Evidence-Based Management Strategies for Oral Complication from Cancer Treatment

An accurate knowledge of the burden of illness, effective prevention and treatment of oral complications associated with cancer therapies is necessary for management of the numerous oral complications of cancer therapy. To establish the impact of oral complications associated with cancer therapy, systematic reviews of the most common oral complications were completed by volunteers primarily from the Oral Care Study Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). A description of the methodology is published elsewhere.(1) Management recommendation and guideline classification was based on criteria of the American Society of Clinical Oncology rating the level of evidence and grade of recommendation.(see Table) (2, 3)

The definition, prevalence and management strategies based on the literature are presented for the following oral complications:

Bisphosphonate Osteonecrosis (BON) (4)
Dysgeusia (5)
Oral Fungal Infection (6)
Oral Viral Infection (7)
Dental Disease (8)
Osteoradionecrosis (ORN) (9)
Trismus (10)
Oral Pain (11)
Xerostomia (12, 13)

Mucositis Guidelines are presented elsewhere.

Table (2,3): Levels and sources of evidence and grade of recommendation

Measure	
Level of Evidence	Source of evidence
I	Meta-analysis of multiple well-designed studies. High powered randomized trials
II	At least one well-designed experimental trial. Low powered randomized trials
III	Well-designed, quasi-experimental studies (e.g. nonrandomized, controlled, single-group, pre-post, cohort)
IV	Well-designed, nonexperimental studies (e.g. comparative and correlational descriptive and case studies)
V	Case reports and clinical examples
Grade of Recommendation	
A	Evidence of type I or consistent findings of multiple types II, III, or IV
B	Evidence of types II, III, or IV with generally consistent findings
C	Evidence of types II, III, or IV, but generally inconsistent findings
D	Little or no systematic empirical evidence
Guideline classification	
Recommendation	This is reserved for guidelines based on Level I or II evidence
Suggestion	Guideline based on Level III, IV, V evidence; implies panel consensus on the interpretation of the evidence
No guideline possible	Used with insufficient evidence to base a guideline because 1) little or no evidence on the practice in question, or 2) the panel lacks consensus on the interpretation of existing evidence

Bisphosphonate Osteonecrosis (BON) (4)

Definition

BON is defined as the presence of necrotic bone anywhere in the oral cavity of an individual on bisphosphonate therapy with no history of radiation of the head and neck.

Prevalence

Mean weighted prevalence of BON = 6.1% for all studies

Studies with documented follow-up = 13.3%;
Studies with undocumented follow-up = 0.7%
Epidemiological studies = 1.2%.

Management

The types of procedures used in published studies have included the following:

Antibiotics=393 (59.7%)
Simple bone sequestrectomy=154 (23.4%)
Bisphosphonate stopped=106 (16.1%)
Conservative therapy=100 (15.2%)
Extensive surgical debridement=84 (12.8%)
Unspecified surgery with antibiotics=45 (6.8%)

IV antibiotics with hospitalization=4 (0.6%)

The response to therapy has been poorly reported with 47% of responses not clearly specified in published studies. BON completely resolved in only 12% of cases, while 33% remained stable and 7% progressed.

Due to flaws in published studies and the paucity of data regarding management strategies, no guideline is possible regarding prevention or treatment strategies (Level of evidence III, Recommendation grade C).

Dysgeusia (5)

Definition

Dysgeusia is an abnormal or impaired sense of taste, an unpleasant alteration of taste sensation, or a distortion or perversion of the sense of taste.

Prevalence

Mean weighted prevalence of dysgeusia

Chemotherapy only = 56.3%
Radiotherapy only = 66.5%
Combined RT and CT = 76%

Management

Zinc gluconate

Suggestion to NOT use zinc gluconate to prevent dysgeusia in head and neck cancer patients, although this has been found to be beneficial in a non-cancer idiopathic Dysgeusia cohort (Level of evidence II, Recommendation grade C).

Amifostine

Recommend NOT to use amifostine solely for the prevention of dysgeusia in head and neck cancer patients (Level of evidence II, Recommendation grade B).

Dietary and educational counseling

Suggestion to use counseling for the prevention of dysgeusia (Level of evidence II, Recommendation grade B).

Oral Fungal Infection (6)

Definition

Oral infection of fungal etiology. Oral candidiasis accounts for the majority of oral fungal infections, with clinical presentations including pseudomembranous candidiasis (thrush), erythematous candidiasis (red appearance), hyperplastic candidiasis (white tissue overgrowth) and angular cheilitis (redness at corners of mouth).

