Long-term complications of cancer therapy: practical guidelines for management

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I have no actual or potential conflict of interest in relation to this presentation
Learning objectives

• Review the most common long-term oral complications of cancer therapy

• Discuss prevention and risk reduction strategies

• Identify effective approaches to management of long-term oral complications of cancer therapy
Cancer treatment related oral changes

• Malignancies with the greatest potential to impact the oral cavity:
  – Head and neck cancers
  – Hematologic cancers
  – Cancers that have metastasized to bone
## Oral complications

- **Direct damage to oral tissues**
  - Surgery
  - Radiation therapy (RT)
- **Indirect damage:**
  - Regional or systemic toxicity associated with:
    - CT
    - Immunotherapy
    - Targeted molecular therapies
- **Supportive care in cancer therapy**
  - Hyposalivation due to use of opioid analgesics and MRONJ
  - Oral infections (common when salivary gland and/or immune function are compromised by cancer therapy)
RT

Early
- Mucositis
- Infections

Early/late
- Dysgeusia
- Dysosomnia
- Hyposalivation
- Neuropathic pain
- Caries
- ORN
- Trismus, fibrosis
- Recurrence, second primary, metastases

Late

RT

Early
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- Infections

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Late
Salivary gland hypofunction

- Ionizing radiation: damage to salivary glands
- Irreversible effects: >25Gy
- Serous acini > mucinous


50-60% decrease

1st week

salivary flow

Additional 20% decrease

7th week
Salivary gland hypofunction

- Xerostomia
- Difficulties talking, tasting, swallowing
- “Bottle of water”
- Wake up at night
- Reduced QoL
- Dental caries
  - cervical, interproximal
- Recurrent oropharyngeal candidiasis

Salivary gland hypofunction: management

- First line treatment:
  - Pilocarpine
  - Cevimeline
- Topical agents/salivary substitutes
- Controversial
  - Acupuncture
  - Low-level laser therapy
Amifostine

H&N CANCER

Amifostine 200mg/m²
IV + RT

RT only

Xerostomia questionnaire
Unstimulated saliva
Stimulated saliva
Patient benefit questionnaire

12
18
24 months

• Reduced incidence of Grade ≥ 2 xerostomia (p = 0.002)
• Increased unstimulated saliva production at 24 months (p = 0.011)
• Reduced mouth dryness scores at 24 months (p < 0.001)
42 yo male with tongue SCC; pre-RT
Rampant caries

Can start **within three months** of the completion of RT

- Maintain optimal oral hygiene
- Sodium fluoride gel 5,000ppm: toothbrush, soft custom-fabricated dental trays
- Chlorhexidine rinses
- Restorations: resin-modified glass ionomer, composite resin, amalgam restorations > conventional glass ionomer restorations

Trismus

- Scar tissue secondary to surgery
- RT: fibrosis and atrophy
- Prevalence: 5%-26% (3-6 months after RT)
- Management
  - Passive stretching
  - Professional device
  - Surgery

Osteoradionecrosis

- Hypoxia (reduction in vascular supply)
- Reduced healing and regenerative capacity
- Trauma (e.g., surgery) → necrosis
- Persistence (greater than 8 weeks) of exposed necrotic bone in the maxilla or mandible
- Exposed bone, disturbance in sensation, infections
- > 60 Gy: 5% risk
- Mandible +++

ORN: management

• **Prevention:**
  – Thorough oral evaluation
  – Extraction of teeth with poor prognosis

• **Post chemo-RT, no ORN**
  – routine dental care/hygiene
  – seek conservative alternatives
  – atraumatic techniques

• **Established ORN**
  – antimicrobial therapies
  – sequestrectomy/debridement
    • +/- HBO therapy
  – surgery in refractory cases

Sultan et al. The Oncologist 2017
<table>
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<tr>
<th>Avoid raising a gingival flap whenever possible, thereby avoiding injury to the periosteum</th>
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<td>Avoid reducing alveolar bone whenever possible; however, mobile or sharp bone fragments should be removed</td>
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<td>Following the extraction, curette the socket and irrigate with saline to ensure the removal of any remaining infected tissue or debris</td>
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<tr>
<td>Re-evaluate the extraction site in approximately two weeks to ensure closure of the gingiva and adequate healing, with additional follow-up scheduled as needed</td>
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The role for HBO therapy?

- **Therapeutic principles**
  - 100% O₂ at 2.4x atmospheric pressure
  - increases vascularity
  - stimulates collagen production

- **Treatment protocol**
  - 20-30/10 for prevention & treatment
  - ~90 minutes/treatment

- **Supporting evidence**

Hyperbaric Oxygen Therapy for Radionecrosis of the Jaw: A Randomized, Placebo-Controlled, Double-Blind Trial From the ORN96 Study Group

Djillali Annane, Joël Depoorter, Philippe Aubert, Maryvonne Villart, Pierre Gélisano, Philippe Gejdos, and Sylvie Chevret

**Abstract**

Purpose

To determine the efficacy and safety of hyperbaric oxygen therapy (HBO) for overt mandibular osteoradionecrosis.

