ORAL BISPHOSPHONATE RELATED OSTEONECROSIS OF THE JAWS

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LECTURE OBJECTIVES

- Learn diagnostic features of osteochemonecrosis (OCN) including pre-OCN (Stage 0).
- Learn the etiology and pathogenesis and why the jaws are the only target.
LECTURE OBJECTIVES

- The incidents and risk factors of OCN will also be clarified.
- Participants will also learn how to treat and prevent it.
PRE-TEST

- 70 Y/O FEMALE WITH NON HEALING SOCKET LR 2\textsuperscript{ND} MOLAR AREA(ON ZOMETA)
  - A) OSTEOMYELITIS
  - B) OSTEOCHEMONECROSIS
80 Y/O female on Fosamax for 10 years. Extraction done 3 months ago (LL). Safe to do implants??
76 y/o female on Fosamax 4 years, off for two. Had extraction (LR) 2 yrs ago but never healed. Last year developed ulcerated torus. ?Treatment
70 y/o female slightly loose PM with significant decay
3900 cGY radiation to nasal cavity and paranasal sinuses 1998 for lymphoma
Long standing (10 year) oral bisphosphonate use.
BISPHOSPHONATES

- Endogenous regulators of bone mineralization (bone resorption inhibitors) which accumulate in hydroxyapatite in mineralized bone
- Over 300,000 patients on I.V. form of these drugs
- 30 Million on oral forms
STRUCTURE
BISPHOSPHONATES
Generics, Brands

- Alendronate  Fosamax
- Etidronate  Didronel
- Ibandronate  Boniva
- Pamidronate  Aredia
- Risedronate  Actonel
- Zoledronate  Reclast, Zometa
INDICATIONS

- Osteoporosis/osteopenia
- Multiple myeloma
- Breast/Prostate cancer
- Hypercalcemia of malignancy
- Cancer related bone lesions/metastases
BISPHOSPHONATES (BP)

- Reduces skeletal complications & bone pain and improves quality of life
- Does not definitely extend life
- Oral forms used for metabolic bone diseases (high turnover) i.e. osteoporosis, & Paget’s disease
BISPHOSPHONATES

- Zometa and Aredia i.v. drugs most associated with intraoral bone necrosis
- These more powerful i.v. drugs used for cancer patients to prevent metastasis and hypercalcemia of malignancy
- I.V. drugs together account for 97% of cases of ONJ
BISPHOSPHONATES

- Weaker, oral drugs used for osteoporosis to prevent fracture.
- Tremendous morbidity and costs associated with hip & vertebral fractures especially.
FRACTURE INCIDENCE AND COST

- Lifetime risk of any fracture at age 50
  - 53% for Caucasian women
  - 21% for Caucasian men
- Fractures are expected to triple in 50 years and costs to rise substantially
- Direct cost is at least $17 billion/year
HIP FRACTURE CONSEQUENCES

- 200,000 women and 100,000 men every year
- Increased morbidity & major reason for nursing home admission
- 30% of patients do not regain their pre-ambulatory status
- 15%-20% excess mortality
FRACTURE REALTIVE RISK REDUCTION

- Vertebral fractures 40%-65%
- Multiple vertebral fractures 75%-95%
- Hip fracture 40%-50%
- Spine fracture in patients on glucocorticoids 70%
These along with Fosamax are newer generation, extremely potent, nitrogen containing, non-metabolizable pyrophosphates.
NITROGEN CONTAINING BP’S

- Stays in bone a long time (12 years)
- Necrosis mainly due to anti-osteoclastic effects
- With long term build up, anti-angiogenesis effect (decrease VEG-F) may occur also
NITROGEN CONTAINING BP’S

- Powerful inhibitor of osteoclastic activity
- Cytotoxic especially to osteoclast precursors and irreversibly inhibits recruitment and activation and shortens life span of osteoclasts
MECHANISM OF ACTION

- Apoptosis
- Inhibition of osteoclast function
- Ongoing bone formation
- Osteoblast
- Bisphosphonate
NITROGEN CONTAINING BP’S

- Bone resorption essential for bone viability
- Without resorption bone accumulates injuries “cracks”
- Leads to bony sclerosis? Avascularity
- Bone breaks down if increased functional demands
ONJ WHY NOW??

- Nitrogen containing (more potent, newer generation) are only bisphosphonates that cause ONJ
- Continuous dose accumulates in bone
- Risk increases proportionally each year
- More patients on more potent drugs continuously, = more cases
BISPHOSPHONATE OSTEOCHENONECROSIS

- Potency of drugs may be similar but absorption is 1% for oral preparations and 50% for i.v.
- 2.5% of cases seen with oral bisphosphonates (alendronate, ibandronate, risedronate)
WHY ONLY THE JAWS???

