Radiation-Induced Oral Mucositis

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Radiation-induced oral mucositis (RIOM) is a major dose-limiting toxicity in head and neck cancer patients. It is a normal tissue injury caused by radiation/radiotherapy (RT), which has marked adverse effects on patient quality of life and cancer therapy continuity. It is a challenge for radiation oncologists since it leads to cancer therapy interruption, poor local tumor control, and changes in dose fractionation. RIOM occurs in 100% of altered fractionation radiotherapy head and neck cancer patients. In the United States, its economic cost was estimated to reach 17,000.00 USD per patient with head and neck cancers. This review will discuss RIOM definition, epidemiology, impact and side effects, pathogenesis, scoring scales, diagnosis, differential diagnosis, prevention, and treatment.

Keywords: chemotherapy, oral mucositis, radiation, radiotherapy, normal tissue injury, pathobiology, mesenchymal stromal/stem cells

DEFINITION

Radiation-induced oral mucositis (RIOM) (Figures 1, 4 and 5C) is one of the major ionizing radiation toxicities and normal tissue injuries that result from radiotherapy (1). RIOM was first termed in 1980 as a side effect of radiotherapy (RT) in cancer patients (2). RIOM is a normal tissue injury lasting between 7 and 98 days, which starts as an acute inflammation of oral mucosa, tongue, and pharynx after RT exposure (1, 3). This coincides with recruitment of various inflammatory cells and release of inflammatory cytokines, chemotactic mediators, and growth factors. RIOM can progress to an acute life-threatening stage as a result of severe physical obstruction of food and water intake with subsequent weight loss and septic complication due to lost protective epithelial and basement membrane barriers. This leads to limitations of local tumor control due to cancer treatment interruption and alterations in radiation dose fractionation (4–7). Studies suggested the stages of progression of RIOM as initial hyperemia and erythema during the preulcer phase, during which there is a release of various pro-inflammatory cytokines from epithelial, vascular, and connective tissue cells at the site of tissue injury. This is followed by the epithelial phase with various degrees of desquamation and basement membrane damage with loss of the protective barrier, which ends with the physical appearance of the ulceration. The postulcerative phase varies depending on the extent of the tissue toxicity. A secondary infection with Gram-negative bacteria or yeast may occur, with microcoagulation of the vasculature that worsens the inflammation by the local ischemia with more necrotic tissue yield. The final stage will be the healing phase and fibrosis (2, 8, 9).

RIOM EPIDEMIOLOGY (INCIDENCE, PREDICTORS, AND RISK FACTORS)

Radiation-induced oral mucositis occurs in up to 80% of head and neck cancer irradiated patients and reaches up to 100% in patients with altered fractionation head and neck cancer. RIOM of grade 3 and 4 have been recorded in 56% of head and neck cancer patients treated with radiotherapy (1, 12).
Many risk factors have been identified for RIOM. These risk factors include concomitant chemotherapy (CT), bad oral hygiene, below average nutritional status, lack of antibiotic use at early stage mucositis, and smoking (13).

Table 1 shows the significant predictors for the prevalence of severe RIOM and the symptoms of RIOM in a longitudinal study of patients with oral cavity cancer among head and neck cancer outpatients of a radiation department at a major medical center in Taiwan (14). This study used the Generalized Estimating Equations to analyze the predictive factors of prevalence of severe RIOM and RIOM-related symptoms. They found that the significant predictors for the prevalence of severe RIOM included type of treatment [RT vs. CCRT], cumulative radiation dose, smoking, and body mass index (BMI). Patients who received CCRT (Coef. 0.145, \( p < 0.05 \)), who have a higher cumulative radiation dose (Coef. 0.000, \( p < 0.01 \)), who are smokers (Coef. 0.090, \( p < 0.01 \)), and who have lower BMI (Coef. 0.005, \( p < 0.05 \)) were at high risk to develop severe RIOM. RIOM-related symptoms were also predicted by type of treatment (RT vs. CCRT) (Coef. 1.618, \( p < 0.05 \)), cumulative radiation dose (Coef. 0.003, \( p < 0.05 \)), and smoking (Coef. 1.759, \( p < 0.001 \)). These significant predictors are implemented by radiation oncologists to minimize and/or prevent the RIOM.

## RIOM Impact and Side Effects

Radiation-induced oral mucositis side effects and sequel include oral pain in 69% of patients, dysphagia in 56% of patients, opioid use in 53% of patients, weight loss of 3–7 kg, feeding tube...
insertion and hospitalization (ICU admission) in 15% of patients, and modification or interruption of treatment in 11–16% of patients (1, 12, 16).

In the United States, RIOM may add up to 1,700.00–6,000.00 USD per patient depending on the inflammatory grade of the injury (12). RIOM treatment adds an economic cost that was estimated to increase up to 17,000.00 USD per patient treated for head and neck cancers (16).

Radiation-induced oral mucositis injury challenges radiation oncologists from many aspects, such as radiation dose limitations, changes in dose fractionation protocol, and dramatic negative effects on patients’ quality of life (1). The major clinical consequences of RIOM include hospital admission or extended hospitalization for total parenteral nutrition, intravenous (IV) analgesia, and IV antibiotics. Sixty-two percent of patients require hospitalization, and 70% of patients with grade 3–4 oral mucositis (OM) require feeding tube insertion. Reduction or cessation of cancer treatment occurs in 35% of patients due to the developed dose-limiting toxicity (17).

**PATHOGENESIS AND SUGGESTED MECHANISTIC PATHWAYS**

The pathophysiology of RIOM is not fully understood. Recent studies proposed that the pathogenesis of RIOM is composed of four phases: an initial inflammatory/vascular phase, an epithelial phase, a (pseudomembranous) ulcerative/bacteriological phase, and a healing phase (2, 5).

At the inflammatory phase, the RT-induced tissue injury results in the release of inflammatory cytokines; e.g., interleukin (IL)-1β, prostaglandins (PGs), and tumor necrosis factor-α (TNF-α) from the resident cells such as epithelial, endothelial, and connective tissue. These mediators might increase the damage by increasing the vascular permeability, leading to more infiltration and recruitment of inflammatory cells. Stem cells travel to the site of the tissue injury with other innate immunity components, e.g., MPO-positive leukocytes, macrophages, and neutrophils (18). On the other hand, there are some anti-inflammatory cytokines, such as IL-10 and IL-11, that work to minimize the injury (18).

The epithelial phase is initiated within a week by the apoptotic and cytotoxic effects of RT on the proliferating basal cells. This is why the recovery period is dependent on the rate of epithelial turnover, which could be enhanced by growth factors like epidermal growth factor and keratinocyte growth factor (KGF) (19).

