

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

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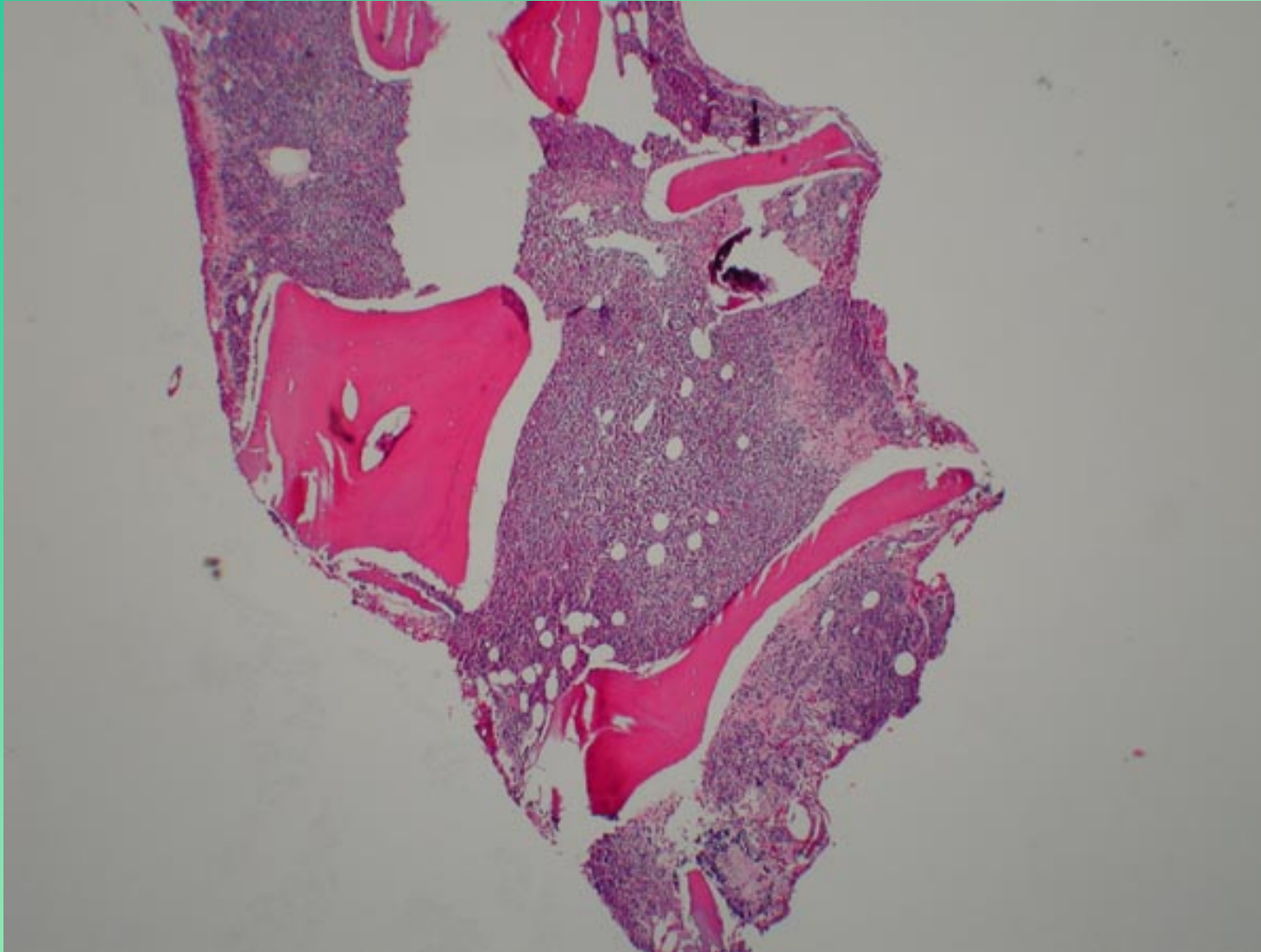


Case Presentation: #1

- 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.....