Prevalence
Weighted prevalence of clinical oral fungal infection (all oral candidiasis)
- Pre-treatment = 7.5%
- During cancer treatment =39.1%
- After the end of cancer therapy = 32.6%

Weighted prevalence of oral candidiasis clinical infection by cancer treatment
- During head and neck radiation therapy = 37.4%
- During chemotherapy = 38%

Weighted prevalence of oral colonization with fungal organisms
- Before cancer treatment = 48.2%
- During cancer treatment = 72.2%
- After cancer treatment = 70.1% .

Weighted prevalence of oral fungal colonization by cancer treatment
- During chemotherapy = 72.8%
- During radiation therapy = 74.5%

Management

Weighted prevalence of clinical oral fungal infection during cancer therapy by preventive treatment regimen

- Fluconazole = 1.9%
- Amphotericin = 2.3%
- Itraconazole =1.5%
- Nystatin alone = 6%
- Clotrimazole and nystatin = 14.6%
- Amifostine = 28.9%
- Placebo/No treatment = 20.3%

Topical antifungal agents
There is inconsistency in the efficacy of topical antifungal agents as antifungal prophylaxis for patients receiving cancer therapy. No recommendation possible (Level of evidence II, Recommendation grade C).

Systemic antifungal agents
Recommend the use of systemic fluconazole for the prevention of oral candidiasis in patients receiving cancer therapy (Level of evidence I, Recommendation grade A).

Oral Viral Infection (7)

Definition:
Oral and perioral manifestations of viral infections; often a local component of a systemic disease.

Scope:

Oral and perioral viral infections are most commonly associated with herpesviruses, particularly herpes simplex virus (HSV). Numerous studies addressed this issue. Information about other oral viral infections (cytomegalovirus (CMV), varicella zoster virus (VZV), Epstein-Barr virus (EBV)) is sparse.

Prevalence of HSV oral and perioral infection:
Weighted prevalence in patients treated with chemotherapy for hematologic malignancies

- Patients with oral ulcerations – sampling oral ulcerations = 49.8%
- Patients – sampling oral ulcerations = 33.8%.
- Patients – sampling independently of the presence of oral ulcerations * = 0%

Weighted prevalence in patients treated with radiotherapy

- Patients with radiotherapy only – sampling oral ulcerations * = 0%
- Patients with radiotherapy and adjunctive chemotherapy – sampling oral ulcerations = 43.2%

Management:
Both acyclovir and valacyclovir are recommended for the prevention of HSV infection (Level of evidence I, Recommendation grade A).

- Prevention may be achieved with acyclovir dose of 800 mg/day or with valacyclovir dose of 500-1000 mg/day
- There are no studies in the literature about protocols for anti-viral treatment.

The presence of HSV reactivation was similar for acyclovir and valacyclovir; However, there may be superiority of valacyclovir compared to acyclovir in respect to toxicity and to cost (depends on the route of administration of acyclovir—PO or IV)

* - Simple prevalence is presented as this finding is based on a single report in the literature.

Dental Disease (8)

Definition:
Dental caries involves decay of the tooth structure, gingival disease is caused by inflammation of the gum tissue surrounding the tooth and a dental infection/abscess is a bacterial infection resulting for a necrotic pulp or from diseased bone/tissue structure surrounding a tooth.

Prevalence
Weighted prevalence for dental caries in patients treated with cancer therapy

- All studies = 28.1%
- Chemotherapy only = 37.3%

Post-radiotherapy = 24%
Post chemotherapy and radiotherapy = 21.4%

Weighted prevalence of severe gingivitis in patients undergoing chemotherapy = 20.3%

Weighted prevalence of dental infection/abscess in patients undergoing chemotherapy = 5.8%

Management
Recommend the use of fluoride to prevent dental caries in patients who are post-radiotherapy. Studies indicated fluoride works regardless of the type of delivery method. (Level of Evidence II, Grade of Recommendation B)

Recommend the use of chlorhexidine to improve oral hygiene, although potential side effects of tooth staining, increased calculus, and taste changes need to be taken into account (Level of evidence II, Recommendation grade B)

Suggest the use of resin-modified glass ionomer, composite resin or amalgam restoration, and not a conventional glass ionomer restoration in patients who have been treated with radiotherapy (Level of evidence III, Recommendation grade B).