After a week, the epithelial breakdown ends with the beginning of the ulceration. This occurs, when epithelial loss leads to disrupted basement membrane, formation of ulcer pseudomembrane, and inflammatory exudate. The ulceration stage is very painful, since the protective barrier that covers the nerve endings at the lamina propria is lost (19). The resulting microcoagulation and neutropenic state facilitate the Gram-negative bacteria and yeast colonization with the production of secondary infection. Bacterial exotoxins aggravate the inflammatory reaction by inducing mononuclear burst with the release of more IL-1β, TNF-α, and nitric oxide (8, 9, 16, 20).

### TABLE 3 | Signaling pathways involved in the development of mucositis (19).

| Signaling pathway                                                                 |
|----------------------------------------------------------------------------------|
| B-cells receptor signaling                                                       |
| Cell cycle: G2/M DNA damage checkpoint receptor                                  |
| Death receptor signaling                                                         |
| Glutamate receptor signaling                                                     |
| Integrin signaling                                                               |
| Nuclear factor-xB signaling                                                      |
| Nitrogen metabolism                                                             |
| PI3K/AKT signaling                                                              |
| P38 mitogen-activated protein kinase signaling                                   |
| SAPK/JNK signaling                                                              |
| Toll-like receptor signaling                                                     |
| Vascular endothelial growth factor signaling                                     |
| Wnt/B-catenin signaling                                                         |

Signaling pathways suggested to be involved in RIOM pathobiology include nitrogen metabolism, Toll-like receptor signaling, nuclear factor-xB (NF-xB) signaling, B-cell receptor signaling, P13K/AKT signaling, cell cycle: G2/M DNA damage checkpoint receptor, p38 mitogen-activated protein kinase (MAPK) signaling, Wnt/B-catenin signaling, glutamate receptor signaling, integrin signaling, vascular endothelial growth factor signaling, IL-6 signaling, death receptor signaling, and SAPK/JNK signaling (Table 3) (10, 19).

In 2004, Sonis suggested five stages (phases) of OM injury induced by radiotherapy (RT) and/or CT: initiation, signaling, amplification, ulceration, and healing (Figure 1) (16).

In 2009, Redding summarized Sonis’ RIOM pathobiology phases (Figure 2). The initiation phase with RT and/or CT injury results in direct and lethal DNA damage with the release of reactive oxygen species (ROS) from epithelial and vascular endothelial cells, fibroblasts, and tissue macrophages. This is followed by amplification of this signal (11). During the primary damage response, the DNA damage and ROS act through three major pathways: (1) fibronectin breakdown, which stimulates the macrophages leading to activation of the matrix metalloproteinases (MMPs), (2) nuclear factor-xB (NF-xB) activation, which stimulates the gene expression and the release of pro-inflammatory cytokines, e.g., TNF-α, IL-1β, and IL-6, and (3) ceramide pathway through sphingomyelinase and ceramide synthase. The end result will be more tissue injury and stimulated apoptosis (11). During the signal amplification phase, there is restimulation of tissue damage and apoptosis by the major pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), NF-xB-mediated gene expression, and ceramide and caspase pathways. The basement membrane protective barrier is lost during the ulceration phase. This leads to Gram-negative and yeast secondary infection potential, which adds more pro-inflammatory reactions and complicates the already existing inflammation. The healing phase starts by matrix signaling to basal epithelial cells to migrate, proliferate, and differentiate (11). Signal amplification during RIOM or CT-induced OM is a main step in this treatment-induced injury, according to Sonis et al. (17). RT and/or CT activate the transcription factor NF-xB in epithelial, endothelial, and mesenchymal cells and macrophages, resulting in upregulation of genes and production of pro-inflammatory mediators.
FIGURE 2 | Redding’s summary of RT and/or chemotherapy (CT)-induced oral mucositis pathobiology (11). Redding has summarized the pathobiology phases of radiation-induced oral mucositis induced by RT and/or CT. In brief, initiation phase with RT and/or CT results in direct and lethal DNA damage, which leads to release of reactive oxygen species (ROS) from epithelial, vascular endothelial, fibroblasts, and tissue macrophages with cycles of amplifications. Within such primary damage response, the DNA damage and ROS lead to three major steps: (1) fibronectin breakdown that activates macrophages ending with stimulation of matrix metalloproteinase; (2) nuclear factor-κB (NF-κB) activation that stimulates the gene expression and release of pro-inflammatory cytokines, e.g., TNF-α, interleukin (IL)-1β, and IL-6; and (3) ceramide pathway through sphingomyelinase and ceramide synthase. The result will be more tissue injury and stimulated apoptosis. During the signal amplification phase, there is restimulation of tissue damage and apoptosis by the major pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), NF-κB-mediated gene expression, and ceramide and caspase pathways. During the ulceration and loss of the protective barrier, secondary infection adds more pro-inflammatory reactions and complicates the already existing inflammation before the healing phase starts by matrix signaling to basal epithelial cells to migrate, proliferate, and differentiate. Republished with the permission of Dr. Redding.

RIOM Grading and Scoring Scales

There has been more than one grading scale for RIOM. Table 4 shows the comparison of different RIOM scoring scales (14, 21–23).

World Health Organization Oral Toxicity Scale measures the anatomical, symptomatic, and functional elements of OM (Figure 4). The Radiation Therapy Oncology Group (RTOG) determined the acute radiation morbidity scoring criteria for mucous membranes. Finally, the Western Consortium for Cancer Nursing Research describes only the anatomical changes associated with OM (24).
3 = lesion >3 cm²) and erythema (score 0–2: 0 = none; 1 = not severe; 2 = severe) on the upper and lower lips, right and left cheeks, right and left ventral and lateral tongue, floor of the mouth, soft palate, and hard palate (23, 28).

All these scoring scales are validated and are required in assessing RIOM and the therapeutic benefits of any new treatment of RIOM.

**DIAGNOSIS OF RIOM**

Radiation-induced oral mucositis can develop within or after 2 weeks from the beginning of RT. Oral assessment guide could be a useful tool for detection of early OM (Table 6) (20). Apart from the early clinical signs and symptoms, CBC with differential is considered the baseline to help radiation oncologists to determine the most susceptible time for developing OM or oral infection. Radiation oncologists can start the RT provided that there is no evidence of any periodontal disease. If at any point RIOM develops, oral lesion culture and antimicrobial therapy are recommended as soon as possible (29). Since renal diseases are considered contributing factors for OM (15), chemistry levels should be regularly monitored by the treating physician (29).