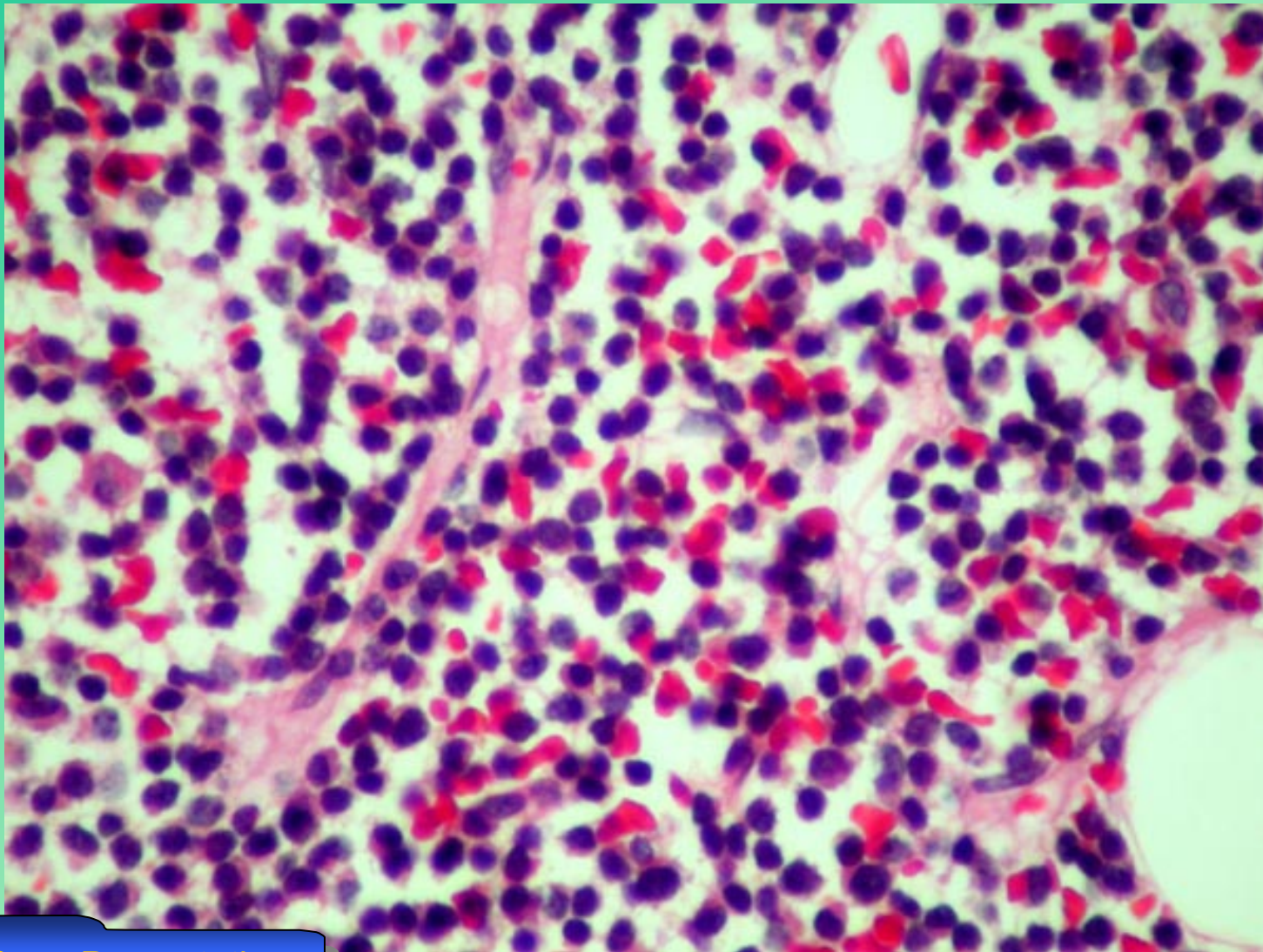
Low Power Bone Marrow Biopsy



Case Presentation

StarkDamleOncology

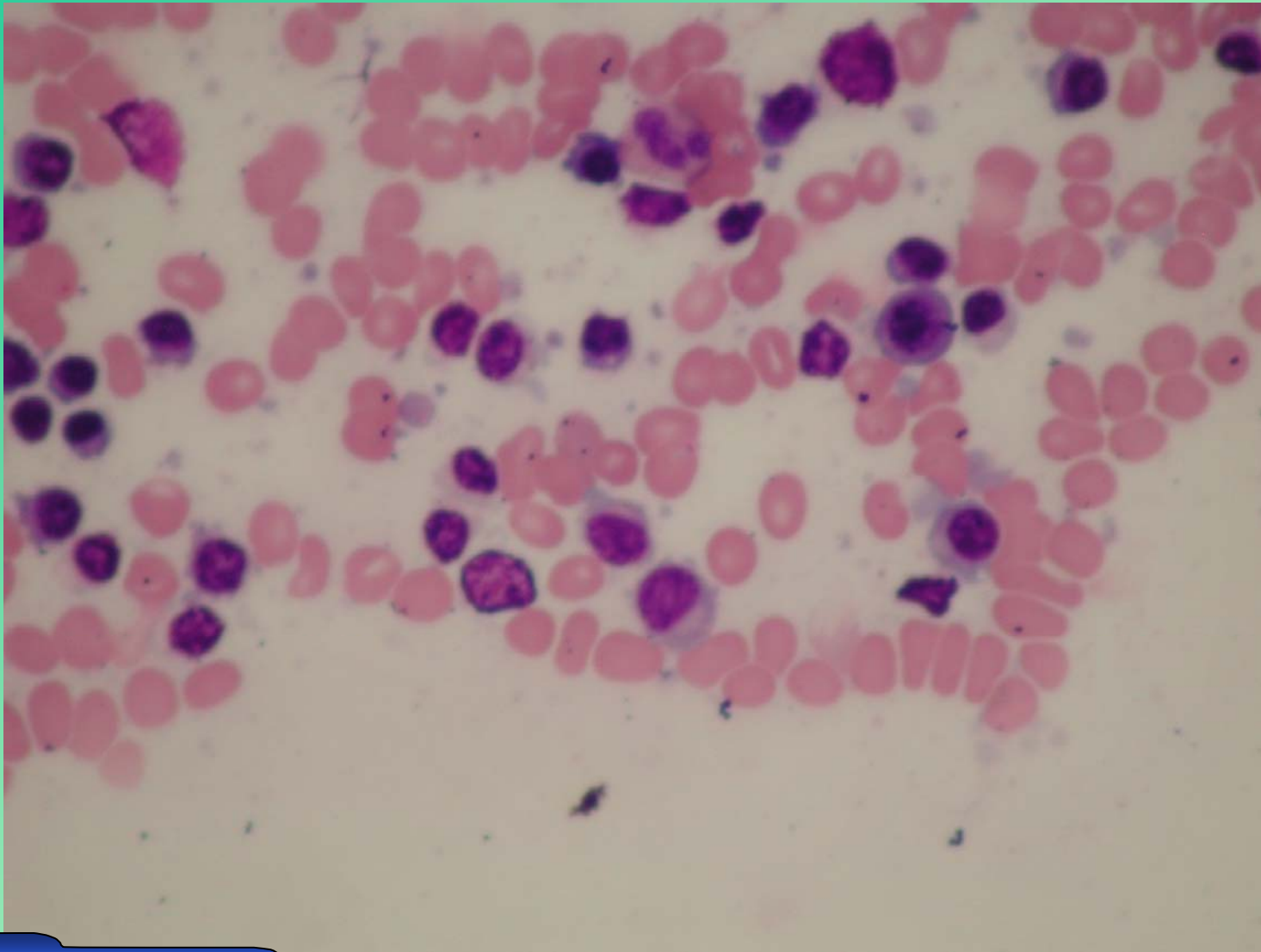
Higher Power Bone Marrow Biopsy



Case Presentation



Bone Marrow Aspirate



Case Presentation



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

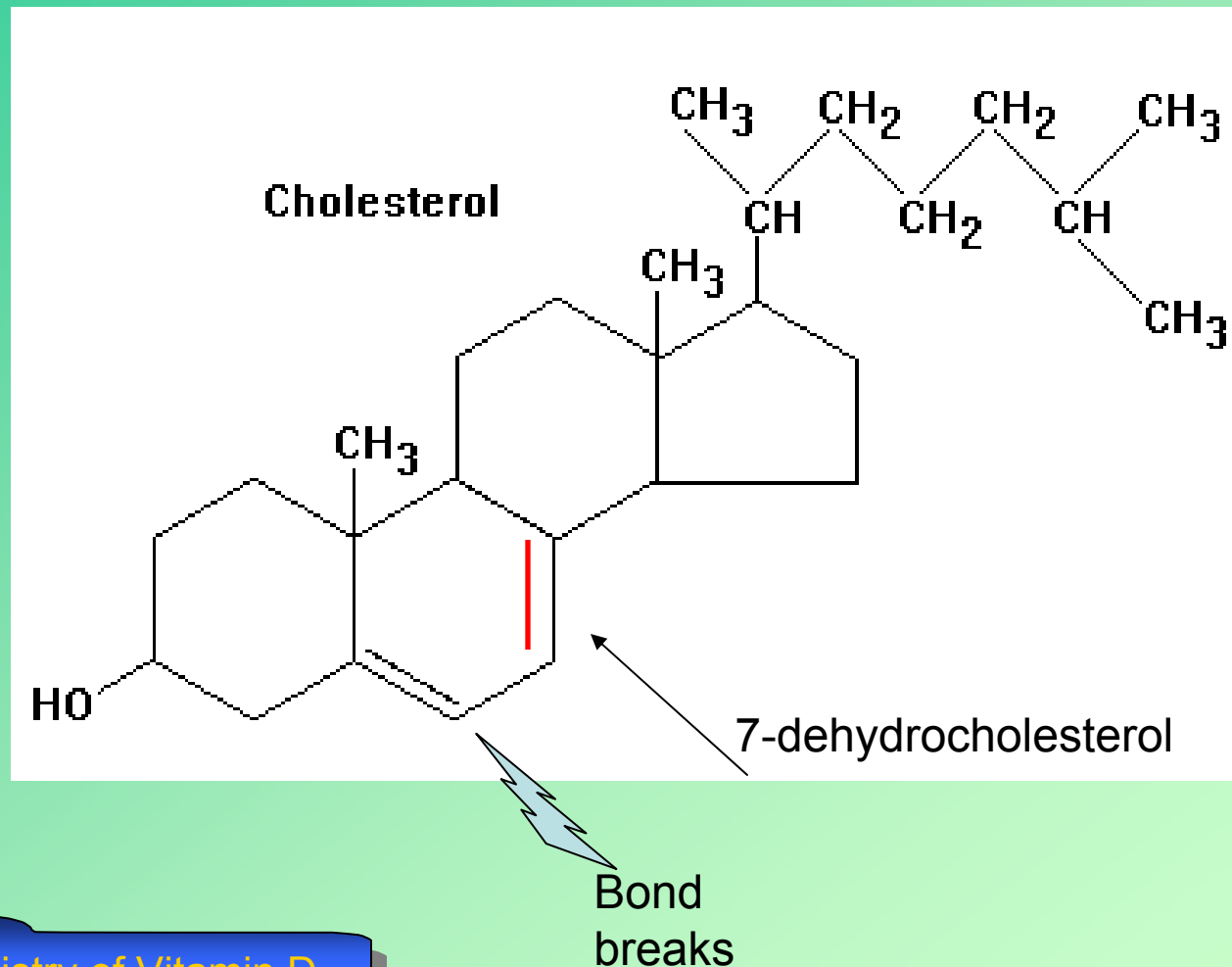


Case #2

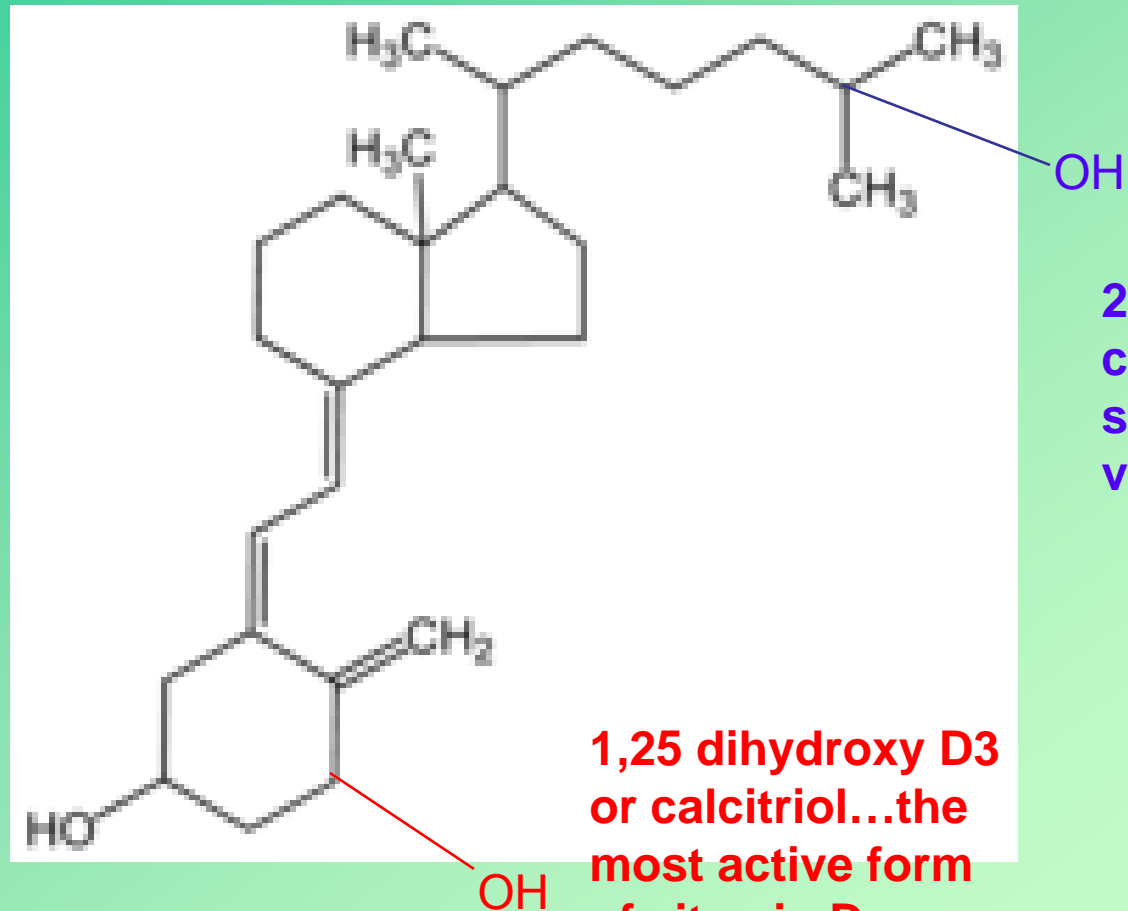
- Started on large doses of intravenous calcium and vitamin D with gradual improvement
- Work up revealed:
 - Ionized Calcium 0.42mmol/l (1.12-1.32 normal)
 - Creatinine 1.4
 - Inorganic phosphate 1.1
 - Magnesium 1.5
 - PTH level 761 (nl < 72 for normocalcemic patient)
 - 24-hr urine calcium and phosphate 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



