Complications of Cancer Therapy, Part II: Metabolic Bone Disease and its Treatment

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Case Presentation: #1

- 70 y.o. woman presented in 2002 with anemia
- monoclonal urinary light chain of about 3 gm/day
- No lytic bone lesions
- Bone Marrow Biopsy performed.....
Low Power Bone Marrow Biopsy
Higher Power Bone Marrow Biopsy
Bone Marrow Aspirate
Case Presentation: #1

• 70 y.o. woman presented in 2002 with anemia
• monoclonal urinary light chain of about 3 gm/day
• No lytic bone lesions
• Bone Marrow Biopsy performed…..
• Treated with melphalan and prednisone initially without benefit
Case #1, continued

• Chemo stopped after a year when no clear-cut benefit could be realized
• In 2004 repeat skeletal survey showed early lytic disease
• Started on Thalidomide with pulse dexamethasone and Zometa with convincing fall in urinary light chain and improvement in anemia
Case #1, continued

- Presented in April, 2006, with swelling on the side of her face
- CT scan obtained....
- ENT consultation obtained
- Diagnosis unclear at first
- Failed to respond to antibiotic therapy
- Saw oral surgeon in August who felt she probably has osteonecrosis of mandible
- Therapy conservative
- Treatment of underlying myeloma continues to be successful; Zometa discontinued
Case #2

- 67 y.o. lady with long history of metastatic breast cancer
- Recently had shown progression of metastases in bone and was started on new chemotherapy and Zometa
- Admitted to the hospital in March, 2006 with weakness, watery diarrhea and hypotension
- Calcium on admission was 3.3
- W/U and treatment undertaken
Case #2

- Started on large doses of intravenous calcium and vitamin D with gradual improvement
- Work up revealed:
  - Ionized Calcium 0.42mmol/l (1.12-1.32 normal)
  - Creatinine 1.4
  - Inorganic phosphate 1.1
  - Magnesium 1.5
  - PTH level 761 (nl < 72 for normocalcemic patient)
  - 24-hr urine calcium and phosphate both very low
  - 1,25 di-hydroxyvitamin D levels normal X 2, an unexpected finding (expectation was that vit D deficiency led to the drop in calcium after bp’s)

- Now for some basic biochemistry…”
Digression: Origin of Vitamin D

[Chemical structure of cholesterol and 7-dehydrocholesterol]

Bond breaks

7-dehydrocholesterol

Cholesterol
Cholecalciferol (Vitamin D3)

25-Hydroxy-D3 or calcidiol...the storage form of vitamin D

1,25 dihydroxy D3 or calcitriol...the most active form of vitamin D
Vitamin D, continued

• The conversion from 25-OH D3 to 1,25 di-OH D3 is important and influenced by a number of factors

• In our case 1,25 was measured but may not have reflected total-body pools of D3 because most vitamin D stored as 25-OH D3.

• Hence patient may still have been overall D-deficient despite normal 1,25 levels.
The Overall Problem

- Metabolic bone disease in cancer patients is mostly a problem of loss of bone: osteopenia and, when more severe, osteoporosis
  - Vitamin D deficiency is common but by itself does not usually cause obvious clinical disease – viz., osteomalacia
- Osteoporosis is a naturally occurring phenomenon, increasing as the population ages
- Widespread use of hormonal manipulations in treatment of cancer greatly exacerbates problem
  - Aromatase inhibitors in the treatment of breast cancer
  - Weak LHRH agonists or orchiectomy in the treatment of prostate cancer
Effect of 2-year treatment with placebo or exemestane on bone mineral density (BMD) of the lumbar spine (A) and femoral neck (B)

Effect of 2-year treatment with placebo or exemestane on two different bone resorption markers
Combating osteoporosis induced by aromatase inhibitors

- Ongoing trial (“Z-FAST”) to see whether Zometa can prevent osteoporosis in women taking Femara; preliminary results:
  - 3.3% difference in BMD at 6 months: Femara with or without Zometa (↑ with and ↓ without)
  - Zometa not FDA-approved in this setting
- Nothing else known at the moment
- To date decrease in BMD in women on aromatase inhibitors has not resulted in increased morbidity, but not enough time has elapsed for comfort
Osteoporosis in the Treatment of Prostate Cancer

• Hormone deprivation with castration or drugs designed to lower testosterone levels results in bone mineral loss
• Fracture rate increases in this setting…
Unadjusted Fracture-free Survival among Patients with Prostate Cancer, According to Androgen-Deprivation Therapy


Dose-dependent impact of Lupron therapy
Bisphosphonates in Benign and Malignant Disease