**DIFFERENTIAL DIAGNOSIS OF RIOM**

Because similar conditions can coexist in immunocompromised patients including cancer patients receiving RT and/or CT, differential diagnosis for RIOM is critical. Table 7 shows possible similar conditions (Figure 5) (20, 31).

**PROGNOSIS OF RIOM**

The general long-term prognosis is reasonably good since most lesions resolve within 2–4 weeks after stopping the RT or CT. Although RIOM is considered a self-limited injury in some patients, it could be a lethal injury in moderately to severely ill patients, which could lead to ICU admission with obligatory cessation of RT. Patient losses are a common event under these circumstances (32).

**PREVENTION OF RIOM**

Maintaining good oral care is the main preventive measure for RIOM to minimize the risk for candidiasis or secondary bacterial infection, especially in hyperfractionated radiotherapy, combined CCRT regimens, or RT combined with a targeted agent due to increased mucositis severity (3). We will summarize the most recent agents and measures to prevent RIOM.

1. Good oral hygiene
   
   Good oral hygiene has been found to be one of the most effective ways to lower the risk of RIOM and minimize its progression. Pre-existing oral pathology, e.g., dental caries, periodontal lesions, pulpal disease, and oral xerostomia, has been linked with increased bacteria colonization and severe RIOM. It is recommended to do early oral examination before starting any mucosal toxic therapy for cancer patients. To help minimize the oral side effects of antineoplastic therapy, it is recommended to eliminate any oral pathology before the beginning of RT. This may be accomplished by performing early histological, cytological, microbiologic, and serologic examinations (2). The Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO) guidelines...
recommend the use of a standardized oral care protocol, e.g., brushing with a soft toothbrush, flossing and the use of non-medicated rinses (saline or sodium bicarbonate rinses) (Table 9) (33–36). The good oral care can be summarized as follows:

- Rinsing with a non-irritating solution, e.g., saline to increase the quality of saliva.
- Daily ultrasonic tooth brushing with fluoride toothpaste.
- Scaling and cleaning.
- Very soft diet with low sugar and non-acidic food and drinks (Table 8).
- Flossing is not recommended due to low platelet count.
- Minimize denture use.

- No smoking or alcohol.
- Other preventive procedures include minimizing the microbial load (will be discussed more in the treatment section) and educating the patient on good oral hygiene, which is mandatory.

2. Cryotherapy has been recommended for CT-induced OM, but no proven role in RIOM due to insufficient evidence (33).

3. Keratinocyte growth factor is an epithelial mitogen that reduces the levels of ROS by activating nuclear factor (erythroid-derived 2)-like 2 and had been used in RIOM with promising results (37–53). It appears to be one of the promising treatment and prevention options for RIOM that has been investigated in clinical trials (39, 43). Palifermin (IV recombinant human...
KGF-1) had been approved by the US-FDA for minimizing OM in hematologic malignancies’ patients who receive myelo-toxic therapies and require hematopoietic cell support after its reliable results in alleviating WHO grade 3 and 4 OM in these patients. Palifermin is delivered IV 3 days before of CT/RT and for 3 days after CT. Palifermin should be avoided on the same day of CT/RT (33).

4. Amifostine is a free-radical scavenger, antioxidant, and cytoprotective agent that was administered subcutaneously (SC) and IV in many clinical trials for RIOM. Amifostine is conventionally given IV before RT or CT. It is approved by the US-FDA to reduce the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer. In addition, it was approved for by the US-FDA to reduce the incidence of moderate to severe xerostomia in patients undergoing postoperative RT for head and neck cancer, where the radiation port includes a substantial portion of the parotid glands (33, 54–62). Although there was a reduction in the pro-inflammatory cytokine production, its side effects, e.g., hypotension and nausea, were recorded, particularly with IV route. Nevertheless, SC injection 60 min before RT in head and neck cancer patients showed marked reduction of these side effects, unfortunately, with reduced efficacy and patient compliance. Only cutane-ous toxicity was noted in SC route of amifostine delivery (54, 55). For moderate to severe RT-induced xerostomia in head and neck cancer patients, the recommended dose of amifostine is 200 mg/m² once daily over 3 min IV, starting 15–30 min before standard fraction RT (1.8–2.0 Gy). Blood pressure should be monitored before, during, and after the IV infusion. Oral 5-HT3 receptor antagonists with/without other antiemetics are recommended before amifostine therapy (63–65).

5. Radiation shields (intraoral devices), midline mucosa-sparing blocks, 3-D and RT field design, intensity-modulated radiation therapy (IMRT), and removal of separable prosthetics are shown in preclinical studies to reduce the radiation scatter and the RIOM injury (66–69).

6. Low-energy helium–neon laser applied before RT showed significant reduction in the duration and the severity of RIOM in head and neck cancer patients (70). MASCC/ISOO guidelines suggest the use of low-level laser therapy in CT-induced OM at centers that can provide the necessary technology and training (33).

### SYMPTOMATIC TREATMENT OF RIOM

No single agent has been approved by the US-FDA for the treatment of RIOM. Symptoms reduction and complications prevention of RIOM, including nutritional support, pain control, prophylaxis, and/or treatment of secondary infections, are consid-ered the main cornerstone in the management of RIOM (34–36). Agents that were investigated and/or applied in RIOM treatment are discussed in the context of recently updated evidence-based preclinical and clinical studies.

#### 1. Locally applied agents

1. Glycyrrhetinic acid/povidone/sodium hyaluronate gel has mechanical action implemented in the relief of pain in RIOM. It adheres to the mucosal surface of the mouth, soothing oral lesions. Nevertheless, the preclinical studies

### TABLE 6 | Oral assessment guide (30).

| Item/grade | 1 | 2 | 3 |
|------------|---|---|---|
| Voice      | Normal | Deeper or raspy | Difficulty talking |
| Swallow    | Normal | Some pain | Unable to swallow |
| Lips       | Smooth pink and moist | Dry or cracked | Ulcerated or bleeding |
| Tongue     | Pink and moist | Coated and shiny or red | Blistered or cracked |
| Saliva     | Watery | Thick | Absent |
| Mucus membrane | Pink and moist | Red and coated | Ulcers |
| Gingiva    | Pink and firm | Edematous or redness | Spontaneous or pressure-induced bleeding |
| Teeth/denture areas | Clean, no debris | Plaque and localized debris | Generalized plaque or debris |