Patients and Methods

This prospective, multicenter, randomized, double-blind, placebo-controlled trial was conducted at 12 university hospitals. Ambulatory adults with overt osteoradionecrosis of the mandible were assigned to receive 30 HBO exposures preoperatively at 2.4 absolute atmospheric pressure minutes or a placebo, and 10 additional HBO dives postoperatively or a placebo. The main outcome measure was 1-year recovery rate from osteoradionecrosis. Secondary end points included time to treatment failure, time to pain relief, 1-year mortality rate, and treatment safety.

Results

At the time of the second interim analysis, based on the triangular test, the study was stopped for potentially worse outcomes in the HBO arm. A total of 68 patients were enrolled and analyzed. At 1 year, six (19%) of 31 patients had recovered in the HBO arm and 12 (32%) of 37 in the placebo arm (relative risk = 0.60; 95% CI, 0.25 to 1.41; P = .23). Time to treatment failure (hazard ratio = 1.33; 95% CI, 0.68 to 2.60; P = .41) and time to pain relief (hazard ratio = 1.00; 95% CI, 0.62 to 1.89; P = .99) were similar between the two treatment arms.

Conclusion

Patients with overt mandibular osteoradionecrosis did not benefit from hyperbaric oxygenation.


Tibbles P, Edelsberg J. NEJM 1996;334:1642-8

Oral cGVHD features

• Resembles immune/autoimmune conditions
  – lichen planus
  – Sjögren syndrome
  – scleroderma

• Often refractory to systemic therapy
  – important role for ancillary care
Principles of management

• Correct diagnosis – know what you are treating
• Symptom > signs
• Optimize efficiency, strategies, patient education
• Preventive care, risk reduction
• Anticipate, manage complications
Oral cGVHD management

- Topical corticosteroids
  - General considerations
  - Gels (2-4x/day, gauze)
    - clobetasol 0.05%
    - fluocinonide 0.05%
  - Solutions (5 min, 2-4x/day)
    - dexamethasone 0.5 mg/5mL
    - clobetasol 0.05%
    - budesonide 3 mg/5mL
- Topical tacrolimus
  - tacrolimus (Protopic) 0.1% ointment (lips)
  - tacrolimus 0.5 mg/5mL
- Combination therapy
- Intraleisional steroid therapy
- Systemic
• 72 yo female
• Hx of AML s/p allo-HCT

• Clobetasol gel 0.05% TID
• Intralesional triamcinolone (5–10 mg per cm² of ulceration)
Secondary cancers

- Risk factors
  - cGVHD
  - duration of IST
  - males>females
  - younger age at allo-HCT?
- Risk of solid tumors increases with time post allo-HCT
  - overall risk 4.6-8.3x >10 y
- Oral cavity SCC
  - 7.01-11.1x overall
  - 25.7-77.9x >10 y

Early

Mucositis, mIAS
Infections

Early/late

CIPN

Late

ONJ

Recurrence, second primary, metastases

CT

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Late
- ONJ
- Recurrence, second primary, metastases
Neuropathic pain

- Chronic pain common
  - >50% H&N pts
  - ~50% inadequate control
- Etiology multifactorial
- Management
  - anticonvulsants
  - opioids
  - antidepressants
  - topical/systemic

Oral dysesthesia

- VEGFR-directed multitargeted tyrosine kinase inhibitors (VR-TKI)
- 747 patients
- Median duration of tx: 3.9 months
- Oral dysesthesia: 21%; median time after tx: 1.9 months
- Treatment:
  - Magic mouthwash (diphenhydramine/lidocaine/Maalox™)
  - Clonazepam 0.1mg/mL
  - OTC palliative rinses (Biotene®, salt water, baking soda)

Medications associated with MRONJ

- **Bisphosphonates**
  - Zoledronic acid (Zometa®, Reclast®)
  - Pamidronate (Aredia ®)
  - Alendronate (Fosamax®)
  - Ibandronate (Boniva®)
  - Risedronate (Actonel®, Atelvia®)
  - Etidronate (Didronel®)
  - Tiludronate (Skelid®)

- **RANK-ligand inhibitor**
  - Denosumab (Xgeva® and Prolia®)

- **Anti-angiogenic agents**
  - Sunitinib (Sutent®)
  - Sorafenib (Nexavar®)
  - Bevacizumab (Avastin®)
  - Ziv-aflibercept (Zaltrap®)

- **Others**
  - Sirolimus (Rapamune ®)

J Gastrointest Oncol. 2016 Dec;7(6):E81-E87
MRONJ: dental considerations

- **Prior to initiation of therapy**
  - All invasive dental procedures should be completed at least 4-8 weeks prior to initiation of therapy

- **Dental follow-up of patients at risk for, or with MRONJ**
  - To prevent and minimize the need for invasive dental procedures

- **Guidelines for extractions in patients at risk for, or with MRONJ**
  - Same as for ORN
  - When indicated, extractions should be completed with the least manipulation and removal of bone as possible
STAGE 0

- No treatment indicated
- Patient education
- Routine follow-up
STAGE I

- Oral antibacterial mouthwash
- Follow up
- Education
STAGE II

- Antibiotics
- Oral antibacterial mouthwash
- Pain control
- Local debridement
Summary

• Treatment for cancer may result in short- and long-term oral complications
• Assess risk factors and modify where possible
• Educate patients/staff
• How to manage long-term oral/dental complications after cancer therapy