Radiotherapy and drug- induced osteonecrosis of the jaw

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UNIVERSITY of DEBRECEN

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BEFEKTETÉS A JÖVŐBE

„The chance of a woman suffering a fracture because of osteoporosis is higher than the chance of experiencing malignant breast cancer or a broad category of CVD events.”

- (*Cauley JA et al.: Incidence of fractures compared to cardiovascular disease and breast cancer: the Women's Health Initiative Observational Study. Osteoporos Int. Dec. 2008)*

- Osteoporosis affects 600.000 women and 300.000 men in Hungary
- By 2065 the number of patients diagnosed with OP will double
- In Europe almost 20% of patients who suffer an osteoporotic fracture dies, which means 150.000 people/year
- In the EU an osteoporotic fracture happens in every 30 seconds

Risk groups

- Osteoporosis
- Malignant diseases with bone metastatic tendency (breast, prostate, lung cancer)
- Myeloma multiplex
- Rheumatoid arthritis
- Fibrosus dysplasia
- Paget-disease
- Osteogenesis imperfecta

There are approximately 100.000 people who recieve bisphosphonate treatment and their number is increasing

Every practicing dentist could meet patients recieving antiresorptive therapy, therefore they need to be aware of their treatment's special features.

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Antiresorptive agents I.
Bisphosphonates

- Inhibition of osteoclast apoptosis and differentiation
- Antiangiogenic effect
- Possible both parenteral and oral administration (50 mg vs 5 mg per year)
- Turnover based, unequal distribution in the skeletal system
- Long biological half life (1-10 years!), accumulation in bones
- Renal elimination
- Inadequate absorption through GIT (appr. 1%)
- BONJ (Bisphosphonate associated Osteonecrosis of the Jaw), BRONJ, BON

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Antiresorptive agents II.
Denosumab (Prolia, Xgeva)

- Human, monoclonal antibody of IgG_2 subclass
- Selective inhibition of osteoclast proliferation, differentiation and function
- Half life is 26 days
- Quick rebound reaction and bone density decreases after stopping the therapy
- No accumulation, therefore constant treatment is needed
- Elimination through reticulohistiocytic system
- 60 mg subcutaneous injection every 6 months
- Osteonecrosis of the jaw has been documented

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Other drugs that can cause osteonecrosis

- **Antiangiogen drugs**
  - Bevacizumab (Avastin)
  - Sunitinib (Sutent)
  - Sorafenib (Nexavar)
  - Pazopanib (Votrient)
  - Axitinib (Inlyta)
- **Monoclonal antibodies**
  - Rituximab (MabThera, Rituxan)
- **m-TOR inhibitors**
  - Everolimus (Afinitor)
  - Temsirolimus (Torisel)
- **TNF-inhibitors**
  - Infliximab (Remicade)
  - Adalimumab (Humira)
  - Etanercept (Enbrel)
- **Methotrexate**

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Risk groups II.

- Malignant tumors
- Autoimmune diseases

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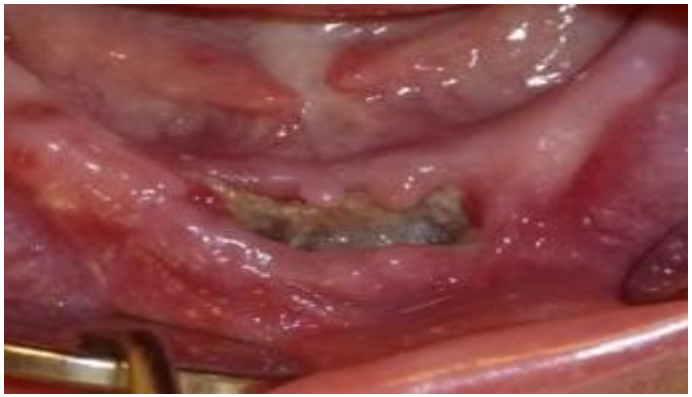
MRONJ

(Medication Related Osteonecrosis of the Jaw)