### TABLE 7 | Differential diagnosis of RIOM (20, 31).

| Disease/injury | Cause | Clinical presentation/lab findings | Severity | Treatment options |
|---------------|-------|-----------------------------------|----------|------------------|
| Oral mucositis | Chemotherapy and radiation therapy | Diffuse redness, ulcers, and pain, particularly in areas where teeth abut tissue | Varies; in BMT setting up to 98% have grade 3/4 | Palliative rinses, narcotics, palifermin in the BMT setting |
| Aphthous stomatitis | Etiology not identified | Single painful ulcer | Localized, but painful; maximum grade 2 | Topical |
| Herpetic mucositis | HSV1 | Usually several spots; ulcerative plaques | Usually grade 1–2 | Acyclovir, valacyclovir, foscarnet |
| Oral thrush | Candida | Varies from painless to mild soreness; whitish plaques | Usually grade 0–1 | Nystatin rinses; fluconazole and other azoles |
| Denture/oral trauma | Dentures | Common in elderly patients with loose-fitting dentures | Can limit calories | Repair, removal of dentures |
| Gangrenous stomatitis | Bacterial infections | Necrotic pseudomembranes | Rare, can be severe | Antibacterials that treat oral aerobes and anaerobes |
| Acute necrotizing stomatitis | Bacterial infections in immune-deficient patients | Pain, fever, necrotic, bloody ulcers | Grade 3/4 | Control of infection |

BMT, bone marrow transplantation; RIOM, radiation-induced oral mucositis; HSV1, herpes simplex virus type 1.
are controversial, and only one clinical trial on unknown results was conducted to date (71).

2. L-Glutamine is a non-essential amino acid that counteracts RT-induced metabolic deficiencies (72). Locally applied L-glutamine reduced the RIOM in a randomized clinical trial (73). Glutamine powder for oral suspension was approved by the US-FDA for topical application in management of CT-induced OM, mainly IOM yet (74).

3. Manganese superoxide dismutase is a detoxifying agent that removes ROS. It was shown to have radioprotective effects against RT-induced colitis, esophagitis, hepatic cells apoptosis, and intestinal and eye injury (75–98). Phase I dose escalation study of GC4419 (manganese-containing macrocyclic ligand complex similar to naturally occurring superoxide dismutase enzymes) in combination with CT/RT for squamous cell cancer of the head and neck has just been completed waiting for results release (NCT01921426).

4. Local anesthetics, e.g., diphenhydramine, viscous xylocaine, lidocaine, and dyclonine hydrochloride, are used for short-term relief of pain associated with RIOM, despite the fact that they can interfere with the taste sensation leading to hypoalimentation (99, 100). Swishing and gargling the anesthetic viscous gel containing 2%
TABLE 9 | Multinational Association for Supportive Care in Cancer/International Society for Oral Oncology (MASCC/iSOO) Clinical Practice Guidelines for oral mucositis (4).

| Intervention/mode of administration | Purpose | Cancer treatment | Level of evidence |
|-------------------------------------|---------|------------------|-------------------|
| Oral cryotherapy for 30 min         | Prevention of OM | Patients receiving bolus 5-fluorouracil chemotherapy | Level II |
| Recombinant human keratinocyte growth factor-1 (palifermin) at a dose of 60 µg/kg per day for 3 days prior to conditioning treatment and for 3 days after transplant | Prevention of OM | Patients receiving high-dose chemotherapy and TBI, followed by autologous stem cell transplantation, for a hematological malignancy | Level II |
| Low-level laser therapy (wavelength at 650 nm, power of 40 mW, and each square centimeter treated with the required time to a tissue energy dose of 2 J/cm²) | Prevention of OM | Patients receiving HSCT conditioned with high-dose chemotherapy, with or without TBI | Level II |
| Patient-controlled analgesia with morphine | Pain reduction | Patients undergoing HSCT | Level II |
| Benzydamine mouthwash | Prevention of OM | Patients with HNC receiving moderate dose radiation therapy (up to 50 Gy), without concomitant chemotherapy | Level II |

Suggestions in favor of an intervention (weaker evidence supports effectiveness in the treatment setting listed)

| Oral care protocols | Prevention of OM | All age groups and across all cancer treatment modalities | Level III |
| Oral cryotherapy | Prevention of OM | Patients receiving high-dose melphalan, with or without TBI, as conditioning for HSCT | Level III |
| Low-level laser therapy (wavelength around 632.8 nm) | Prevention of OM | Patients undergoing radiotherapy, without concomitant chemotherapy, for HNC | Level III |
| Transdermal fentanyl | Pain reduction | Patients receiving conventional or high-dose chemotherapy, with or without TBI | Level III |
| 2% morphine mouthwash | Pain reduction | Patients receiving chemoradiation for HNC | Level III |
| 0.5% doxepin mouthwash | Pain reduction | All patients with OM-induced pain | Level IV |
| Systemic zinc supplements administered orally | Prevention of OM | HNC patients receiving radiation therapy or chemoradiation | Level III |

Recommendations against interventions (strong evidence indicates lack of effectiveness in the treatment setting listed)

| PTA (polymyxin, tobramycin, amphotericin B) and BCoG (bacitracin, clotrimazole, gentamicin) | Prevention of OM | Patients receiving radiation therapy for HNC | Level II |
| Iseganan antimicrobial mouthwash | Prevention of OM | Patients receiving high-dose chemotherapy, with or without TBI, for HSCT or in patients receiving radiation therapy or concomitant chemoradiation for HNC | Level II |
| Iseganan antimicrobial mouthwash | Prevention of OM | Patients receiving high-dose chemotherapy, with or without TBI, for HSCT or in patients receiving radiation therapy or concomitant chemoradiation for HNC | Level II |
| Sucralfate mouthwash | Prevention of OM | Patients receiving chemotherapy for cancer (I), or inpatients receiving radiation therapy (I) or concomitant chemoradiation (II) for HNC | Level I, II |
| Sucralfate mouthwash | Treatment of OM | Patients receiving chemotherapy for cancer (I), or in patients receiving radiation therapy (II) for HNC | Level I, II |
| Intravenous glutamine | Prevention of OM | Patients receiving high-dose chemotherapy, with or without TBI, for HSCT | Level II |

Suggestions against interventions (weaker evidence indicates lack of effectiveness in the treatment setting listed)

| Chlorhexidine mouthwash | Prevention of OM | Patients receiving radiation therapy for HNC | Level III |
| Granulocyte-macrophage colony-stimulating factor mouthwash | Prevention of OM | Patients receiving high-dose chemotherapy, for autologous or allogeneic HSCT | Level II |
| Misoprostol mouthwash | Prevention of OM | Patients receiving radiation therapy for HNC | Level III |
| Systemic pentoxifylline, administered orally | Prevention of OM | Patients undergoing HSCT | Level III |
| Systemic pilocarpine, administered orally | Prevention of OM | Patients receiving radiation therapy for head and neck cancer (III), or patients receiving high-dose chemotherapy, with or without TBI, for HSCT (II) | Level II and III |

OM, oral mucositis; HSCT, hematopoietic stem cell transplantation; TBI, total body irradiation; HNC, head and neck cancer.

