and older = 1200 mg
Vitamin D
Total Serum 25 (OH)D

**Deficiency**
1) Loading Dose
   - Ergocalciferol 50,000 Units weekly x 12 weeks
   - Maintenance

**Insufficiency**
Ergocalciferol every 1-4 weeks
Calcium with Vitamin D

**Normal**
Through diet or maintenance calcium with Vitamin D

**Always replace with Calcium**

<table>
<thead>
<tr>
<th>Table 1. Vitamin D Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Insufficiency</td>
</tr>
<tr>
<td>Deficiency</td>
</tr>
</tbody>
</table>

*Source: Reference 15.*
Vitamin D Functions

• Many uses in the body
  – Promotes absorption of calcium from the small intestine
  – Maintain blood levels of calcium and phosphate for bone formation, mineralization, growth, and repair
  – Improves muscle strength and immune function
  – Reduces inflammation
Vitamin D and Cancer

• Roles in prevention of
  – Colon cancer
  – Breast cancer
The Women’s Health Initiative is the largest study looking at supplemental Calcium and Vitamin D use in order to decrease Bone Loss and decrease Fracture Risk.

Subgroup analysis also looked at the incidence of certain cancers in those 36,000 postmenopausal women who took Ca + D supplements.
DEXA Scan: Interpretation

- T-Score: the number of standard deviations above or below the mean for a healthy 30 year old adult of the same sex and ethnicity as the patient
Which Breast Cancer Patients Should be Scanned?

• All Women Over the Age of 65
• All Women with Medically or Surgically Induced Menopause
• Baseline Prior to Initiation of aromatase inhibitor and at least every 2 yrs throughout treatment
Management of Osteopenia/Osteoporosis

Fosamax (alendronate sodium) tablets

Actonel Once-a-Week

Boniva ibandronate sodium 150 mg tablet

Reclast (zoledronic acid) injection 5 mg/100 mL for infusion

Now approved for a new indication!
FDA-Approved Agents for Women With or at Risk for Osteoporosis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Drug Class</th>
<th>Recommended Dose and Schedule</th>
<th>Prevention</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>Bisphosphonate</td>
<td>One 35-mg tablet qw</td>
<td></td>
<td>One 70-mg tablet qw</td>
</tr>
<tr>
<td></td>
<td></td>
<td>One 5-mg tablet qd</td>
<td></td>
<td>One 10-mg tablet qd</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Bisphosphonate</td>
<td>One 5-mg tablet qd</td>
<td></td>
<td>One 5-mg tablet qd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>One 35-mg tablet qw</td>
<td></td>
<td>One 35-mg tablet qw</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Two 75-mg tablets qm*</td>
<td></td>
<td>Two 75-mg tablets qm*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>One 150-mg tablet qm</td>
<td></td>
<td>One 150-mg tablet qm</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Bisphosphonate</td>
<td>One 2.5-mg tablet qd</td>
<td></td>
<td>One 2.5-mg tablet qd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>One 150-mg tablet qm</td>
<td></td>
<td>One 150-mg tablet qm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 mg IV q3m</td>
<td></td>
<td>5 mg IV qy</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>Bisphosphonate</td>
<td>5 mg IV q2y</td>
<td></td>
<td>5 mg IV qy</td>
</tr>
</tbody>
</table>

*Taken on 2 consecutive days.

- Use of bisphosphonates recommended for AI-induced bone loss

**FDA-Approved Agents for Women With or at Risk for Osteoporosis**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Drug Class</th>
<th>Recommended Dose and Schedule</th>
<th>Prevention</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denosumab*</td>
<td>RANKL-targeted MAb</td>
<td></td>
<td>120 mg SQ q6m</td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
<td>SERM</td>
<td>One 60-mg tablet QD</td>
<td>1 60-mg tablet qd</td>
<td></td>
</tr>
<tr>
<td>Estrogen†</td>
<td>Steroid hormone</td>
<td>Different formulations and dosing schedules available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcitonin‡</td>
<td>Peptide hormone</td>
<td></td>
<td>1 intranasal spray qd (200 IU)</td>
<td></td>
</tr>
</tbody>
</table>

*For women with osteoporosis at high risk for fracture.
†For women at significant risk of osteoporosis.
‡Women must be ≥ 5 yrs postmenopause.
Duration Bisphosphonate Therapy

- Postmenopausal women with femoral neck T-score < -2.5 after 3-5 yrs of oral bisphosphonate therapy are appropriate candidates for continued treatment
- Postmenopausal women with existing vertebral fracture and T-score ≤ -2.0 may also benefit from continued treatment
- Postmenopausal women with T-score > -2.0 unlikely to benefit from continued treatment