- Alveolar bone remodeling depends more on osteoclasia than any other bone.

- Remodeling rate of mandible is 10x that of any other bone and alveolus remodels 2-3x faster than the rest of the mandible.
WHY ONLY THE JAWS???

- BP’s localize to areas where osteoclasts are remodeling bone 8 x more than normal bone
- i.e. 240X more bisphosphonate in area of periodontal disease (crest of ridge, PDL, area above mandibular canal)
WHY ONLY THE JAWS???

- Local lesions (ulcers, plaque, trauma) increase need for bone remodeling significantly

- Infection, perio disease, bacterial lipo-polysaccharides and inflammation increase bone remodeling and concentration of bisphosphonates in bone
RAT ANIMAL MODEL

- Replicates clinical, radiographic and histologic features of BON
- Rats given Zometa & Dexamethasone for 1-3 weeks before extractions
- Controls healed normally experimental had non-healing ulcers **then** BON
  - Sonis S et al. Oral Oncol 2008 Aug18
MUCOSAL DAMAGE

MARKEDLY THINNED MUCOSA

INJURY- MUCOSITIS EXTRATION/TRAUMA

COLONIZATION INFECTION/BIOFILM FORMATION

DAMAGED BONE

DELAYED BONE HEALING SOFT TISSUE HEALS

DECREASED OSTEOCLASTIC BONE RESORPTION

PATHOGENESIS OF BON
IV PATIENT THIN MUCOSA MULTIPLE PAINFUL AREAS
DRAMATICALLY THIN MUCOSA BONE EXPOSURE
THIN MUCOSA WITH BONE EXPOSURE
THIN MUCOSA WITH BONE EXPOSURE
PATHOGENESIS OF BON COLONIZED BONE/ ACTINO
CASE STUDY

SOFT TISSUE CHEMONECROSIS VS LYMPHOMA
DENOSUMAB (PROLIA)

- New fully human monoclonal antibody to RANKL (receptor activator of nuclear factor-kB ligand) the dominant promoter of bone resorption.
MECHANISM OF ACTION
OPG AND RANKL

- RANKL is produced by osteoblasts in response to pro-resorptive stimuli (PTH, IL-1, TNF)
- It binds and activates RANK (receptor activator of nuclear factor Kb) a receptor found on osteoclasts and osteoclast precursors.
BISPHOSPHONATES

- Lesions developed after 2-180 months on meds
- Zometa average 9 months, Aredia 14
BON FROM ORAL BISPHOSPHONATES

- UF COD Merck sponsored study 36 confirmed patients with BON
- All female and 98% had osteoporosis
- One patient had breast cancer
ORAL BISPHOSPHONATES

- Alendronate average 46 (62) months
- For oral medications
  - earliest 1.5 yr (+ radiation)
  - 31/36 3+yrs
  - range 18-180 months
  - average 5.15 years
- Alendronate has a 10 year half life
DEFINITION: BISPHOSPHONATE INDUCED OSTEOCHONEMONECROSIS

- Painless (43%) or painful (57%) exposure of avascular bone, mand (51%), max (24%) both (3%)
- Pain is indication of infection
- Exposure present $\geq 6-8$ weeks
- No response to Tx
- No history of radiation
BISPHOSPHONATE
OSTEOCHEMONECROSIS
CLINICAL MANIFESTATIONS

- Exposed bone +/- Pain - 100%
- Supra alveolar sclerosis - 100%
- Bony expansion
- Delayed onset of symptoms 3-12 months
EXPOSED BONE
EXPOSED BONE
TEETH LOST
SUPRA- ALVEOLAR SCLEROSIS
BONEY EXPANSION/DELAYED ONSET 8 MONTHS
BONEY EXPANSION/DELAYED ONSET 8 MONTHS
TRIGGER BISPHOSPHONATE OSTEOCHRONEMONECROSIS

1. None- spontaneous bone necrosis: large lobular tori, mylohyoid ridge etc. - 25%(42%)
2. Tooth extraction -38%(54%)
3. Periodontal disease & surgery 100% (if applicable) most common trigger
4. Implants 3.4%(2) and apico <1%
SPONTANEOUS VS. TRAUMA ??
SPONTANEOUS???
TOOTH EXTRACTION
PERIO SURGERY
 IMPLEMENTS & OCN

ON ALENDRONATE SINCE 2004
SERUM-C-TERMINAL TELOPEPTIDE (CTX)