Criteria for each level of evidence (34).

Level I: evidence obtained from meta-analysis of multiple, well-designed, controlled studies; randomized trials with low false-positive and false-negative errors (high power).

Level II: evidence obtained from at least one well-designed experimental study; randomized trials with high false-positive and/or false-negative errors (low power).

Level III: evidence obtained from well-designed, quasi-experimental studies such as non-randomized, controlled single-group, pretest-posttest comparison, cohort, time, or matched case-control series.

Level IV: evidence obtained from well-designed, non-experimental studies, such as comparative and correlational descriptive and case studies.

Level V: evidence obtained from case reports and clinical examples.
### TABLE 10 | Radiation-induced oral mucositis (RIOM) the clinical trials that have been done until 2001 [2].

| Injury | Reference          | Randomized/controlled/double blind | P/T         | Application/doses                                      | Results                                                                 |
|--------|--------------------|------------------------------------|-------------|--------------------------------------------------------|-------------------------------------------------------------------------|
| RT     | Shieh et al. (241) | Yes/yes/no                          | P           | Instructions on oral care                              | Significant reduction                                                   |
| RT     | Perch et al. (68)  | No/no/no                            | P           | Midline mucosa-sparing blocks                          | Decreased mucositis without affecting tumor control                     |
| RT     | Rugg et al. (242)  | No/no/no                            | P           | Smoking during RT                                      | Higher mucositis incidence in smokers                                   |
| RT     | Scherlacher et al. (243) | Yes/no  | P           | Sucralfate vs. standard oral hygiene                  | Significant reduction of incidence and severity of mucositis            |
| RT     | Allison et al. (148) | Yes/no  | P + T       | Sucralfate + fluconazole vs. standard oral care       | Significant reduced severity and symptomatic relief                     |
| RT     | Franzen et al. (145) | Yes/yes/yes | P         | Sucralfate vs. placebo                                | Significant lower incidence of severe mucositis                         |
| RT     | Makkonen et al. (147) | Yes/yes/yes | P         | Sucralfate vs. placebo                                | Only slight protective effect of sucralfate                              |
| RT     | Epstein et al. (148) | Yes/yes/yes | P + T  | Sucralfate vs. placebo                                | Non-significant reduction of oral discomfort                             |
| RT     | Meredith et al. (144) | Yes/yes/yes | T         | Antacid, diphenhydramine, lidocaine ± sucralfate      | Non-significant reduction of severity                                    |
| RT     | Cengiz et al. (142) | Yes/yes/yes | P + T   | Sucralfate vs. placebo                                | Decreased severity                                                      |
| RT     | Carter et al. (244) | Yes/yes/yes | P         | Sucralfate vs. placebo                                | No difference                                                           |
| RT     | Barker et al. (100) | Yes/yes/yes | P + T   | Oral hygiene + sucralfate vs. diphenhydramine + kaolín-pectin | No difference                                                           |
| RT     | Feber et al. (245) | Yes/yes/no                           | P           | Hydrogen peroxide vs. saline                          | Significantly more oral discomfort                                       |
| RT     | Spijkervet et al. (246) | Yes/yes/yes | P + T   | Chlorhexidine vs. placebo                             | No difference                                                           |
| RT     | Foote et al. (117) | Yes/yes/yes                          | P + T       | Chlorhexidine vs. placebo                             | Slight aggravation                                                      |
| CT + RT | Ferretti et al. (247) | Yes/yes/yes | P + T   | Chlorhexidine vs. placebo                             | Significant reduction of incidence and severity in the CT group only     |
| CT + RT | Rahn et al. (157) | Yes/yes/no                           | P           | Nystatin, rutosides, immuno-globulines, panthenol ± PVP-iodine | Significant reduction                                                   |
| CT + RT | Adamietz et al. (159) | Yes/yes/no | P         | Nystatin, rutosides, immuno-globulines, panthenol ± PVP-iodine | Significant reduction                                                   |
| CT + RT | Hasenau et al. (248) | No/yes/no                           | P           | Hydrogen peroxide, PVP-iodine, dexpanthenol, nystatin | Lower incidence and severity of oral mucositis                           |
| RT     | Spijkervet et al. (227) | No/yes/no   | P         | Lozenges of polymyxin, tobramycin, amphotericin vs. historical controls | Lower incidence of mucositis                                             |
| RT     | Mathews et al. (228) | Yes/yes/no                           | P           | Sucralfate + (ciprofloxacin or ampicillin) + clotrimazole vs. sucralfate | Significant reduction of incidence and severity                          |
| RT     | Symonds et al. (249) | Yes/yes/yes                          | P           | Pastilles containing polymyxin, tobramycin, amphotericin vs. placebo | Significant reduction of severe mucositis                                |
| RT     | Okuno et al. (250)  | Yes/yes/yes                          | P + T       | Lozenges of polymyxin, tobramycin, amphotericin vs. placebo | Significant reduction of oral discomfort, no objective difference       |
| RT     | Okuno et al. (250)  | Yes/yes/no                           | T           | Amphotericin + colistin + tobramycin + chlorhexidine vs. placebo | Decreased oral discomfort                                               |
| RT     | Symonds et al. (249) | Yes/yes/yes                          | P           | Amphotericin + tobramycin + polymyxin vs. placebo     | Significant reduction of the incidence of severe mucositis              |
| RT     | Spijkervet et al. (227) | No/yes/no | P         | Amphotericin + tobramycin + polymyxin vs. historical chlorhexidine or placebo group | Significant reduction of severity of mucositis                           |
| RT     | Carl et al. (251)  | No/yes/no                            | P + T       | Chamomile vs. historical group                        | Low incidence of mucositis                                              |
| RT     | Fidler et al. (126) | Yes/yes/yes                          | P           | Chamomile vs. placebo, cryoprophylaxis in all patients | No difference                                                           |
| RT     | Abdelaal et al. (252) | No/no/no    | P         | High-dose betamethasone                               | Impressive prevention of mucositis incidence                             |
| RT     | Kim et al. (253)   | Yes/yes/yes                          | P + T       | Benzydamine vs. placebo                               | Significant reduction (less pain)                                       |