Denosumab Indications for Osteoporosis Treatment

- High-affinity human monoclonal antibody that binds RANK ligand
  - RANK ligand promotes maturation, activation, and survival of osteoclasts
- Inhibits formation and activation of osteoclasts
- SC administration (60 mg every 6 mos)
- Current FDA-approved osteoporosis-related indications
  - Treatment of osteoporosis in postmenopausal women
  - Treatment to ↑ bone mass in men with osteoporosis
  - Treatment to ↑ bone mass in women who are receiving adjuvant aromatase inhibitor treatment for breast cancer and who are at high risk for fracture
  - Treatment to ↑ bone mass in men who are receiving ADT for nonmetastatic prostate cancer and who are at high risk for fracture
# Select Adverse Events With Bone-Modifying Therapy for Osteoporosis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonate, oral</td>
<td>Esophagitis, heartburn, dysphagia, GI symptoms, ONJ</td>
</tr>
<tr>
<td>Bisphosphonate, IV</td>
<td>Fatigue, fever, nausea/vomiting, ONJ</td>
</tr>
<tr>
<td>Denosumab, SC</td>
<td>Fatigue, hypocalcemia, hypophosphatemia, ONJ</td>
</tr>
<tr>
<td>Raloxifene, oral</td>
<td>Thromboembolic events, hot flashes/night sweats, influenzalike symptoms, leg cramps, peripheral edema, arthralgia</td>
</tr>
<tr>
<td>Calcitonin, intranasal</td>
<td>Rhinitis, epistaxis, sinusitis, back pain</td>
</tr>
</tbody>
</table>

Raloxifene

• SERM approved for the treatment of osteoporosis in postmenopausal women

• Approved for the prevention of Breast Cancer in High Risk Women or in Women with Osteoporosis

Tamoxifen

• SERM – can improve bone density.

• Currently used for Prevention and treatment for breast
Adjuvant Bisphosphonates in Early Breast Cancer
Do Bisphosphonates Have Anti-Tumor Activity as Well?

- European Study looked at 1800 premenopausal women taking goserelin + tamoxifen or goserelin + anastrazole and randomized them to zoledronate vs placebo.

- The study demonstrated 3.2% absolute decrease in disease progression in the patients treated with bisphosphonate therapy.

NEJM 09; 360:679-691.
Variable Efficacy of Bisphosphonates in an Unselected Patient Population

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Overall DFS, HR (95% CI)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>AZURE[1]</td>
<td>3360</td>
<td>0.98 (0.85-1.13)</td>
<td>.79</td>
</tr>
<tr>
<td>ABCSG XII[2]</td>
<td>1803</td>
<td>0.71 (0.55-0.92)</td>
<td>.011</td>
</tr>
<tr>
<td>ZO-FAST*[3]</td>
<td>1065</td>
<td>0.66 (0.44-0.97)</td>
<td>.04</td>
</tr>
<tr>
<td>NSABP-B34[4]</td>
<td>3323</td>
<td>0.91 (0.78-1.07)</td>
<td>.27</td>
</tr>
<tr>
<td>GAIN[5]</td>
<td>2994</td>
<td>0.95 (0.77-1.16)</td>
<td>.59</td>
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<tr>
<td>Z-FAST[6]</td>
<td>602</td>
<td>0.79 (0.45-1.39)</td>
<td>.42</td>
</tr>
<tr>
<td>E-ZO-FAST[7]</td>
<td>527</td>
<td>1.74 (0.83-3.67)</td>
<td>.14</td>
</tr>
</tbody>
</table>

*Intent-to-treat population.

ZO-FAST

• Zoledronate Letrozole Adjuvant Synergy Trial

> 1000 Women
treated with AI therapy
randomized to immediate Bisphosphonate therapy vs bisphosphonates only after a fracture or when the BMD dropped to < -2.0

• Demonstrated 41% relative risk reduction in disease recurrence in the group treated immediately with zoledronate

Ongoing Phase III Trials of Antitumor Properties of Bone-Targeted Agents

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>Primary Outcomes</th>
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<tbody>
<tr>
<td>SWOG 0307</td>
<td>ZA vs clodronate vs ibandronate</td>
<td>DFS, OS</td>
</tr>
<tr>
<td>NATAN</td>
<td>ZA after neoadjuvant chemo</td>
<td>EFS</td>
</tr>
<tr>
<td>D-CARE</td>
<td>Dmab 120 mg/mo for 6 mos, then 120 mg q3m vs placebo</td>
<td>Bone metastasis–free survival</td>
</tr>
<tr>
<td>HOBOE</td>
<td>Triptorelin + tamoxifen vs triptorelin + letrozole vs triptorelin + letrozole + ZA</td>
<td>DFS</td>
</tr>
<tr>
<td>SUCCESS</td>
<td>FEC-D vs FEC-DG → 2 yrs of ZA vs 5 yrs of ZA</td>
<td>DFS</td>
</tr>
<tr>
<td>ABCSG-18</td>
<td>Dmab 60 mg q6m vs placebo</td>
<td>Time to first fracture</td>
</tr>
</tbody>
</table>
Prevention of Skeletal-Related Events in Women With Breast Cancer Metastasized to Bone
The Vicious Cycle of Bone Metastasis