• Overwhelming evidence for their role in treating (benign) post-menopausal osteoporosis
• Drugs in use:
  – Alendronate (Fosamax) weekly
  – Risedronate (Actonel) weekly
  – Ibandronate (Boniva) monthly
  – Intravenous Ibandronate quarterly (reserved for intolerance to oral agents)
• Just now coming into wide use; reimbursement issues predominate; convenience, low toxicity, efficacy profile not in question
Intravenous Ibandronate

- Recently approved; first intravenous bp approved for the prevention of osteoporosis
- Advantages:
  - Given only four times per year
  - No gastrointestinal side effects
  - Cost comparable to oral preparation
  - Commercial carriers currently covering
  - Available at your oncologist’s office (!)
Impact of daily Alendronate (Fosamax) on lumbar spine BMD over 2 years

Bisphosphonates in the treatment of Malignant Disease

- Originally used in the treatment of malignant hypercalcemia
- Highly effective and non-toxic
- Typically work from 24-48 hours after administration
- Not suited for immediate treatment of life-threatening hypercalcemia
Bisphosphonates in Malignancy, continued

• Classic study in 1996 showing benefit of Pamidronate (Aredia) in preventing fractures...
Kaplan-Meier Estimates of the Time to the First Skeletal Complication in Patients with Breast Cancer and Multiple Myeloma

Prevention of Skeletal Complications, continued

• Subsequent study established the slight superiority of Zolendronic Acid (Zometa) over Pamidronate (Aredia) in the prevention of fractures in women with metastatic breast cancer
• Much improved convenience (short infusion duration)
• The data...
Benefit seen only in patients with established lytic lesions

Zometa 8 mg proved too toxic; reduced to 4 mg in mid-trial
Potential Complications of Intravenous Bisphosphonate Therapy

- Predictable small increase in serum creatinine which is reversible with cessation of drug
- Hypocalcemia not generally a problem unless....
Complications of Bisphosphonates, continued

- Hypoparathyroidism pre-exists in which case severe hypocalcemia can result.
- Vitamin D deficiency pre-exists in which case hypocalcemia can result and effect of drug can be blunted...
- Hypocalcemia in turn leads to secondary hyperparathyroidism and severe hypophosphatemia.
- Role of acute inhibition of bone resorption in producing hypophosphatemia as well.
- Mechanisms of derangements in metabolism are just beginning to be understood.
Problem of Vitamin D deficiency

- Up to 50% of women over 70 are Vitamin D deficient
- Has led to recommendation for routine D supplementation in women receiving intravenous bisphosphonates
- Hard data on improved outcome not available yet
- Role of D supplements with weaker, oral bp’s not clear; now included in a single pill (“Fosamax Plus D”)
- Our case #2 illustrates complexity of problem and our lack of thorough understanding of pathophysiology
Potential Complications of Bisphosphonate Therapy

- Predictable small increase in serum creatinine which is reversible with cessation of drug
- Hypocalcemia not generally a problem unless….
- Osteonecrosis of the mandible
Clinical presentation of osteonecrosis of the jaw


Bisphosphonate Complications
Axial CT scans showing a diffuse osteonecrotic/ostemyelitic process involving almost the whole mandible

Fistulous tracts from Osteonecrosis of Mandible

ONJ: Pathophysiology

- Bisphosphonates reduce bone turnover: both osteoclastic and osteoblastic activity
  - Clinically reduction of osteoblastic activity predominates
  - Reduction in osteoblastic activity may lead to "hypodynamic bone*" with resultant decreased "biomechanical competence*"
- Seen almost exclusively with intravenous bp’s
- Incidence in patients with myeloma and breast cancer probably about 5%

ONJ: Risk Factors*

- Prior head-and-neck radiotherapy
- Chemotherapy
- Corticosteroids
- Periodontal disease or infection
- Recent dental surgery
- Trauma from ill-fitting dentures
- Smoking
- Alcoholism
- Duration of bp therapy

*Ruggiero et al JOP Jan 2006 pp. 7-14
ONJ: Clinical Presentation

• Long (?) silent period
• Often discovered by accident during dental examination wherein exposed bone is discovered
• Symptoms include:
  – Primarily pain
  – Soft-tissue swelling
  – Loosening of previously stable teeth
  – Fistulous tract formation
ONJ: Diagnosis

- X-ray to rule out osteomyelitis or metastasis
- Cultures to rule out Actinomycosis
- What is left is a clinical/radiological diagnosis
ONJ: Treatment