Def.: Exposed bone, or bone can be probed intra- or extraorally in the maxillofacial region persisting for more than 8 weeks with no history of regional radiation therapy in a patient who recieved antiresorptive treatment.*(American Association of Oral and Maxillofacial Surgeons)*



Main etiological factors: (may occur spontaneously as well)

- Parodontitis
- Extractions
- Removable dentures (minor mucous membrane irritation)

- Diabetes and smoking may contribute
- Incurable, only its progression can be slowed down
- Significant loss of quality of life
- Risk evaluation is not possible

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Symptoms

- Pain
- Swelling of soft tissues and signs of inflammation
- Tooth mobility
- Foetor ex ore
- Discharge
- Exposed bone without mucoperiosteum
- “The tooth extraction wound isn’t healing”

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Stages

Stage	Criteria
Risk group	Asymptomatic patient having undergone antiresorptive therapy
0	Non-specific clinical findings and symptoms with or without radiological abnormalities, no evidence of exposed bone
1	Asymptomatic exposed nectrotic bone without soft tissue infection
2	Presence of necrotic and exposed bone associated with pain and/or signs of inflammation, with or without purulent discharge
3	Presence of necrotic and exposed bone associated with pain and signs of inflammation, and at least one of the following: • Bone necrosis extending the alveolar process • Radiological sign of bone necrosis reaching the base of mandible or maxillary sinus • Pathological fracture, oro-antral, oro-nasal or oro-cutaneous communication

1st stage

2nd stage

3rd stage

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Special treatment

Anamnesis

- Osteoporosis (men too!)
- Malignant diseases (breast, prostate, kidney, lung, myeloma multiplex,…), bone metastasis?
- Previous or ongoing antiresorptive therapy?
- What kind of medication?
- For how long?
- Documentation!

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Prevention

- Before starting the antiresorptive therapy (expected in case of postmenopausal women)
- Oral hygiene education, instructions, motivation
- Radical pre-antiresorptive-therapy dental management (similar to pre-radiotherapy)
- Tight control
- Close follow-up, long-term management

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Patient guidance

- Emphasize the side-effects of the drug
- Highlight the importance of the individual's own role, oral hygiene, dental management, ect.
- Risk assessment is not possible (**β**-CTx can be helpful, but cannot predict osteonecrosis)
- Onset chance is approx. 0,1% - but it can considerably rise in case of iv. administration and when risk factors are present
- Risk can be reduced, but is always present
- Regarding the primary disease, antiresorptive therapy usually cannot be suspended. Due to their long half life and accumulation tendency we would not even significnatly benefit from it. - Consult with the therapist!
- Informed consent form

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Conservative and prosthetic dentistry

- Following the profession's guidelines, no compromises
- Preventing pulp necrosis underneath larger fillings
  - Attentive pulp protection, observe in questionable cases, temporary fillings
  - Tight control, vitality tests
- Precisely fitting dental restorations, consultation with dental technician
- Fixed restorations are preferred to removable dentures
- Avoid iatrogenic mucous irritation and ulcers
- Education, instruction, follow-ups, revision (soft reline, correction)

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Endodontics

- Root canal treatment is always preferred over tooth extraction
- Routine techniques and instruments
- The healing ability of the periapical tissues is maintained during anitresorptive therapy
- Avoid manipulation over the apex
  - Keep the working length
  - Corpus alienum (sealer, instrument fragments)

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Orthodontics and Pediatric Dentistry

- There haven’t been any cases of MRONJ reported in the pediatric patient group
- Increasing number of middle-aged patients undergoing orthodontic treatment
- Teeth are reported to be more difficult to move during bisphosphonate therapy
- Routinely applied forces may not be as efficient as expected (considering a given time)
- Compromised osteoblast-osteoclast balance
- Individual decision

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Periodontology

- Treatment plan, explanation, information
- Oral hygiene education and instructions
- Make root surfaces cleanable
- The aim is to maitain a balanced periodontal status so that extractions would be avoided
- Surgery is not contraindicated but bone exposition must be minimalised
- GTR and bone grafts depend on individual decision