(Continued)
### TABLE 10 | Continued

| Injury | Reference | Randomized/controlled/double blind | P/T | Application/doses | Results |
|--------|-----------|-----------------------------------|-----|-------------------|---------|
| RT     | Epstein et al. (156) | Yes/yes/yes | P + T | Benzydamine vs. placebo | Significant reduction of incidence and severity |
| RT     | Samaranayake et al. (254) | Yes/no/no | P | Benzydamine vs. chlorhexidine | No difference (more discomfort) |
| CT + RT | Prada et al. (255) | Yes/yes/yes | P + T | Benzydamine vs. placebo | Significant reduction |
| RT     | Huang et al. (73) | Yes/yes/yes | P | Parenteral glutamine vs. placebo | No difference |
| CT + RT | Portepec et al. (256) | No/yes/no | P | PGE2 or nothing | Significant reduction (less pain) |
| RT     | Matejka et al. (171) | No/yes/no | T | PGE2 tablets four times a day | Reduction of mucositis severity |
| CT + RT | Hasenau et al. (256) | No/no/no | P + T | P + T hydrogen peroxide, nystatin | Lower incidence of mucositis |
| RT     | Rothwell et al. (100) | Yes/yes/yes | P | Hydrocortisone, nystatin, tetracyclines, diphenhydramine vs. placebo | Significant reduction of incidence |
| RT     | Maciejewski et al. (257) | No/yes/no | P | Applied to one side of buccal mucosa | Significant reduction compared with contralateral side |
| RT     | Barker et al. (100) | Yes/yes/yes | Oral hygiene + sucralfate vs. diphenhydramine + kaolin-pectin | No difference |
| CT + RT | Mills (197) | Yes/yes/yes | T | Capsaicin in a candy vehicle | Significant temporary pain relief |
| CT + RT | Bourhis et al. (258) | No/yes/no | P | Beta-carotene or nothing | Decreased severity in the treatment group |
| RT     | Kourkourakis et al. (259) | Yes/yes/yes | P | Amifostine or saline | Significant reduction of mucositis |
| RT     | Schonekas et al. (260) | No/yes/no | P | Amifostine vs. controls | Significant reduction of mucositis |
| RT     | Wagner et al. (261) | Yes/yes/no | P | Amifostine or nothing | Significant reduction of mucositis |
| CT + RT | Buntzell et al. (262) | Yes/yes/no | P | Amifostine or nothing | Significant reduction of mucositis and xerostomia |
| CT + RT | Peters et al. (263) | Yes/yes/no | P | Amifostine or nothing | No significant difference |
| CT + RT | Vacha et al. (264) | Yes/yes/no | P | Amifostine or nothing | Trend toward reduction of mucositis |
| CT + RT | Tsaki et al. (199) | Yes/yes/no | P | Vitamins C + E, glutathione ± azelastine | Significant reduction |
| RT     | Pillsbury et al. (165) | Yes/yes/yes | P | Indomethacin vs. placebo | Significant delay of mucositis onset |
| CT + RT | Mose et al. (201) | No/yes/no | P | l.m. immunoglobulins | Significant reduction in CT + RT patients, no difference in RT |
| RT     | Wagner et al. (265) | Yes/yes/no | P | RT + GM-CSF vs. historical control | Significant lower severity of mucositis |
| RT     | Maikonen et al. (140) | No/yes/no | P | Sucralfate ± GM-CSF | No difference |
| RT     | Kannan et al. (193) | No/yes/no | P | RT + GM-CSF | Lower incidence of severe mucositis |
| CT + RT | Rosso et al. (266) | No/yes/no | P | GM-CSF vs. historical control sig. lower incidence of severe mucositis | Lower incidence of severe mucositis |
| RT     | Mascarin et al. (267) | Yes/yes/no | P | RT ± G-CSF | Less treatment interruptions only |
| RT     | Schneider et al. (268) | Yes/yes/yes | P | RT ± G-CSF | Significant reduced incidence of severe mucositis |
| CT + RT | Bubley et al. (236) | Yes/yes/yes | P | Acyclovir vs. placebo | No impact upon incidence and severity of mucositis |

RT, radiotherapy; P/T, prevention or treatment; CT, chemotherapy; HD-CT, high-dose chemotherapy; BMT, bone marrow transplantation; TBI, total body irradiation; i.m., intramuscular; GM-CSF, granulocyte-macrophage colony-stimulating factor.

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Lidocaine and holding 5 mL of it in mouth for 1 min then spitting it out before meals have been shown to be helpful for better alimentation (101). One clinical trial showed dyclonine hydrochloride to have a superior effect among all other agents without significant difference recorded (102). The most effective anesthetic agent is still to be determined. Benzocaine gel is another locally applied bioadhesive agent containing benzyl alcohol (10%) and is...
used to relieve pain and facilitate eating and drinking in mild and moderate RIOM (103). Benzocaine-containing lozenges are diluted to alleviate the pain sensation and mechanical sensitivity in mild to moderate OM (104, 105). The “magic mouthwash” (lidocaine, diphenhydramine, magnesium aluminum hydroxide) and morphine mouth washes are preferable and have been reported by patients to be effective in alleviating pain in RIOM (106–108).

5. The application of corticosteroids mouthwashes has shown promising results. The limited availability of a large-scale data is a gap that should be bridged through relevant clinical studies (109).

6. Allopurinol and uridine were shown to be effective in reducing 5-fluorouracil oral toxicity in preclinical studies (110–114). Despite these results, they were ineffective approaches in randomized clinical trials as a therapy to reduce the treatment-related oral toxicity (115, 116).

7. Chlorhexidine is a biguanidine exhibiting broad-spectrum antibacterial and antimitotic activities. The clinical trials done with chlorhexidine concluded that it cannot be recommended for the prophylaxis or the treatment of RIOM (117–120). Alcohol-containing chlorhexidine mouth rinse should be avoided during clinical oral ulceration. Therefore, the MASCC/ISOO guidelines recommend against the use of chlorhexidine mouth rinse for prevention or treatment OM (33).

8. Artificial saliva spray is an over-the-counter agent frequently used to alleviate mucosal dryness in mild cases of RIOM (121).

9. Chamomile has anti-inflammatory, antipeptic, anti-spasmodic, and antibacterial effects. It was investigated with encouraging results as an emulsion therapy for CT-induced mucositis (122–126). Studies are needed for its application in RIOM to determine its efficacy.