- Can predict risk of ORN from bisphosphonates
- Specific marker of bone T/O
- Octapeptide cleaved from type I collagen by osteoclasts during bone resorption
- Marker of osteoclast activity
SERUM-C-TERMINAL TEOLOPEPTIDE (CTX)

- CTX <100pg/ml = high risk for ORN
- CTX 101-150pg/ml = moderate risk
- CTX >150 = Low risk
PREDICTING RISK: CTX VS. X-RAY FEATURES

- 20 Patients on BP with pre-op CTX value < 150 pg/ml
- 20/20 extraction site healed completely w/o complications
- 55 extraction patients on BP with pre-op x-ray findings
- 29 developed BRON 26 did not
PREDICTING RISK: CTX VS. X-RAY FEATURES

- 83% (24/29) with BON had widened PDL associated with extracted teeth
- Only 11% (3/26) pts who did not develop BRON had widened PDL

- Predicting Risk for Bisphosphonate-Related Osteonecrosis of the Jaws: CTX Versus Radiographic Features Oral Surg:2010 e-pub ahead of print
EARLIEST SIGNS

- Sclerosis: lamina dura/crest of ridge, alveolar process
- Widened PDL
- Incipient bifurcation involvement
- Pain-pre-ocn
2005  

2006  

[Comparison of dental X-rays from 2005 and 2006]
ORAL FOSAMAX
OSTEOCHEMEONECROSIS

- Alendronate first introduced 1993
- 30 million Rx for oral forms of bisphosphonate (190 million in world)
FOSAMAX (ALENDRONATE) & OSTEOCHENONECROSIS

- Incidence 0.01-0.04%, in Australia
- Following extractions, 0.09-0.34%.
- Kaiser-Permanente survey 13,946
- Prevalence in patients receiving long-term oral bisphosphonate therapy 0.1% (1:1,000).
CO-MORBIDITIES

- Other possible associated risk factors
  - LT steroid use (22%) (UF 12%)
  - Diabetes
  - Smoking (UF 15%) & Obesity
  - Radiation # 1 potent factor!!

- Shorten time to development don’t cause OCN
LONG TERM STEROIDS AND FOSOMAX
RADIATION & FOSAMAX

2006 1.5 yrs Alendronate

2010 D/C Alendronate 2006
RADIATION & ORAL BON

- 368 ORN patients
- Mean radiation dose 7430cGY
- 2.2% on oral bisphosphonates
- Overall incidence ORN 12%
- Not on OB (n=360) 10.8%
- On OB (n=8) 62.5% p=.001
  - Sandow et al UF COD research day
Radiation & Oral BON

- Radiation is strongest co-factor for BON not an exclusion factor
- Patients with combination oral BP and radiation have highest risk
- Also worst outcomes 7/8 patients stable, one resected
- No cures
NEWEST RECOMMENDATIONS
ORAL BP + EXPOSED BONE

- *If systemic conditions permit,* modification or cessation of oral bisphosphonate in consultation with the physician and patient.
WHY A DRUG HOLIDAY??

- Bisphosphonates accumulate about 7% a year, remains in bone indefinitely
- Become toxic in jaws after 3-5 years
WHY A DRUG HOLIDAY??

- **19% Fracture rate** (non-vertebral) if on bisphosphonate for 5 years *then off for 5 years*
- **18.9%** if on **10 years straight**

- JAMA Black et al Dec 27, 2006; 296(24): 2927
WHY A DRUG HOLIDAY??

- For many women d/c alendronate for up to 5 years does not significantly increase fracture risk.
- Woman at high risk for vertebral fractures may benefit from continued therapy.
  - JAMA Black et al Dec 27, 2006;296(24): 2927
However definite increase occurs in bone remodeling after a few months of cessation of BP therapy.

It may not effect fracture rates but it demonstrates improved ability to remodel and heal bone lesions.

WHY A DRUG HOLIDAY??

- Intermittent therapy may be wave of future
- Zolendronate (Reclast) 5mg IV 1x/yr >> 10 mg alendronate/day/yr
- Approved by the FDA in August 2007.
- A single, large, prospective placebo-controlled study established its efficacy through three years of treatment
- Two cases of BON were reported, one each in the treatment and control groups,
I.V. IBANDRONATE

- Oral dose 150 mg q month
- 1% absorbed = 1.5 mg/month
- I.V. 3 mg q 3 months
- 50% absorbed dose = .5 mg/month
- But more effective!
- ?less BON?
Mean Percent Change (95% CI) from Baseline in Lumbar Spine BMD at One Year in Patients Treated with BONIVA 2.5 mg Daily Oral Tablet or BONIVA Injection 3 mg Once Every 3 Months