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

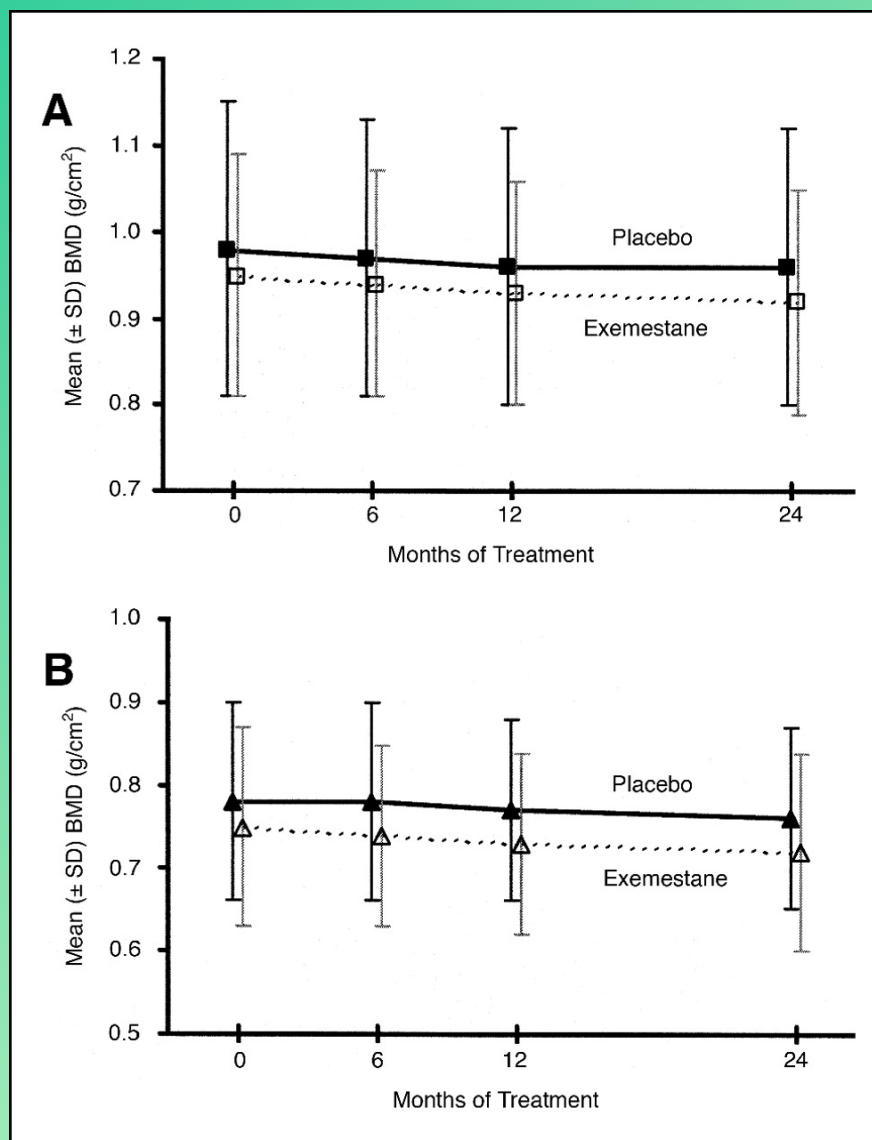


The Overall Problem

- 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

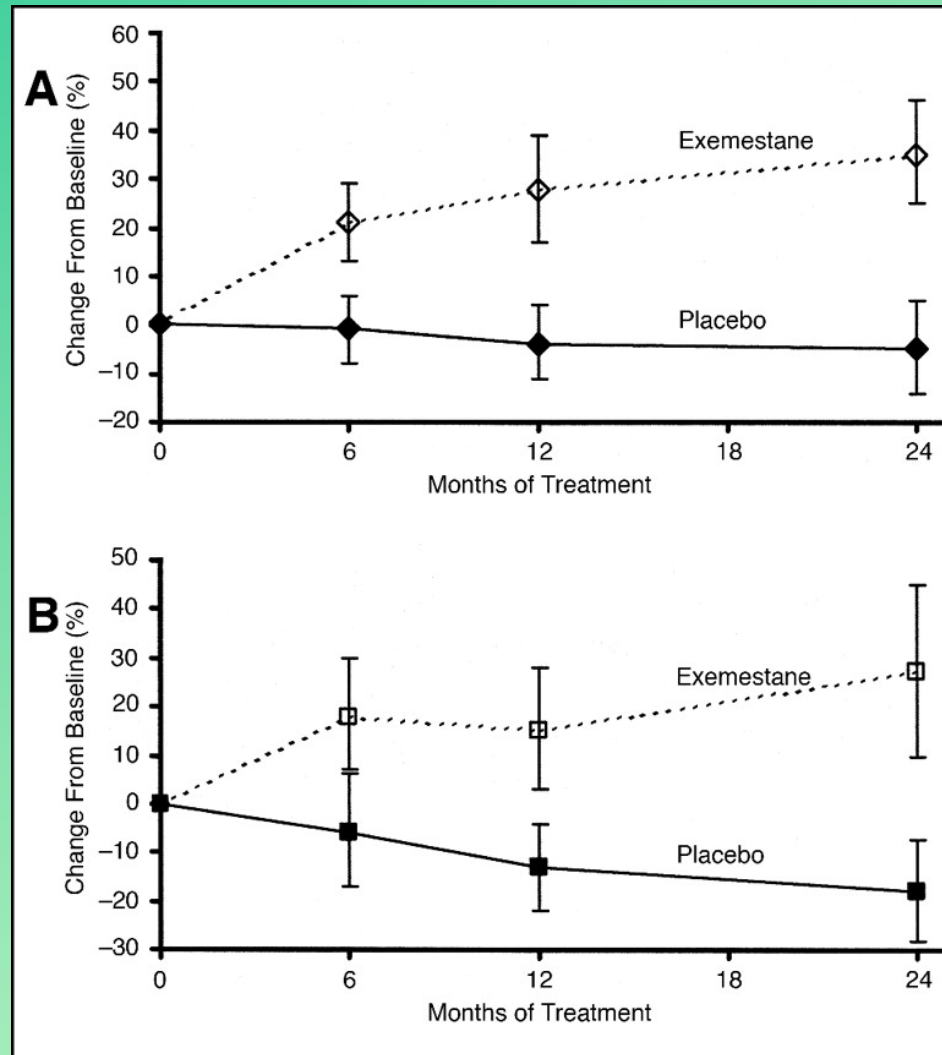


Effect of 2-year treatment with placebo or exemestane on bone mineral density (BMD) of the lumbar spine (A) and femoral neck (B)



Lonning, P. E. et al. J Clin Oncol;
23:5126-5137 2005

Effect of 2-year treatment with placebo or exemestane on two different bone resorption markers



Meta MBD and aromatase inhibitors



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...