- No “best available” therapy defines at the present
- Large surgical debridement has not yielded good outcomes
- Antibiotics topically or systemically have been tried with uneven results
- Removable appliance or protective stent can be used to protect exposed bone from further trauma or infection
- If patient already has dentures be sure they fit well, are taken out at night and are thoroughly and regularly cleaned
- Hyperbaric oxygen: being studied; preliminary results uneven
Understanding ONJ: Clinical Trials and Research Directions*

*Courtesy of Novartis
Ongoing/Planned Clinical Trials in Oncology examining ONJ

• Ongoing clinical trials
  – ZOMETA 2105: Open March 2006
  – SWOG 0307: Open November 2005

• Planned clinical trials
  – SWOG: US ONJ Registry Trial
OPTIMIZE-2 (Trial 2352)

- Prospective, randomized, controlled trial
- Breast cancer with bone metastases, second year of therapy (N = 1,650)
- ZOMETA every 4 weeks versus every 12 weeks versus treatment discontinuation
- **ONJ monitoring**
  - Baseline oral examination and panoramic x-ray
  - Tracking of dental procedures
  - Follow-up dental examination with any symptoms
  - Referral to oral surgeon if ONJ is suspected
Patients with breast cancer + bone metastases
• Pretreated with 9 to 12 doses of ZOMETA during previous 10 to 12 months

N = 1,650

Study Design:
OPTIMIZE 2 (ZOMETA Trial 2352)

Randomization 2:2:1

Tx Group A, n = 660  ZOMETA q 4 wk

Tx Group B, n = 660  ZOMETA q 12 wk*

Tx Group C, n = 330  Placebo q 4 wk*

Study drug infusions every 4 weeks

*Primary endpoint:
Time to first SAE

First study drug infusion

0 4 8 12 16 20 24 28 32 36 40 44 48 52 weeks

weeks analysis*

Rescue: ZOMETA q 4 wk after first SAE.

Bisphosphonate Complications
ZOMETA Trial 2105

- Phase I prospective, randomized, open-label study
- Multiple myeloma or breast cancer with bone metastases (n = 72)
- ZOMETA 4mg every 4 weeks or every 12 weeks
- ONJ monitoring: same as for OPTIMIZE-2
Patients with multiple myeloma and breast cancer + bone mets
Pretreated with 9 to 12 doses of ZOMETA during prior year

N = 72

Tx Group A, n = 36  ZOMETA q 4 wk
Tx Group B, n = 36  ZOMETA q 12 wk

Randomization 1:1

First study Drug infusion
Study drug infusions every 4 weeks
Last study Drug infusion

ZOMETA Trial 2105: Trial Design

Bisphosphonate Complications
SWOG Trial 0307

- Stage I to IIIa breast cancer (N = 6,000)
- Randomized open-label study to determine the relative efficacy of 3 bisphosphonates for the prevention of bone metastases
  - ZOMETA versus ibandronate versus clodronate
- Dental examination at baseline and at end of study in addition to routine dental monitoring and care throughout study
- First patient enrolled January 2006
- Interim analyses: 2010, 2012
- Study conclusion expected in 2015

Bisphosphonate Complications
SWOG 0307: Study Design

- Stage I, II, and III breast cancer on standard adjuvant therapy (N = 6,000); bone metastasis prevention trial

ZOMETA 4 mg IV q mo x 6 mo, q 3 mo x 2.5 yr*

Ibandronate 50 mg PO daily x 3 yr*

Clodronate 1,600 mg PO daily x 3 yr*

*Daily supplemental calcium (1,000 to 1,500 mg) and vitamin D (400 to 800 IU).
SWOG US ONJ Registry Trial

• A large, prospective study of ZOMETA is planned to assess the incidence and associated risk factors for development of ONJ in cancer patients treated for the approved oncology indications of ZOMETA

• Proposal for study is currently under review at SWOG for inclusion in the *Intergroup* mechanism
Research Directions: Current and Future Needs

- Investigate pathogenesis and natural history of ONJ
- Elucidate risk factors for ONJ
- Develop and test prevention and management strategies
Further Perspective

• Women without cancer vastly outnumber the number of patients currently receiving bp’s as adjunct to the therapy of metastatic disease to bone

• With aging of the population and reduction in mortality from cardiovascular disease and cancer, degenerative diseases become even more important:
  – Osteoporosis
  – Alzheimer’s Disease
  – Osteoarthritis
  – Diabetes/Obesity
There is a pressing need to develop effective, low-risk strategies to prevent osteoporosis and the associated morbidity and societal costs. Existing strategies are moderately effective but long-term toxicity is only now being uncovered. Risk/benefit ratios will be further defined with additional studies, with populations at risk of toxicity better defined. Newer treatments as always may make this discussion moot.