* 3 mg q 3 mo vs 2.5 mg daily: p<0.001
NEWEST RECOMMENDATIONS PATIENTS ON ORAL BISPHOSPHONATES

- Lesions less severe from oral meds (Alendronate)
- Respond better to local therapy
- More predictable, reversible and amenable to surgery
TREATMENT

- Spontaneous resolution *can* occur
- Discontinuation of oral bisphosphonates for 6-12 months *may result* in spontaneous sequestration or resolution following debridement
TREATMENT

- Conservative sequestrectomy may help but avoid surgery if patient still on BP!!!
- Surgery seems to trigger bad outcomes even in patients on oral bisphosphonates
- The effectiveness of hyperbaric oxygen therapy is undetermined but it appears to increase amounts of VEG-F and counters this bisphosphonate effect
UF ORAL BON OUTCOMES

- 91% completely healed
- 9% stable with continuing disease
- 0% worse despite intermittent therapy
UF ORAL BON TREATMENTS

- Minimal surgery (sequestration) - 12%
- Major surgery (resection) - 6%
- Medical management (antibiotics) - 9%
- Combination therapy (medical & minor surgery) - 73%
TREATMENT

- For elective surgery (oral BP patients only) discontinue oral bisphosphonate for 3-4 months, do necessary surgery then allow 3-4 more months for healing.

- Antibiotic therapy and chlorhexidine rinses may be helpful for prevention.
POST FOSOMAX HEALING
POST FOSOMAX HEALING
BONY SEQUESTRUM
CONSERVATIVE SEQUESTRECTOMY
8 MONTHS LATER!!
POST FOSOMAX HEALING
POST FOSOMAX HEALING
1 YEAR OFF FOSAMAX
Position Paper on Bisphophonate-Related Osteonecrosis of the Jaws

- American Association of Oral and Maxillofacial Surgeons
- Position Paper on Bisphophonate-Related Osteonecrosis of the Jaw—2009 Update
- Approved by the Board of Trustees January 2009
- Task Force on Bisphophonate-Related Osteonecrosis of the Jaws: Salvatore L. Ruggiero, DMD, MD, Associate Professor, Division of Oral
Management Strategies for Patients Treated with Bisphosphonates

**Prevention of BRON**

- Therefore, *if systemic conditions permit*, initiation of bisphosphonate therapy should be delayed until dental health is optimized. This decision must be made in conjunction with the treating physician and oncologist.
PREVENTION AND TREATMENT

- Pre-medication dental evaluation **BEFORE** start bisphosphonate
- Extraction avoidance **AFTER** to prevent or reduce problem
- *If systemic conditions permit*, the clinician may consider discontinuation of oral bisphosphonates for a period of three months prior to and three months following elective invasive dental surgery in order to lower the risk of BRONJ.
Prevention AFTER Bisphosphonates

- Dental evaluation **every 4 months**
- Prophy and Fluoride Trays
- Endo and crown abscessed teeth
  (Cut off crown at gingival level if it is not restorable)
- Splint 1+ and 2+ mobile teeth
- **Remove abscessed and 3+ mobile teeth**
EXPERT PANEL
RECOMMENDATIONS PATIENTS ON ORAL BISPHOSPHONATES

- Non-surgical Endodontics is preferred to extraction.
- Periodontal disease, conservative perio first
EXPERT PANEL
RECOMMENDATIONS PATIENTS ON
ORAL BISPHOSPHONATES

- Conservative surgery if unresolved
  avoid guided bone regeneration
- If extractions necessary conservative
  approach with primary closure
- Immediate pre and post surgery use
  peridex rinse (gentle) and then rinse
  2x/day for two months.
EXPERT PANEL
RECOMMENDATIONS PATIENTS ON ORAL BISPHOSPHONATES

- Elective dentoalveolar surgery not contraindicated in OBP group
- Patients MUST be adequately informed of small risk of compromised bone healing.
- Efficacy of systemic marker of bone turnover to assess risk of BON in patients at risk will require further research before it can be considered valid.
EXPERT PANEL RECOMMENDATIONS PATIENTS ON ORAL BISPHOSPHONATES

- For patients on an oral bisphosphonate for > 3 years +/- steroid medication prescribing provider should be contacted to consider discontinuation of OPB for 3 months prior to oral surgery, *if systemic conditions permit.*

- The bisphosphonate should not be restarted until osseous healing has occurred.
Staging and Treatment Strategies: *At risk category*

- No exposed/necrotic bone in patients who have been treated with either oral or IV bisphosphonates
- No treatment indicated
- Patient education
Specifically, a Stage 0 category was added to include patients with non-specific symptoms, or clinical and radiographic abnormalities that may be due to bisphosphonate exposure.
STAGE 0: PRE-OCN???