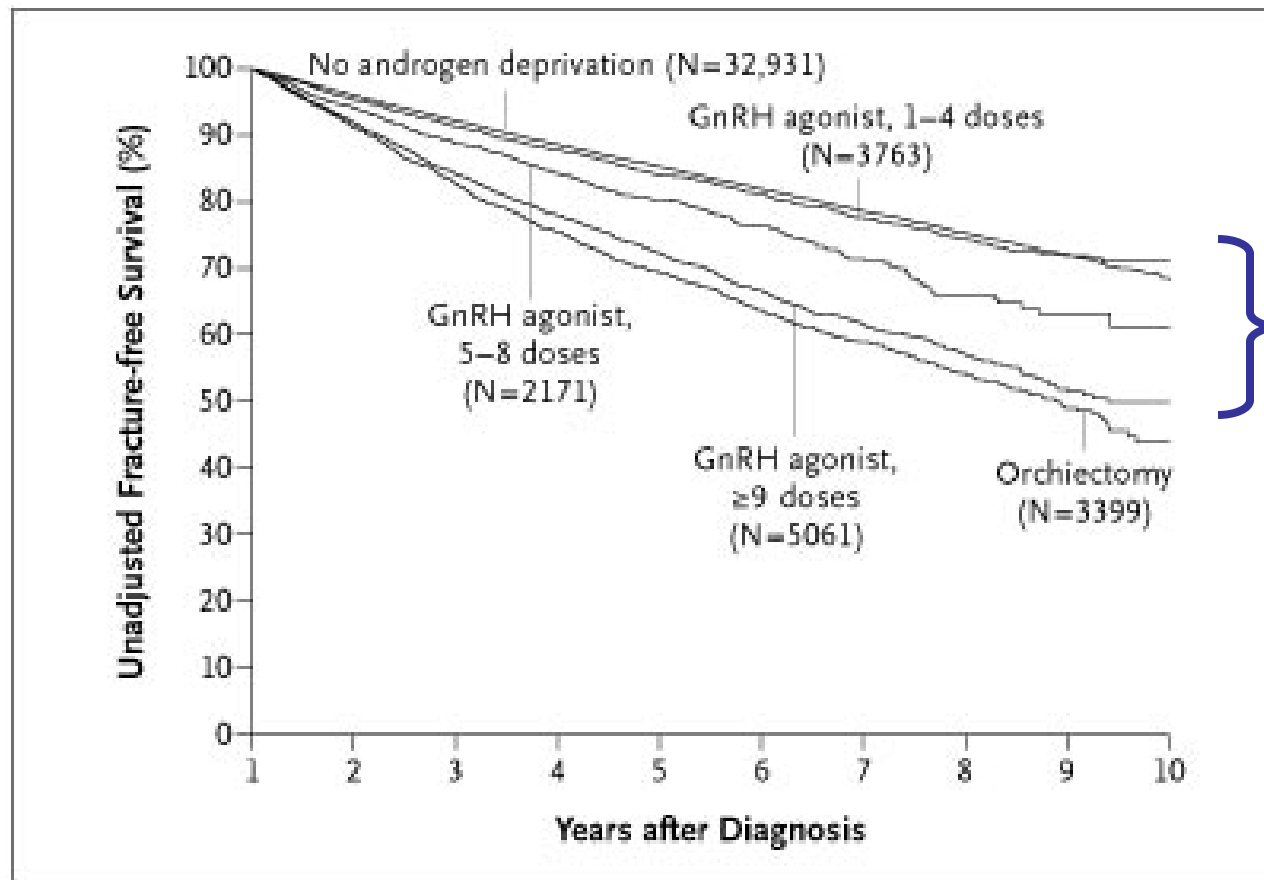
Meta

MBD an

MBD and Androgen Deprivation



Unadjusted Fracture-free Survival among Patients with Prostate Cancer, According to Androgen-Deprivation Therapy



