Osteonecrosis of the Jaw (ONJ)

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OBJECTIVES

• Update on ONJ (do we need a new name?)
• Current Definition: American Academy of Oral and Maxillofacial Surgeons
• Diagnosis of ONJ
• Management
  • Patients with ONJ
  • Patients being treated with DONJ who need dental care
ONJ: HOW MANY ACRONYMS ARE NECESSARY???

- Osteochemonecrosis
- ARONJ: antiresorptives osteonecrosis of the jaw
- BIONJ: bisphosphonate-induced osteonecrosis of the jaw
- BONJ: bisphosphonates osteonecrosis of the jaw
- BRONJ: bisphosphonates-related osteonecrosis of the jaw
- DIONJ: drug-induced osteonecrosis of the jaw
- DRONJ: denosumab-related osteonecrosis of the jaw
- MRONJ: medication-related osteonecrosis of the jaw
DRUGS REPORTED TO CAUSE ONJ (DONJ)

- Drugs Associated with Osteonecrosis of the Jaw
  - Bisphosphonates (alendronate, risedronate, ibandronate, pamidronate, zoledronate)
    - Osteoporosis, bone metastasis, hypercalcemia of malignancy, other bone diseases
  - Denosumab (Prolia, Xgeva)
    - Osteoporosis, hypercalcemia of malignancy, osteolytic bone metastasis of solid tumors
  - Antiangiogenic (Tki - VEGF pathway)
    - Sunitinib (Sutent): GIST, Advanced renal cell carcinoma, pancreatic neuroendocrine tumors
    - Sorafenib (Nexavar): Hepatocellular carcinoma, advanced renal cell carcinoma
    - Cabozantinib (Cometriq): Progressive unresectable, locally advanced or metastatic thyroid carcinoma
  - Antiangiogenic (monoclonal antibody)
    - Bevacizumab (Avastin): Metastatic colorectal, advanced nonsquamous non-small cell lung, metastatic kidney, glioblastoma

BISPHOSPHONATES IN DERMATOLOGY

  - BMD increases lumbar spine and femoral neck with alendronate therapy

  - Bis + adequate calcium citrate and Vit D:
    - Males > 50 or postmenopausal patient
    - Beginning or receiving doses over 7.5 mg prednisone equivalent daily
    - Anticipated duration of ≥ 3 months
    - High risk patients would have a lower dose threshold for intervention
    - Men < 50 and postmenopausal women with prevalent fragility fracture also require intervention

- Romosozumab (sclerostin)??

- 22 publications used in prevalence analysis
- No randomized trials, meta-analysis or quality of life papers found
- Overall weighted prevalence: 39,124 patients – mean prevalence of 6.1%
- 927 patients 13.3% in studies with documented follow-up
- Prevalence in studies with undocumented follow-up was 0.7% in a sample of 8,829 patients
- Epidemiological studies: 29,368 patients – prevalence of 1.2%

“Of 5723 patients enrolled, 89 (1.6%) patients were determined to have ONJ: 37 (1.3%) received zoledronic acid and 52 (1.8%) received denosumab (P = 0.13).”

**Table 2. Systemic risk factors**

<table>
<thead>
<tr>
<th>Systemic risk factors</th>
<th>Patients with ONJ (N = 89)</th>
<th>Patients without ONJ (N = 5634)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbid conditions, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia (Hg &lt;10 g/dL)</td>
<td>40 (44.9)</td>
<td>2304 (40.9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20 (22.5)</td>
<td>874 (15.5)</td>
</tr>
<tr>
<td>Other drugs, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroidsa</td>
<td>65 (73.0)</td>
<td>3512 (62.3)</td>
</tr>
<tr>
<td>Chemotherapy agents</td>
<td>63 (70.8)</td>
<td>3871 (68.7)</td>
</tr>
<tr>
<td>Antiangiogenicsb</td>
<td>14 (15.7)</td>
<td>450 (8.0)</td>
</tr>
</tbody>
</table>

*aExcludes ocular and inhaled preparations.
*bIncludes bevacizumab, sunitinib malate, and sorafenib.