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Dentoalveolar surgery

- Alternative solutions? (artificially created radix, spontaneous loss of teeth)
- Dental infections have to be treated the same way (incision, drainage)!
- 0,12% CHX pre- and postop. (2 times/day for 2-4 weeks)
- Antibiotic therapy (on the preop. 3rd day amoxicillin+clavulanic acid 1000mg 2x1)
- Atraumatic technique, closure by primery intent
- First, “experimental” case

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Treating manifest osteonecrosis

- Prevent progression with conservative treatment
  - Betadine, iodoform gauze
- Radiological follow-up (OPT, CT/CBCT, scintigraphy)
- In case of exacerbation administer antibiotics (even consider prolonged use)
- Careful debridement
- Sequestrectomy if sequester is present
- Surgical intervention on the maxilla and mandible only if absolutely necessary

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Osteoradionecrosis

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- The most serious side effect after irradiation
- Potential deformities
- Quality of life severely affected

Pathology

- Marx: Osteoradionecrosis – cumulative damage of the irradiated tissues caused by radiation
- Not a direct effect of trauma or bacterial infection
- Complex metabolic failure in the hypovascularised, hypocellular and hypoxic tissues
- Damaged cells can not get their replacement with healthy ones
- Fibrosis, increasing amount of collagen and extracellular elements
- Missing healing potential

- Progressive, irreversible devitalisation of the irradiated bone
- More common in the mandible - thick cortical, end-artery
- Symptoms: pain, exposed necrotic bone in the oral cavity, pathological fractures, purulent discharge, fistules, trismus
- Usually after extraction, but can appear without any invasive treatment
- Lack of proper oral hygiene, smoking, alcohol abuse increase the risk

Treatment

- Careful antiseptic irrigation of the soft tissue borders, removal of debris and controlling the inflammation
- Roboration
- Pain management
- Surgical treatment (removal of necrotic bone: sequestrectomy, mandibule resection)
- Hyperbaric oxigen therapy

- Main goal is prevention

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Intraoral checkup before radiotherapy

- Aim: Keeping the integrity and function of the mucosa, teeth, parodontal tissues and salivary glands
- Prevention of side effects
- Complete intraoral examination
- Treat/remove all possible causes before irradiation that could potentially cause complications
- Improving oral hygiene
- Urgent treatment! Postponing the irradiation - progression of the tumor

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Intraoral examination

- Anamnesis
- Previous tumors
- Risk factors: smoking, diabetes, arteriosclerosis, vascular diseases
- Type and size of tumor
- Dental treatments
- Evaluation of oral hygiene
- Complete dental and intraoral examination (mucosa, dentition, periodontal status, TMJ)
- Complementary methods: OPG, periapical Xray, sialometry, vitality test
- Prognosis of the tumor
- Palliative of curative treatment
- Planned field and dose of irradiation
- Obligatory to examine all the teeth

Prevention

- Absolute indication of extraction:
  - Excessive caries, radix
  - Radix relicta with radiolucency
  - Periapical radiolucency
  - Periodontal disease, pocket depth above 5 mm, furcation involved, II-III. mobility
  - Partially erupted wisdoms, or not full bony-impaction
  - Lack of proper oral hygiene

Extractions

- Timing: at least 2, but better, 3 weeks prior to irradiation
- Antibiotic profilaxis
- Smooth bone edges
- Primery closure, sutures
- Avoid fibrin/collagen haemostatic sponges if possible

- If chemotherapy is in progress:
- Thrombocytes < 50000/mm3: preparing the patient is necessary
- If leukocytes is under 2000/mm3, or granulocytes under 1000/ mm3, the extraction must be postponed

Oral hygiene during radiotherapy

- Brushing after every meal
- Flossing
- Fluoridation
- Rinsing, but avoid mouthwashes with alcohol
- Passive mouth opening techniques

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After irradiation

- Improved oral hygiene
- Avoid extraction for at least 3 years
- If unavoidable, atraumatic technique, periop. antibiotics, sutures
- Pentoxiphyllin and Vitamin-E

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