Dose-dependent impact of Lupron therapy

Shahinian V et al. N Engl J Med 2005;352:154-164

Meta MBD MBD and Androgen Deprivation



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

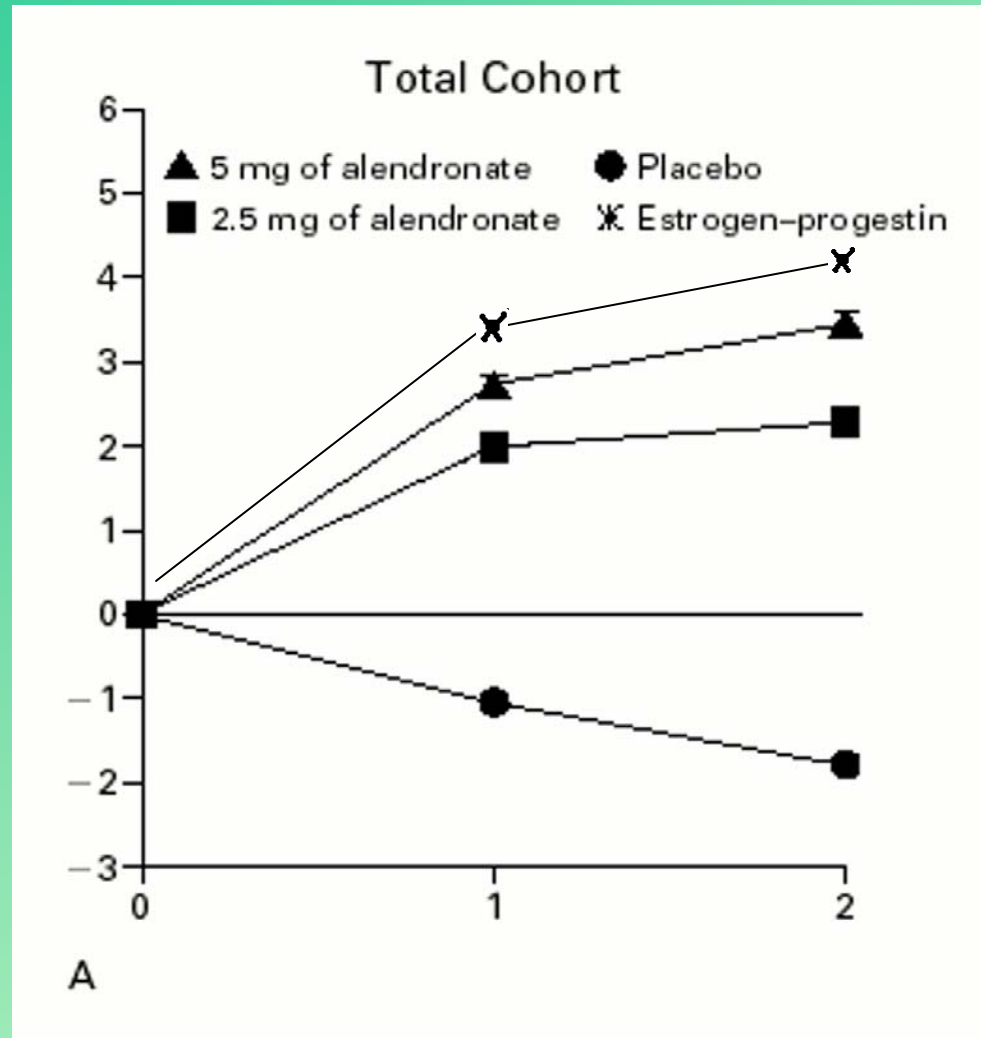


Intravenous Ibandronate

- 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



Hosking D et al. N Engl J Med 1998;338:485-492

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

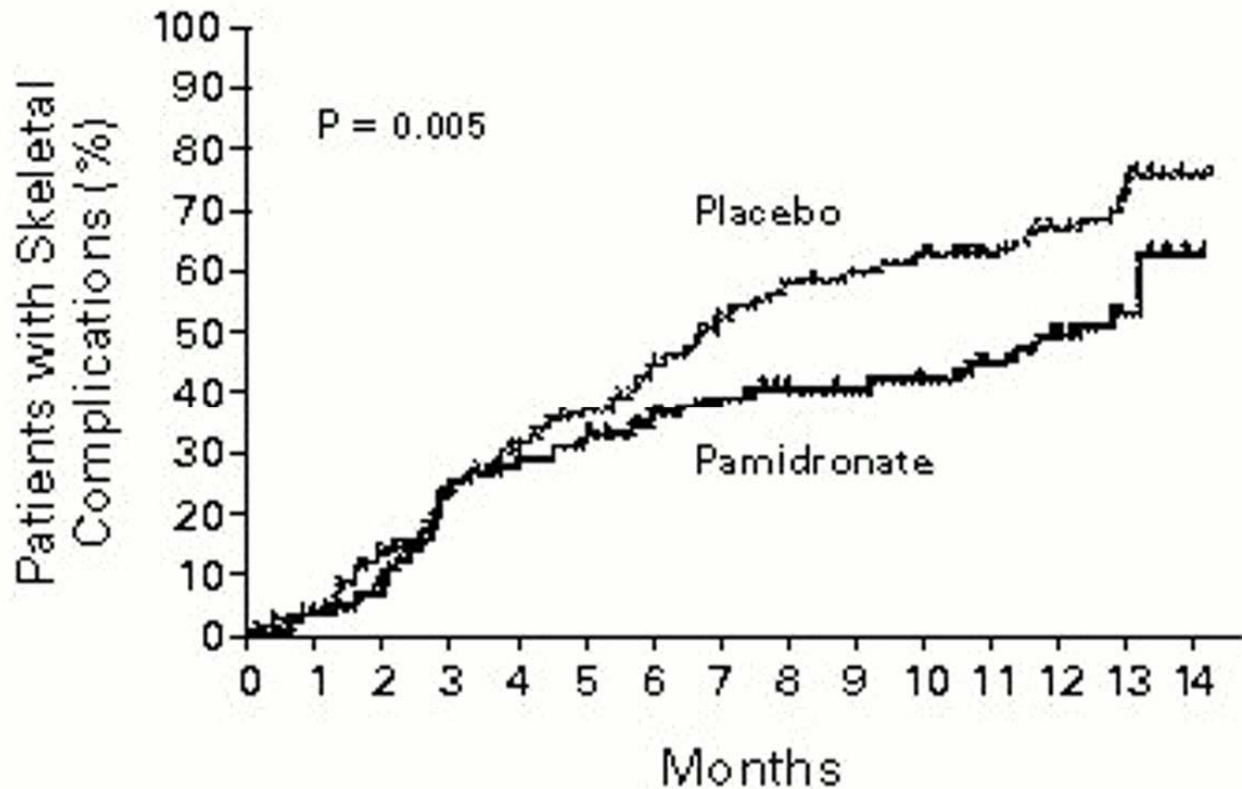


Bisphosphonates in Malignancy, continued

- 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

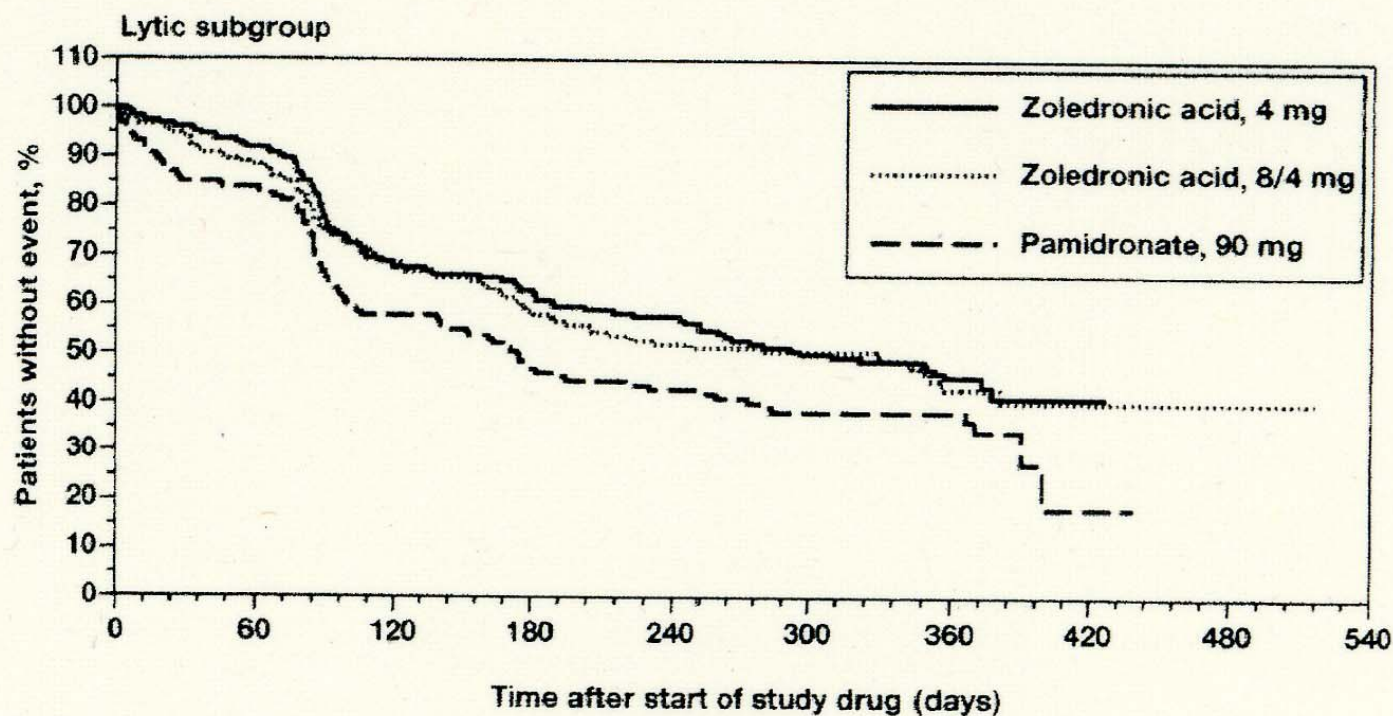


Hortobagyi G et al. N Engl J Med 1996;335:1785-1792

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...





	No. of patients at risk									
Zoledronic acid, 4 mg:	190	165	110	96	85	71	52	1	0	0
Zoledronic acid, 8/4 mg:	176	149	111	83	69	63	42	5	1	0
Pamidronate, 90 mg:	162	128	84	62	50	40	31	1	0	0