No guideline possible due to the lack of well designed studies regarding the benefits of various types of toothpaste, pre-cancer therapy dental intervention, honey, and cheese on dental health (Level of evidence III, Recommendation grade C).

Osteoradionecrosis (ORN) (9)

Definition

ORN is characterized by a nonhealing area of exposed mandibular and maxillary bone of at least 6 months duration in a patient who has been previously treated with head and neck radiation therapy (RT) for cancer.

Prevalence

Mean weighted prevalence in conventional RT = 7.4%
Mean weighted prevalence in intensity modulated RT = 5.2%
Mean weighted prevalence in RT and chemotherapy = 6.8%
Mean weighted prevalence in brachytherapy = 5.3%

Note: Most cases involve the mandible, versus the maxilla.

Management

The following guidelines are based on the systematic review of the evidence (9):

No guideline is possible regarding the use of prophylactic HBO therapy for the prevention of ORN in patients requiring post-RT dental extractions (Level of evidence III, recommendation grade C).

Use of single therapy HBO therapy for the treatment of ORN is NOT recommended (Level of evidence II, Recommendation grade B).

No guidelines are possible at the present time relative to other ORN prevention and treatment strategies (Level of evidence III, Recommendation grade C).

Given the state-of-the-science relative to ORN and as with guideline utilization in general, practitioners should also incorporate their clinical expertise and judgment in determining optimal management of ORN for their patients.

Further research is this field is needed, in order to strengthen the comprehensive evidence base on which future guidelines can be based.

Trismus (10)

Definition
Trismus is defined as the tonic contraction of the muscles of mastication and results in a limited ability to open the mouth. This has been associated with radiotherapy (RT) to the temporomandibular joint and muscles of mastication.

Prevalence
Weighted prevalence for conventional RT = 25.4%
Weighted prevalence for intensity modulated RT = 5%
Weighted prevalence for combined RT and chemotherapy = 30.7%

Management
Suggestion that Therabite® System may be effective in the reduction of RT-induced trismus (Level of evidence III, Recommendation grade B).

No guideline is possible regarding the use of pentoxifylline to prevent RT-induced trismus (Level of evidence IV, Recommendation grade C).

No guideline is possible regarding the use of physiotherapy in the prevention of RT-induced trismus, although may be beneficial in overall trismus management (Level of evidence IV, Recommendation grade B).

No guideline possible regarding botulinum toxin injections for the treatment of RT-induced trismus, although there may be some improvement of pain scores and masticator spasms (Level of evidence III, Recommendation grade B).

No guideline possible regarding use of Dynasplint® Trismus System in the reduction of RT-induced trismus, although may have some benefit for reduction of contracture of the muscles of mastication (Level of evidence III, Recommendation grade B).

Oral Pain (11)

Definition
Cancer-associated pain in the orofacial region is common and can be directly related to the malignancy or is a consequence of cancer therapy.

Prevalence
Pain is common in patients with HNC and reported by approximately half of patients prior to cancer therapy, 81% during therapy, 70% at the end of therapy and still 36% at 6 months post-treatment.

VAS Pain level (0-100) in Head and Neck Cancer patients
Pre-treatment = 12/100
Immediately post-tx = 33/100
One month post-tx = 20/100

EORTC QLQ C30 Pain level (0-100) in Head and Neck Cancer Patients
Pre-treatment = 27/100
3 month post-tx = 30/100
6 month post-tx = 23/100
12 month post-tx = 24/100

Management
Clinical trials for the treatment of oral pain in cancer patients is often a secondary outcome with mucositis the primary outcome. Therefore, please refer to the Mucositis Guidelines <insert link to MASCC address> for management strategies for orofacial pain, which is most commonly the result of mucositis.