10. Honey has been investigated in many preclinical studies due to its mucosal protective effect that was confirmed as a reduction in the incidence and severity of RIOM (127–132). However, the available clinical trial used only Manuka honey, and it appears to contradict the preclinical studies' results (133). More studies are needed to confirm the therapeutic potential of honey in RIOM.

11. Sucralfate is a basic aluminum salt of sucrose sulfate that was used as mouthwash to reduce the intensity of RIOM and CCRT-induced mucositis as well (39, 100, 134–151). Despite its long application history, it is considered to have little effect in RIOM when compared to oral hygiene and symptomatic mucositis therapy (2). MASCC/ISOO Mucositis Guidelines did not find enough evidence for the beneficial application of sucralfate in OM (34).

12. Vitamin A and its derivatives have anti-inflammatory and epithelial proliferative effect (152). Topical tretinoin has been shown to reduce the oral complications during bone marrow (BM) transplantation (153).

13. Vitamin-E (tocopherol) has been shown to lower the oxidative damage of the oral mucosa and reduce the incidence of symptomatic RIOM in head and neck cancer patients in a randomized double-blind clinical trial (152, 154).

14. Sodium alginate was shown to reduce the discomfort and the severity of RIOM in a randomized clinical trial (155).

15. Benzydamine hydrochloride is a non-steroidal antimicrobial, anti-inflammatory, anesthetic, and analgesic agent that reduces pro-inflammatory cytokine production, scavenges the ROS, and acts as membrane stabilization and as an antimicrobial agent (118, 156, 157). When compared with chlorhexidine, patients with RIOM treated with benzydamine hydrochloride found more discomfort (118). Benzydamine hydrochloride failed to be approved by the US-FDA for OM management. Because of a negative interim analysis, a recent phase III trial for benzydamine hydrochloride therapy in RIOM was stopped (33).

16. Povidone-iodine is an antiviral, antibacterial, and anti-fungal agent. Randomized clinical study showed that povidone-iodine reduces the incidence, severity, and duration of CCRT-induced OM, in addition to its advantages of being cheap and easily applied (118, 158–160).

17. Capsaicin is an inhibitor of neutrophils that reduces the pain sensation. One clinical trial showed that orally applied capsaicin caused temporary relief of pain in mucositis caused by RT and CT (161). However, more studies are needed for optimization of its analgesic effect.

II Systemically applied agents

1. Cyclooxygenase-2 inhibitors that have different mechanisms of action were applied in the management of RIOM. They suppress NF-κB, reduce pro-inflammatory cytokine production, and inhibit angiogenesis (162–164). A randomized placebo-controlled trial showed that prophylactic systemic administration of indomethacin, a COX-2 inhibitor, significantly lowered the severity and delayed the onset of RIOM (165). In addition, PG E1 and E2 showed improvement in OM induced by RT and CT in few studies; however, their application is still controversial (166–172).

2. N-acetylcysteine is an antioxidant that has been shown to suppress NF-κB activation (173, 174). Because of its proven radioprotective role in RT-induced dermatitis, bone injury, liver toxicity, and intestinal injury (173–188), N-acetylcysteine was recommended as a candidate for a trial in RIOM. In a placebo-controlled phase II trial of patients with head and neck cancer, N-acetylcysteine significantly reduced the severity of RIOM (33).

3. Colony-stimulating factor and granulocyte-macrophage colony-stimulating factor (GM-CSF) systemic therapy recruit neutrophils to the tissue injury site (189). Local application of GM-CSF mouthwash was shown marked alleviation of RIOM in several studies (2). Nevertheless, in clinical trials, its systemic application therapeutic value appears controversial (190, 191). SC GM-CSF reduced the severity of OM in patients treated with accelerated RT (192). In another randomized clinical study, systemic GM-CSF reduced the incidence of RIOM; however,
| NCT number | Title | Conditions | Last updated |
|------------|-------|------------|--------------|
| NCT02508389 | A Study of GC4419 Protection against Radiation Induced Oral Mucositis in Patients with Head & Neck Cancer | Radiation-Induced Oral Mucositis | 23 November 2015 |
| NCT00698204 | Cox-2 Inhibition in Radiation-Induced Oral Mucositis | Oral Mucositis | 7 May 2014 |
| NCT00814359 | Magic Mouthwash Plus Sucralfate Versus Benzydamine Hydrochloride for the Treatment of Radiation-Induced Mucositis | Head and Neck Cancer|Mucositis | 19 January 2011 |
| NCT01400620 | Safety and Efficacy of IZN-6N4 Oral Rinse for the Prevention of Oral Mucositis in Patients with Head and Neck Cancer | Oral Mucositis | 9 November 2015 |
| NCT00051441 | Safety & Efficacy Study of Benzydamine Oral Rinse for the Treatment of Oral Mucositis (Mouth Sores) Resulting From Radiation Therapy for Cancer of the Oral Cavity, Oropharynx, or Nasopharynx | Stomatitis|Radiation Effects | 17 May 2011 |
| NCT02608879 | Oral Care Protocol for the Management of Chemotherapy and Radiation Therapy-Induced Oral Mucositis | Oral Mucositis|Oral Cancer | 17 November 2015 |
| NCT01465308 | The Effect of Honey on Xerostomia and Oral Mucositis | Head and Neck Cancer | 7 October 2014 |
| NCT01375088 | Assessing the Preventing and Therapeutic Effect of Propolis in Radiotherapy Induced Mucositis of Head and Neck Cancers | Radiation-induced Mucositis of Oral Mucous Membranes | 21 November 2012 |
| NCT01066741 | Prevention of Radiation-induced Severe Oral Mucositis in Oral Cavity, Oropharynx, Hypopharynx, and Cervix Cancer | Oropharynx Cancer|Hypopharynx Cancer | 31 October 2012 |
| NCT00006994 | S9908: Glutamine in Treating Mucositis Caused by Radiation Therapy in Patients with Newly Diagnosed Cancer of the Mouth or Throat | Cancer-related Problem/Condition|Head and Neck Cancer|Pain | 17 November 2015 |
| NCT02430298 | Topical/Oral Melatonin for Preventing Concurrent Radiochemotherapy Induced Oral Mucositis/ Xerostomia Cancer Patients | Head and Neck Cancer | 12 May 2015 |
| NCT02397486 | The Impact of Pentoxifylline and Vitamin E on Radiotherapy-induced Toxicity in Head & Neck Cancer Patients | Head and Neck Neoplasms | 27 May 2015 |
| NCT01941992 | Role of SAMITAL® in the Relief of Chemoradiation (CT-RT) Induced Oral Mucositis in Head and Neck Cancer Patients | Head-and-neck Squamous Cell Carcinoma|Oral Mucositis | 24 March 2015 |
| NCT01318889 | Dexamethasone Mouthwash to Treat Oral Mucositis | Oral Mucositis ([Ulcerative] Due to Radiation | 5 July 2011 |
| NCT02016807 | ZeroTolerance Mucositis: Managing Oral and Alimentary Mucositis with High Potency Sucralfate—ProThelial | Oral Mucositis|Nausea|Vomiting|Diarrhea | 16 December 2013 |
| NCT00293462 | GM-CSF Mouthwash for Preventing and Treating Mucositis in Patients Who Are Undergoing Radiation Therapy for Head and Neck Cancer | Head and Neck Cancer|Mucositis|Radiation Toxicity | 14 May 2013 |
| NCT00728585 | Palifermin in Preventing Oral Mucositis Caused by Chemotherapy and/or Radiation Therapy in Young Patients Undergoing Stem Cell Transplant | Breast Cancer|Graft vs. Host Disease|Kidney Cancer|Leukemia|Lymphoma|Mucositis|Multiple Myeloma|Plasma Cell Neoplasm|Myelodysplastic Syndromes|Neuroblastoma|Ovarian Cancer|Sarcoma|Testicular Germ Cell Tumor | 30 May 2013 |
| NCT02604329 | Feasibility Study of a Protocol to Treat Pediatric Oral Mucositis by Low-Level Laser Therapy | Oral Mucositis | 12 November 2015 |
| NCT02075749 | Comparing Triamcinolone Acetonide Mucoadhesive Films with Licorice Mucoadhesive Films | Mucositis | 9 July 2014 |
| NCT01385748 | Efficacy and Safety Study of Clonidine Lauriad® to Treat Oral Mucositis | Oral Mucositis | 7 June 2015 |
| NCT01707641 | Effect of Lactobacillus Brevis CD2 in Prevention of Radio-chemotherapy Induced Oral Mucositis in Head and Neck Cancer | Mucositis | 19 May 2014 |