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

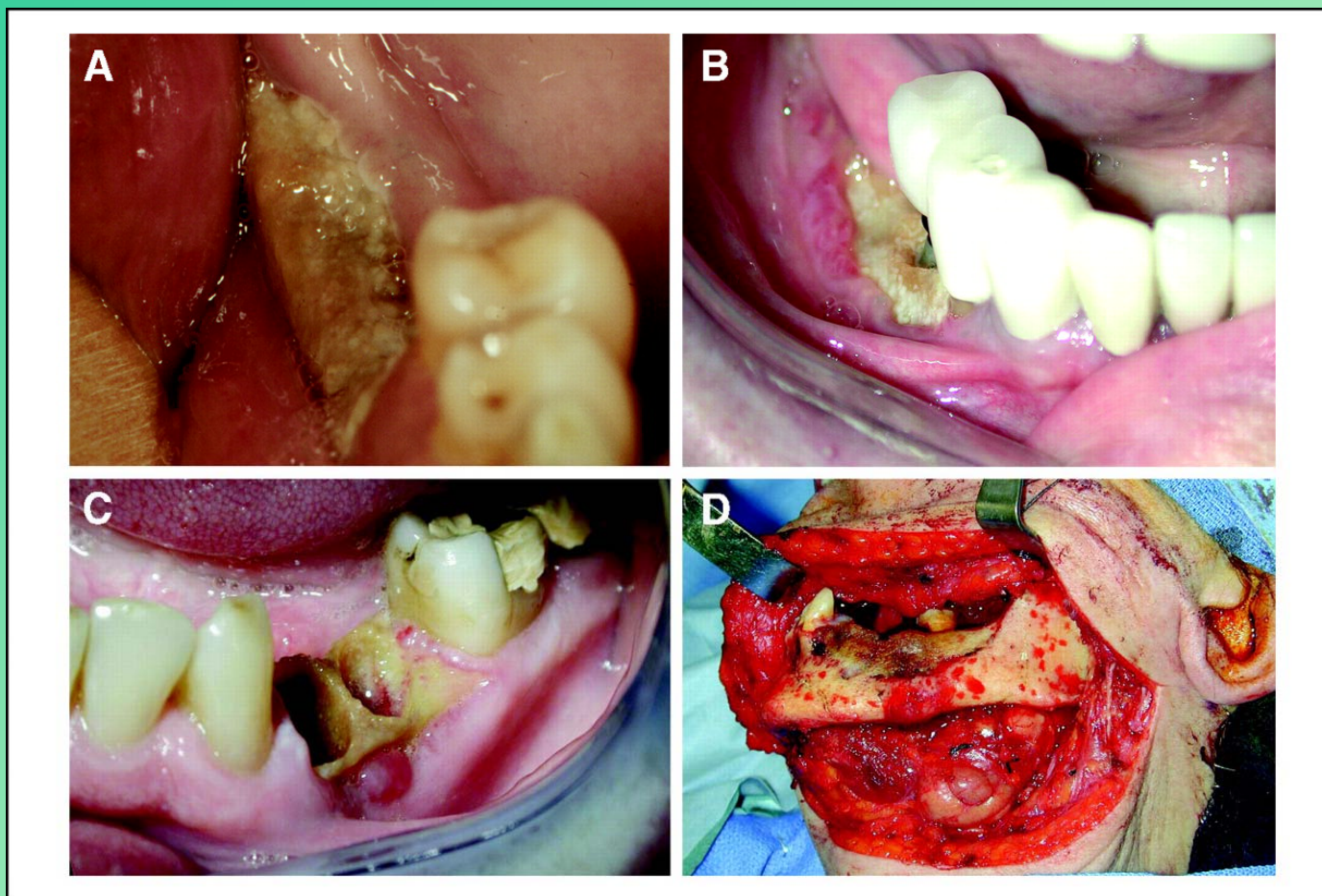


Potential Complications of Bisphosphonate Therapy

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

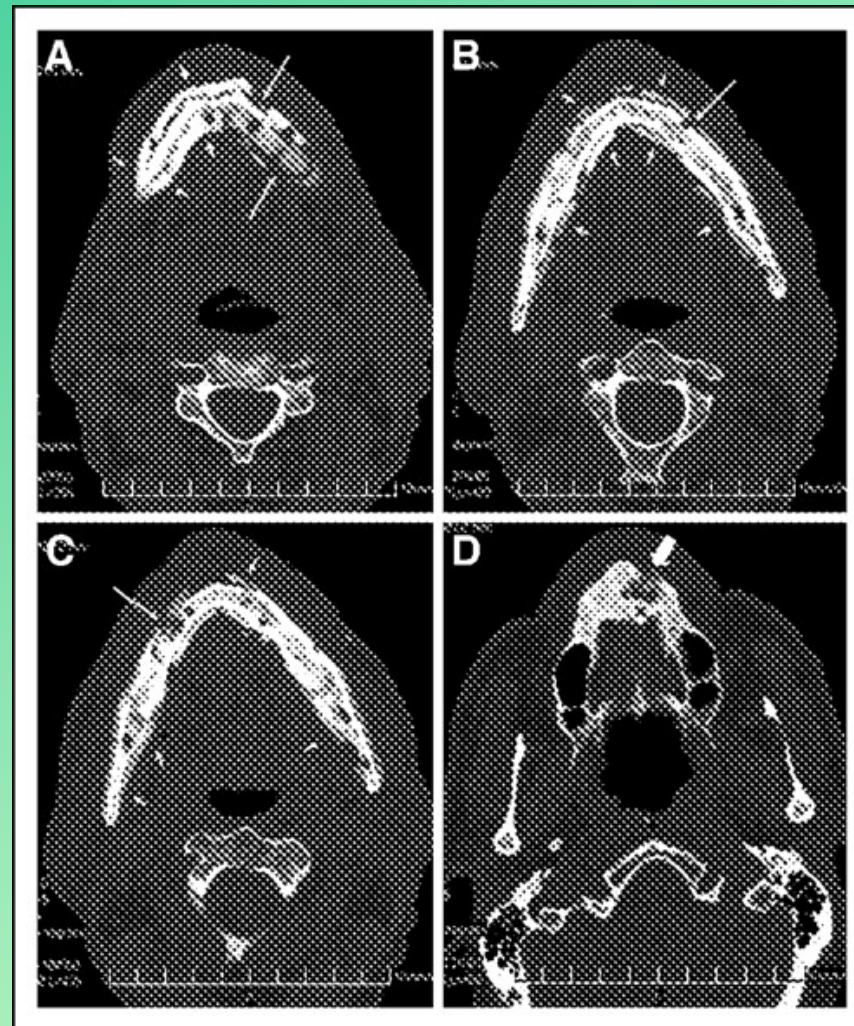


Clinical presentation of osteonecrosis of the jaw



Badros, A. et al. J Clin Oncol; 24:945-952 2006

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



Bisphosphonate Complications

Mignogna, M. D. et al. J Clin Oncol; 24:1475-1477 2006



Fistulous tracts from Osteonecrosis of Mandible



Mignogna, M. D. et al. J Clin Oncol; 24:1475-1477 2006

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%

***Woo et al Annals of Int. Med.144:753, 2006**



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**

Bisphosphonate Complications



Ongoing/Planned Clinical Trials in Oncology examining ONJ

- Ongoing clinical trials
 - ZOMETA 2352 (OPTIMIZE-2): Open January 2006
 - 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



Study Design: OPTIMIZE 2 (ZOMETA Trial 2352)

- Patients with breast cancer + bone metastases
- Pretreated with 9 to 12 doses of ZOMETA during previous 10 to 12 months

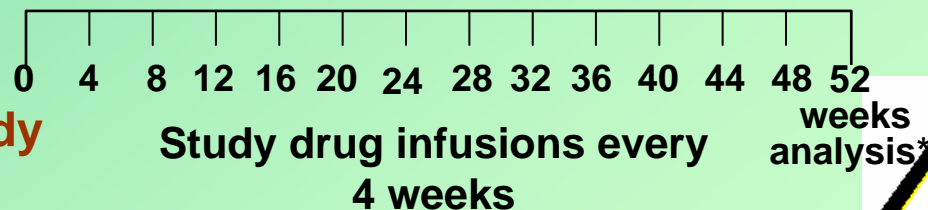
N = 1,650

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*



**First study
drug
infusion**

***Primary endpoint:
Time to first SAE**

cue: ZOMETA q 4 wk after first SAE.