**Table 3. Oral events and location of ONJ**

<table>
<thead>
<tr>
<th>Oral eventa, n (%)</th>
<th>Zoledronic acid (N = 37)</th>
<th>Denosumab (N = 52)</th>
<th>All (N = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tooth extraction</td>
<td>24 (64.9)</td>
<td>31 (59.6)</td>
<td>55 (61.8)</td>
</tr>
<tr>
<td>Coinciding oral infection</td>
<td>17 (45.9)</td>
<td>26 (50.0)</td>
<td>43 (48.3)</td>
</tr>
<tr>
<td>Jaw pain</td>
<td>25 (67.6)</td>
<td>48 (92.3)</td>
<td>73 (82.0)</td>
</tr>
<tr>
<td>Location of ONJ, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mandible</td>
<td>31 (83.8)</td>
<td>34 (65.4)</td>
<td>65 (73.0)</td>
</tr>
<tr>
<td>Maxilla</td>
<td>5 (13.5)</td>
<td>15 (28.8)</td>
<td>20 (22.5)</td>
</tr>
<tr>
<td>Both</td>
<td>1 (2.7)</td>
<td>3 (5.8)</td>
<td>4 (4.5)</td>
</tr>
</tbody>
</table>

*aTooth extraction reported during the study; jaw pain and oral infection noted either before or at the time ONJ was diagnosed.
 ONJ, osteonecrosis of the jaw.
DENOSUMAB AND THE RISK OF ONJ

- Total of 8963 patients (assigned to Dmab alone or in combination at any dose or frequency)
- Overall incidence of ONJ was 1.7% (95% CI: 0.9-3.1)
- Use of Dmab is associated with an increased risk of ONJ when compared with BPs and Placebo. The increased risk was not statistically significant between Dmab and BP treatment
Epidemiology ONJ: Denosumab Studies – Amgen (02/09/2015)

Prolia® (denosumab) and ONJ in cancer patients undergoing hormonal ablation therapy 60mg/6 months


No cases of ONJ adjudicated positive during the trials by an independent blinded panel
ONJ AND ANTIANGIOGENICS


• Retrospective multicenter (9 centers throughout Italy)

• Consecutive Renal Cell Carcinoma patients with diagnosis of ONJ, no history of RT, and history of exposure to targeted agents at the time of ONJ diagnosis

• Data on 44 ONJ cases, Zometa (93%) and Sunitinib (80%) of the cases. Other meds included sorafenib, bevacizumab

• Everolimus, ridaforolimus, associated with a bisphosphonate or an antiangiogenic
ANTIANGIOGENICS AND ONJ

BEUSELINK B ET AL. CONCOMITANT ORAL TYROSINE KINASE INHIBITORS AND BISPHOSPHONATES IN ADVANCED RENAL CELL CARCINOMA WITH BONE METASTASES. BRIT J CA 2012; 107:1665-1671

- CONCOMITANT USE OF BISPHOSPHONATES AND TKI IN RENAL CELL CARCINOMA PATIENTS WITH BONE INVOLVEMENT PROBABLY IMPROVES TREATMENT EFFICACY BUT IS ASSOCIATED WITH A HIGH INCIDENCE OF ONJ. OVERALL ONJ INCIDENCE OF 10% IN PATIENTS USING BOTH DRUGS.


Zoledronic acid + Sunitinib = 29% ONJ (6 cases)
Patients with ONJ = Improved median survival of 31.6 months
Patients without ONJ = 14.5 months median survival
EXPERIENCE WITH ONJ ADJUDICATION

WHO IS THE CULPRIT?

• From 2006 to date: over 1,000 cases with some type of oral involvement, from different parts of the world adjudicated

• Trials and post-market

  • Cases of ONJ can develop rather quickly after the administration of Dmab in patients previously exposed to bisphosphonates (oral and i.v.) *
    ▫ A few weeks after administration of Dmab
    ▫ Risk of ONJ with denosumab seems to be the same as that of bisphosphonates
    ▫ Is there an adding effect of the drugs?
    ▫ Main deficiency observed is poor documentation and the difficulty in making the diagnosis of ONJ

DEFINITION: OSTEOENCEROSIS OF THE JAW (ONJ) – AAOMS 2014 UPDATE

1. Current or previous treatment with antiresorptive or antiangiogenic agents

2. Exposed bone or bone that can be probed through an intraoral or extraoral fistula (e) in the maxillofacial region that has persisted for more than eight weeks

3. No history of radiation therapy to the jaws or obvious metastatic disease to the jaws
DIAGNOSIS OF ONJ

- Patient history
  - Medical History: is the patient taking one of the DONJ?
  - Oral complaint: pain, discomfort, tingling/paresthesia, bad breath, pus, swelling
  - Dental history and past treatment of the oral problem: recent dental extraction? Surgery? Trauma? Local and systemic antibiotics?