Salivary gland hypofunction and xerostomia

Definition

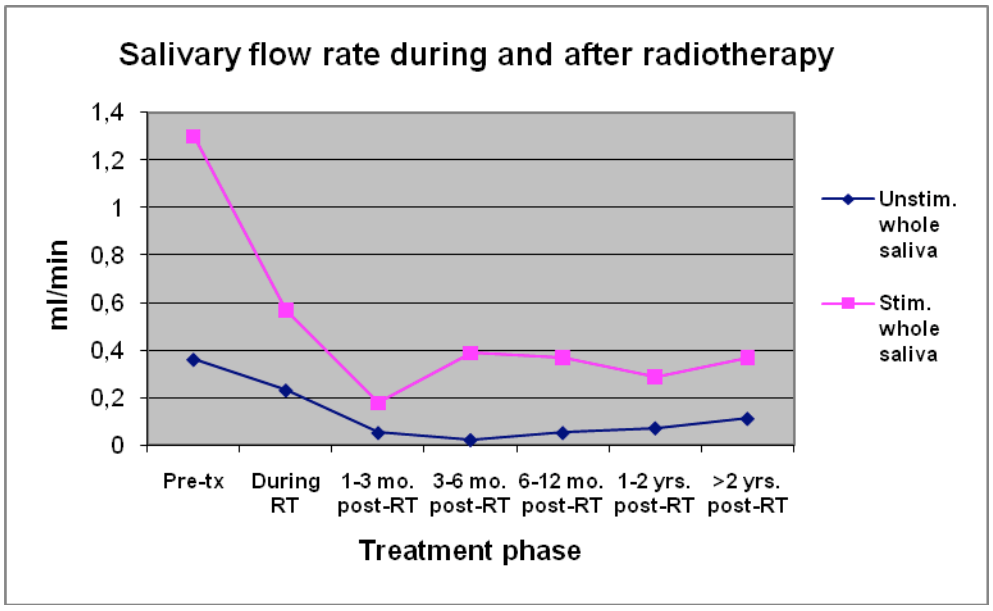
Salivary gland hypofunction is a decrease in salivary secretion, with pathological low saliva secretion as ≤ 0.1 ml/min for unstimulated whole salivary flow and ≤ 0.5 ml/min for stimulated whole salivary flow. Xerostomia is defined as the subjective complaint of dry mouth.

Prevalence (12)

Weighted prevalence of xerostomia in head and neck cancer patients by type of radiation therapy (RT)

- All studies
  - Pre-tx = 6%
  - During RT = 93%
  - 1-3 months post-RT = 74%
  - 3-6 months post-RT = 79%
  - 6-12 months post-RT = 83%
  - 1-2 years post-RT = 78%
  - > 2 years post-RT = 85%
- Conventional RT
  - Pre-tx = 10%
  - During RT = 81%
  - 1-3 months post-RT = 71%
  - 3-6 months post-RT = 83%
  - 6-12 months post-RT = 72%
  - 1-2 years post-RT = 84%
  - > 2 years post-RT = 91%
- Intensity-modulated radiation therapy (IMRT)
  - Pre-tx =12%
  - During RT = 100%
  - 1-3 months post-RT = 89%
  - 3-6 months post-RT = 73%
  - 6-12 months post-RT = 90%
  - 1-2 years post-RT = 66%
  - > 2 years post-RT = 68%

Salivary Flow Rates



Unstimulated and stimulated whole saliva flow changes during and after radiotherapy in the head and neck region.

Management (13)

The panel recommends the use of parotid sparing IMRT for prevention of salivary gland hypofunction and xerostomia in head and neck cancer patients (Level of evidence II, Recommendation grade A).

No guideline possible for use of amifostine to prevent xerostomia during RT for head and neck cancer due to lack of consensus on the interpretation of existing evidence (Level of evidence II, Recommendation grade C).

The panel recommends the use of oral pilocarpine following radiation therapy in head and neck cancer patients for improvement of xerostomia. The improvement of salivary gland hypofunction may be limited (Level of evidence II, Recommendation grade B).

The panel cannot recommend the use of oral pilocarpine during radiotherapy in head and neck cancer patients for improvement of xerostomia as the results of the various randomized clinical trials were equivocal (Level of evidence II, Recommendation grade C).

No guideline possible for use of gustatory and masticatory stimulation due to little evidence on which to base a guideline since this has been sparsely addressed specifically for patients suffering from xerostomia induced by cancer therapies (Level of evidence III, Recommendation grade D).

The panel recommends the use of oral mucosal lubricants/saliva substitutes for short-term improvement of xerostomia following radiation therapy in head and neck cancer patients (Level of evidence II, Recommendation grade B).

The panel suggests that the obtained level of sparing by submandibular salivary gland transfer might be of clinical significance (Level of evidence IV, Recommendation grade B).

The panel suggests the use of acupuncture to stimulate salivary gland secretion and to alleviate xerostomia (Level of evidence II, Recommendation grade C).

No guideline possible for hyperbaric oxygen treatment of xerostomia due to no evidence on which to base a guideline (Level of evidence IV, Recommendation grade D).

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