Bisphosphonate Complications



ZOMETA Trial 2105

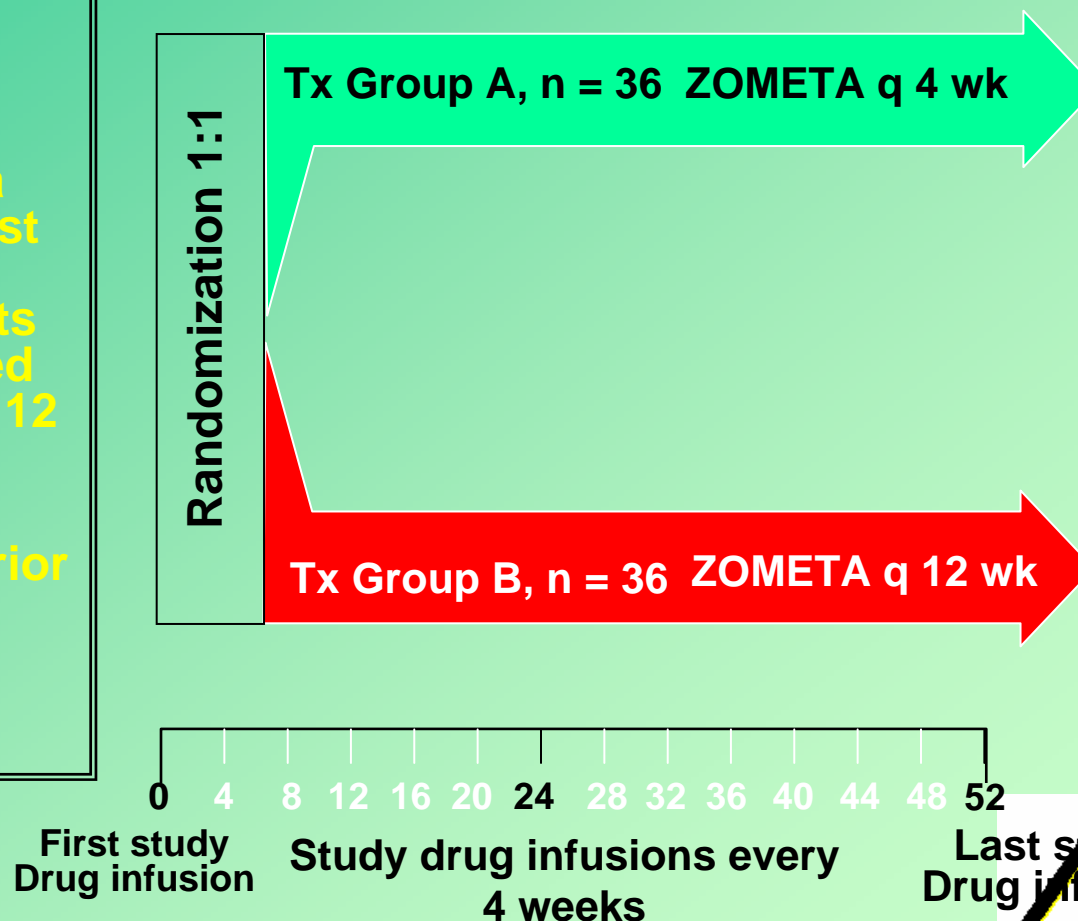
- Phase I prospective, randomized, open-label study
- Multiple myeloma or breast cancer with bone metastases (n = 72)
- ZOMETA 4mg every 4 weeks or every 12 weeks
- ONJ monitoring: same as for OPTIMIZE-2



ZOMETA Trial 2105: Trial Design

- Patients with multiple myeloma and breast cancer + bone mets
- Pretreated with 9 to 12 doses of ZOMETA during prior year

N = 72

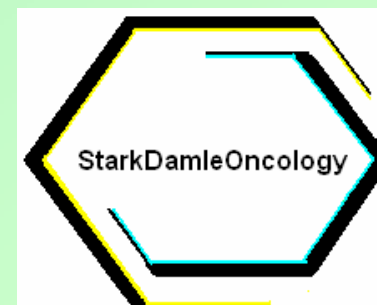


Bisphosphonate Complications

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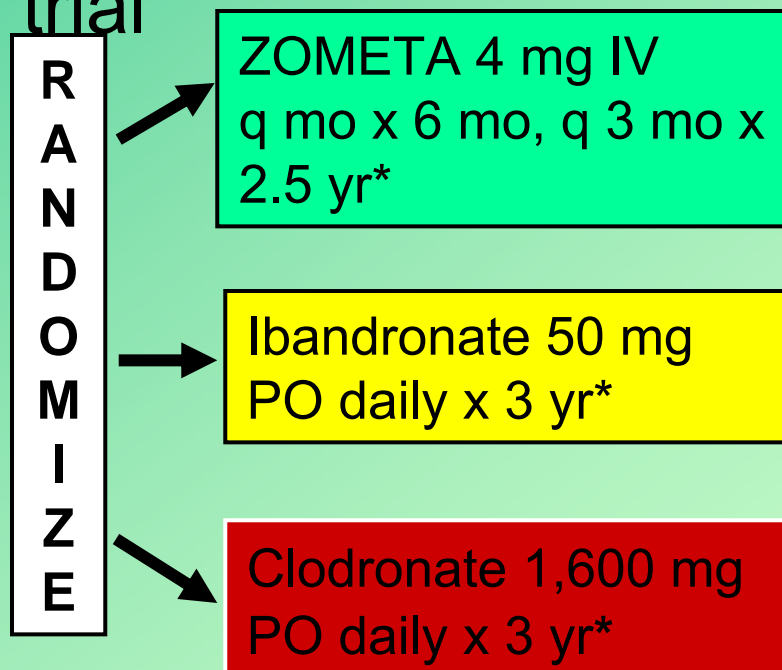
SWOG Trial 0307

- 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



SWOG 0307: Study Design

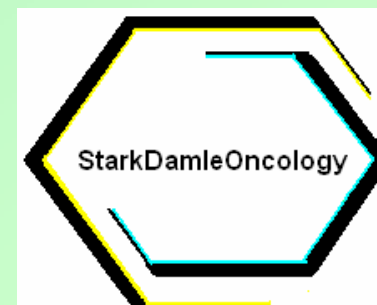
- Stage I, II, and III breast cancer on standard adjuvant therapy (N = 6,000); bone metastasis prevention trial



*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



Perspective, continued

- 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