- Clinical evaluation
  - Exposed bone and/or, infection, purulent secretion, abscess formation, fistula

- Radiographic evaluation
EARLY DIAGNOSIS
Patient in pain came to the UT emergency room for evaluation. Taking ibandronate for 4-5 years. Tooth #28 was extracted several weeks ago. Management of the non-healing extraction site by her dentist and topical and systemic antibiotics did not help. Exposed necrotic bone.
NON-EXPOSED NECROTIC BONE

- Italian multicenter study
- 799 patients adjudicated for ONJ based on the traditional definition.
- 607 (76%) patients confirmed with ONJ
- 192 (24%) could not be confirmed because clinically visible necrotic bone could not be visualized.
CLINICALLY NON-VISIBLE BONE (SUSPICIOUS)

- Metastatic breast cancer patient taking i.v. bisphosphonate
- Sudden onset of clinical signs and symptoms that appeared to be of dental or periodontal origin. Patient had a tooth extracted months before consultation (#18). Healing was complicated.
- Source area causing pain could not be precisely identified
- Dentist treated what seemed to be a routine problem (endo, perio)
- Symptoms persisted and got worse.
- Diagnosis of ONJ should be considered!
Final endo x-ray 2006

Recall 05 2007
- CT Scan of a prostate cancer patient in a clinical trial of Dmab/Bis
- Severe Pain
- Edentulous, could no longer wear his denture
- No Bone Exposure
- Could not have his denture adjusted to a good fit
Risk for ONJ

- Taking a DONJ for osteoporosis or cancer
- Presence of dental/periodontal disease
- Individual predisposition (only a small percentage of patients taking DONJ develop the condition)
- Situations that may affect the risk:
  - Time on the drug; the longer, the higher the risk
  - Changing drugs, from a bisphosphonate to denosumab
  - Cancer patient taking a bisphosphonate associated with an antiangiogenic
What is the meaning of generalized osteosclerosis?

What is the meaning of sclerosis of the lamina dura?
BONE TURNOVER AND BONE SUPPRESSION


**Conclusion:** Mandible had significantly lower bone turnover than the maxilla, but 2/3rds of ONJ cases occur in the mandible. Bone turnover was not overly suppressed.


**Conclusion:** There was a tendency to increase bone turnover in those patients taking denosumab. The bone turnover of the jawbone is not significantly changed either by a bisphosphonate or denosumab.

It seems **unlikely** that oversuppression of bony turnover in the jawbones plays an important part in the pathogenesis of ONJ.
How abnormal is bone remodeling?
The importance of dental disease

Aghaloo TL et al. Periodontal disease and bisphosphonates induce ONJ in the rat. JBMR 2011; 26: 181-1882
The importance of dental disease

Aghaloo TL et al. Periodontal disease and bisphosphonates induce ONJ in the rat. JBMR 2011; 26: 181-1882

• Bone exposure observed in 21% of animals treated with BP

• 47% of the same animals had osteonecrosis both radiographically and histologically.

• Bone necrosis precedes mucosal retraction and bone exposure

• Osteocytes necrosis precedes clinical bone exposure

• The presence of dental disease such as periodontitis creates the perfect environment for the development of ONJ

Should we start taking biopsies?
WHAT ABOUT DENTAL EXTRACTIONS?

• Dental extractions in patients taking antiresorptives have been blamed as the cause of ONJ.

• We have always questioned this possibility because there was never an explanation of the diagnosis that lead to the extraction

• Work with the Athens group

Courtesy
Prof. Ourania Nicolatou Galitis
COLLABORATION WITH THE ATHENS GROUP

- 57 y.o male, lung cancer dx in Feb 2014. Standard chemo and bevacizumab (7 infusions)
- Pain of 1 week duration, gingival swelling, mobility of #s 13 and 14 and a fistula.
- Widening of the PDL
- Extraction of both teeth. Pain and swelling persisted. 5wks f.u. Patient died

Courtesy
Prof. Ourania Nicolatou Galitis
Periodontal disease preceding osteonecrosis of the jaw (ONJ) in cancer patients receiving antiresorptives alone or combined with targeted therapies: report of 5 cases and literature review

Ourania Nicolatou-Galitis, DDS, a Evangelia Razis, MD, b Dimitra Galiti, DDS, MSc, a Evangelos Galitis, DDS, MSc, c Stefanos Labropoulos, MD, b Antonis Tsimpidakis, MD, b Joseph Sgouros, MD, d Athanasios Karampeazis, MD, e and Cesar Migliorati, DDS f

Objective. We present clinical and radiologic data of periodontal tissue involvement preceding the appearance of osteonecrosis of the jaw (ONJ) in 5 patients with solid tumors, who received antiresorptives alone or in combination with targeted therapies.

Study Design. Five patients with osteonecrosis before dental extraction were studied.