Tumor cells produce factors that stimulate osteoblasts to secrete RANKL

Bone resorption releases growth factors from the bone matrix that may perpetuate tumor activity

Bone resorption releases growth factors from the bone matrix that may perpetuate tumor activity

Overexpression of RANKL drives increased formation, function and survival of osteoclasts, leading to excessive bone resorption

Osteoblasts and other bone cells increase expression of RANKL

Bone Health

- Bone Density Scans—What You Need to Know
- Risk Factors for Bone Loss and Fractures
- The Latest Medicines, Vitamins, and Supplements
- The Top Ten Facts You Must Know about Bone Health

DEXA
Exercise
Vitamin D
Calcium
Bone Targeted Therapy
Bisphosphonates Reduce SREs in Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Duration, Mos</th>
<th>Patients With SRE, %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipton et al*[^1]</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Placebo</td>
<td></td>
<td>64</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>▪ Pamidronate</td>
<td></td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Rosen et al[^2]</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Pamidronate</td>
<td></td>
<td>49</td>
<td>NS</td>
</tr>
<tr>
<td>▪ Zoledronic acid</td>
<td></td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Kohno et al[^3]</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Placebo</td>
<td></td>
<td>50</td>
<td>.003</td>
</tr>
<tr>
<td>▪ Zoledronic acid</td>
<td></td>
<td>30</td>
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</tbody>
</table>

*Includes HCM.

## FDA-Approved Agents for Prevention of SREs

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<th>Recommended Dose and Schedule</th>
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<tbody>
<tr>
<td>Zoledronic acid</td>
<td>Bisphosphonate</td>
<td>4 mg IV q3-4w</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>Bisphosphonate</td>
<td>90 mg IV q3-4w</td>
</tr>
<tr>
<td>Denosumab</td>
<td>RANKL-targeted MAb</td>
<td>120 mg SQ q4w</td>
</tr>
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FDA-Approved Agents for Prevention of SREs

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</table>

- Both ASCO and NCCN recommend all 3 agents\(^{[1,2]}\)
  - No agent is recommended over another
  - Bone-modifying agent therapy is only recommended for patients with evidence of bone metastases
  - Patients should receive a dental exam and preventive dentistry before initiating bone-modifying agent therapy

Skeletal Complication Risk: Incremental Benefits in Breast Cancer

No bisphosphonate
64% risk at 2 yrs

Pamidronate
~ 20% risk reduction

Zoledronic acid
Additional ~ 20% risk reduction

Denosumab
Additional 18% risk reduction

64%
51%
34%
27%

Calcium and heart disease
Fosamax and thigh fracture
Bisphosphonate Use and the Risk of Subtrochanteric or Femoral Shaft Fractures in Older Women

< 1% risk in patient’s with Osteoporosis

Vitamin D replacement
Whether vitamin D is associated with reduced risks of breast cancer
Suggestion of an association

Benefit from Multivitamin
No clear benefit
Concern of Long-term Bisphosphonate Use

- Bisphosphonate use for > 5 yrs
  - associated with increased risk of subtrochanteric and atypical femoral shaft fractures
- Inhibition of osteoclasts may inhibit bone turnover and lead to increased bone deposition by osteoblasts,
  - Is this bone sturdy bone or just dense, brittle bone?
- Very little data exists to support the use of bisphosphonates beyond 5 yrs
- The current recommendation is to discontinue use by 5 yrs.
- Further research needed
  - Determine validity of association
  - Identify key risk factors for these events with long-term bisphosphonate therapy

Bone Health in Patients With Cancer: NCCN Task Force Report

• Patients with cancer may be at increased risk for bone loss and fracture due to therapy or age
• To accurately assess the risk of bone loss or fracture, full history and physical exam, followed by
  - BMD screening and FRAX analysis
• Initial strategies for preventing bone loss
  - lifestyle modifications &
  - calcium and vitamin D supplements
• patient’s BMD T-score should guide additional therapeutic intervention strategies

Guidance for Women With Breast Cancer Initiating AI Therapy: Summary

T-score > -2.0, no risk factors

- Exercise
- Calcium and vitamin D supplements

Monitor risk status and BMD q12m*

Any 2 of the following risk factors
- T-score < -1.5
- Aged younger than 65 yrs
- Low BMI (< 20)
- Family history of hip fracture
- Personal history of fragility fracture after 50 yrs of age
- Oral corticosteroid use of > 6 mos
- Smoking (current or history of)

T-score < -2.0

Exercise

Treatment including bisphosphonates, denosumab, Calcium, and vitamin D supplements

Monitor BMD on case by case basis for IV bisphosphonates; q12-24m for oral bisphosphonates

*If ≥ 10% decrease in BMD (≥ 4% to 5% if osteopenic at baseline), investigate secondary causes and begin antiresorptive treatment. Use lowest T-score from 3 sites.

REMEMBER!!

It takes a team to take care of bone related problems
THANK YOU