PTS HAVE NON SPECIFIC SYMPTOMS OR
SYMPTOMS MIMIC DENTAL DISEASE
FUNCTIONAL CT SCAN
STAGE 0: PRE-OCN

Patients have clinical features that may be related to BP exposure.
STAGE 0: PRE-OCN

- Many cases are silent
STAGE 0 PRE-OCN???
Staging and Treatment Strategies: *Stage 1*

- Exposed/necrotic bone in asymptomatic patients who have no evidence of infection
- Antibacterial mouth rinse
Staging and Treatment Strategies: *Stage 1*

- Clinical follow-up on a quarterly basis
- Patient education and review of indications for continued bisphosphonate therapy
Staging and Treatment Strategies: *Stage 2*

- Exposed/infected bone pain and erythema +/-purulent drainage
- Symptomatic treatment broad-spectrum oral antibiotics: penicillin, cephalexin, clindamycin, or fluoroquinolone
Staging and Treatment Strategies: *Stage 2*

- Most microbes sensitive to penicillin
- Quinolones, metronidazole, clindamycin, doxycycline and erythromycin used patients allergic to penicillin.
Staging and Treatment Strategies: *Stage 2*

- Microbial cultures analyzed for Actinomyces
- Antibiotic regimen should be adjusted according to sensitivity.
- Refractory cases, require combination antibiotic therapy, long-term antibiotic maintenance, or a course of I.V. antibiotics
Staging and Treatment Strategies: \textit{Stage 2}

- Treat pain with Pen VK 500mg Q.I.D. and chlorhexidine mouth rinse until pain free and
- Add Flagyl 500mg T.I.D. if pain persists
- Only superficial debridements to relieve soft tissue irritation
Staging and Treatment Strategies: Stage 3

- Pathologic fracture
- Exposed bone with inflammation, infection or pain
Staging and Treatment Strategies: Stage 3

- Not responsive to antibiotics due to volume of necrotic bone
- Extra oral fistula
- Osteolysis extending to inferior border
Staging and Treatment Strategies: Stage 3

- Antibacterial mouth rinse
- Antibiotic therapy and pain control
- Surgical debridement/resection for longer term palliation of infection and pain
Staging and Treatment Strategies: Stage 3

- Surgical debridement has been variably effective in eradicating the necrotic bone.
- Surgical treatment should be delayed if possible.
Staging and Treatment Strategies: Stage 3

- Loose segments of bony sequestrum should be removed without exposing uninvolved bone.
- Symptomatic patients with pathologic mandibular fractures may require segmental resection and immediate reconstruction with a reconstruction plate.
Staging and Treatment Strategies: Stage 3

- The extraction of symptomatic teeth within exposed, necrotic bone should be considered since unlikely that the extraction will exacerbate the necrotic process.

- Patients with established BRON should avoid elective dentoalveolar surgical procedures.
POST-TEST

- 70 Y/O FEMALE WITH NON HEALING SOCKET LR 2\textsuperscript{ND} MOLAR AREA (ON ZOMETA)
  - A) OSTEOMYELITIS
  - B) OSTEOCHONDMONECROSIS
POST-TEST

- 80 Y/O female on Fosamax for 10 years. Extraction done 3 months ago (LR). Safe to do implants??
POST-TEST

- 76 y/o female on Fosamax 4 years, off for two. Had extraction (LR) 2 yrs ago but never healed. Last year developed ulcerated torus. ?Treatment
POST TEST: 11 MONTHS LATER TOTAL 35 MONTHS
POST TEST - EXTRACT

#13 & 14 ??

- 70 y/o female slightly loose PM with significant decay
- 3900 cGY radiation to nasal cavity and paranasal sinuses 1998 for lymphoma
- Long standing (10 year) oral bisphosphonate use.
2 MONTHS POST SIMPLE EXTRACTION #13, 14
CONCLUSION

- Add radiographic features to criteria for BON.
- Add additional Stage 0 category also called pre-osteocochemonecrosis
- Patients have radiographic and/or clinical signs (pain) of BON before bone exposure occurs.
CONCLUSION

- There is an increased risk of complications in surgery patients actively on a bisphosphonate.
- Radiation is a co-morbidity for BON not an exclusion factor.
CONCLUSION

- In Shands database 5/8 patients with both developed BON
- Bisphosphonates should be used with caution in these patients.