Results. Periodontal involvement was evidenced by pain, bleeding, fistula, purulence, swelling, periodontal pocket, and tooth mobility. Combined endoperiodontal lesions were considered in 1 patient. Duration of symptoms before ONJ diagnosis lasted 8 to 24 weeks. Routine therapy was performed in 2 of 5 patients. Widening of the periodontal ligament was observed in 4 patients, and dense alveolar bone was seen in 1 patient. Local complications of ONJ required dental extractions in 4 of 5 patients. Spontaneous tooth exfoliation was observed in 1 patient. Alveolar bone biopsies, after the extraction in 2 patients, confirmed osteonecrosis. Osteonecrosis healed in 2 patients—1 after the dental extraction and 1 after 3 dental extractions and surgical debridement. Postextraction socket healed in 1 patient, and the area with exposed bone remained asymptomatic. Osteonecrosis progressed in 2 patients.

The importance of a correct diagnosis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Clinical and Radiographical Findings</th>
<th>Is ONJ the only possible diagnosis?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Is the patient taking one of the medications associated with ONJ?</td>
<td>• Can exposed necrotic bone be clinically visualized?</td>
<td>• History of radiation therapy to the Head &amp; Neck?</td>
</tr>
<tr>
<td>What type, time on therapy?</td>
<td>Presence of fistula, pus drainage, pain, paresthesia?</td>
<td>Metastatic disease to the jaw bones?</td>
</tr>
<tr>
<td>Comorbidities, cancer, osteoporosis?</td>
<td>Recent surgical procedure?</td>
<td>Osteomyelitis?</td>
</tr>
<tr>
<td></td>
<td>No visible exposed bone but suspicious radiographic area corresponding to the clinical complaint?</td>
<td>Routine dental infection?</td>
</tr>
</tbody>
</table>
CB – PROSTATE CANCER STAGE 4
ONJ MANAGEMENT: MEDICAL OR SURGICAL?

- Medical therapy
- Surgical
FACTORS THAT INFLUENCE THE DECISION BETWEEN SURGICAL OR MEDICAL TREATMENT

• General health and cancer prognosis could be determinant of the decision. Patients with advanced cancer tend not to respond well to therapy.

• Patient quality of life evaluation

• Decision to go surgical first varies from one treatment center to another

• Determination of initial response to medical therapy
ONJ MANAGEMENT

- Early diagnosis - easier management
- Medical management: AAOMS stages 0-2
  - Frequent follow-up
  - Antimicrobial rinses
  - Systemic antibiotics – active infection/paresthesia
  - Minor local debridement/ elimination of sharp bone edges


ONJ MANAGEMENT

• Surgical management: AAOMS stage 3
  • Resection
  • Bone/soft tissue grafting
  • Primary closure


OTHER FORMS OF THERAPY


IS THERE A ROLE FOR HBO?


- HBO therapy at 2 atm for 2 hours - twice/day and continuation of either conservative care or surgery

- “Clinically HBO appears to be a useful adjunct to ONJ treatment, particularly in more severe cases”
CAN WE PROVIDE DENTAL CARE TO PATIENTS TAKING DONJ?

- 84 y.o. white female
- Full mouth extractions and dentures – undergraduate dental clinic
- Medical history
  - Osteoporosis
  - Diabetes type II
  - Hypercholesterolemia
- Medications
  - Lipitor
  - Gliburide
  - Alendronate – 6 years
CAN WE PROVIDE DENTAL CARE TO PATIENTS TAKING DONJ?

- Patient discontinued Alendronate under the guidance of her MD
- Oct/12/2012: Extraction of #s 4 & 6
- Nov/16/2012: Extraction of #s 7, 8, 9, 10
- Jan/03/2013: Extraction of #s 14, 15, 18 + alveoloplasty
- Feb/05/2013: Extraction of #s 2, 3 + alveoloplasty
- March/13/2013: Extractions of #s 21-27 + alveoloplasty

6 months f.u.
November 13th, 2008
5 weeks post-extraction

Follow-up march 12, 2009
5 months post-extraction

Migliorati C et al assessing the association between bisphosphonate exposure and delayed mucosal healing after tooth extraction. Jada 2013; 144:406-14
DRUG HOLIDAY?

- What is the rational?
- Differences between treating a patient on DONJ without ONJ and with ONJ?
- Does the type of antiresorptive matter?
- Risk of skeletal complications v.s. benefits of the oral treatment.


- “Independent of treatment modality and MRONJ stage at presentation, discontinuing BP before or at treatment initiation is associated with faster resolution of MRONJ symptoms compared with continuing the drug throughout jaw treatment.”

- “Continuation of drug use may delay resolution of maxillofacial symptoms by approximately 6 months.”
CAN ONJ BE PREVENTED?

• Ideal: stabilization or elimination of oral disease prior to starting therapy. Oral disease appears to be important for the development of ONJ!
• Protocols that have instituted oral hygiene and in which dental treatment was done prior to starting therapy have demonstrated a decrease in ONJ development
Thank you!

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