(Continued)
| NCT number     | Title                                                                 | Conditions                                                                 | Last updated    |
|---------------|-----------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------|
| NCT00613743   | Effect of Topical Morphine (Mouthwash) on Oral Pain Due to Chemo- and/or Radiotherapy Induced Mucositis | Cancer|Mucositis                                                                 | 12 January 2010 |
| NCT00431925   | Can Cytokines Predict the Severity of Acute Mucositis and the Need for Gastrostomy Tubes (PEG)? | Oral Mucositis|Xerostomia|Weight Loss|Head and Neck Cancer | 9 August 2007 |
| NCT01806272   | Recombinant Human Granulocyte Macrophage Colony-Stimulating Factor (rhGM-CSF) Treating Oral Mucositis | Nasopharyngeal Cancers                                                     | 27 March 2013   |
| NCT01876407   | Effectiveness of Low Energy Laser Treatment in Oral Mucositis Induced by Chemotherapy and Radiotherapy in Head and Neck Cancer | Oral Mucositis                                                             | 30 April 2012   |
| NCT00584597   | A Trial of Homeopathic Medication TRAUMEEL S for the Treatment of Radiation-Induced Mucositis | Mucositis|Head and Neck Cancer                                                     | 10 December 2010 |
| NCT00615420   | A Randomized Placebo-Controlled Trial of Manuka Honey for Oral Mucositis Due to Radiation Therapy for Cancer | Radiotherapy-Induced Mucositis|Head and Neck Cancer                                                       | 22 May 2012     |
| NCT01898091   | Herbal Mouthrinse for Oral Mucositis Study                            | Oral Mucositis                                                             | 21 September 2015|
| NCT01772706   | Laser Mucite ORL: Effectiveness of Laser Therapy for Mucositis Induced by a Radio-chemotherapy in Head and Neck Cancer | Oral Squamous Cell Carcinoma|Squamous Cell Carcinoma of Oropharynx|Squamous Cell Carcinoma of Hypopharynx|Oral Mucositis | 17 January 2013 |
| NCT01837446   | Morphine Mouthwash for Management of Oral Mucositis in Patients with Head and Neck Cancer | Stomatitis                                                                 | 22 April 2013   |
| NCT02309437   | Early Use of Opioid to Control Local Mucosa Pain Induced by Irradiation in Nasopharyngeal Carcinoma Patients | Nutrition Disorders|Quality of Life                                                             | 3 December 2014 |
| NCT01668849   | Edible Plant Exosome Ability to Prevent Oral Mucositis Associated with Chemoradiation Treatment of Head and Neck Cancer | Head and Neck Cancer|Oral Mucositis                                                             | 12 May 2015     |
| NCT01975688   | A Pharmacokinetic Study of Single Doses of Sativex in Treatment-Induced Mucositis | Head and Neck Squamous Cell Carcinoma                                      | 12 May 2015     |
| NCT01252498   | Evaluation of the Role of Prostaglandins In Radiation-induced Mucositis | Cancer of the Head and Neck|Radiotherapy                                                               | 3 February 2014  |
| NCT01840436   | Efficacy of MUCIPLIQ on the Incidence of Radio-chemotherapy-Induced Mucositis in Patients Suffering From Oral Cancer | Oral Mucositis|Carcinoma in Situ of Upper Respiratory Tract | 15 May 2014     |
| NCT00699569   | Hyperimmune Colostrum and Oral Mucositis                              | Head and Neck Cancer                                                       | 22 July 2008    |
| NCT02555501   | Oral Mucositis and Laser Therapy Associated with Photodynamic Therapy  | Oral Mucositis                                                             | 18 September 2015|
| NCT02050503   | Intranasal Transmucosal Fentanyl Pectin for Breakthrough Cancer Pain in Radiation-Induced Oropharyngeal Mucositis | Breakthrough Pain|Mucositis|Radiotherapy|Chemotherapy|Head and Neck Cancer | 16 March 2015 |
| NCT01883908   | Acupuncture in Reducing the Severity of Chemoradiation-Induced Mucositis in Patients with Oropharyngeal Cancer | Mucositis|Oropharyngeal Cancer                                                       | 3 September 2015 |
| NCT01432873   | Oral Selenium Therapy for the Prevention of Mucositis                 | Mucositis|Hematopoietic Stem Cell transplantation                                    | 31 May 2012     |
another study did not show the same result (140, 193). Systemic GM-CSF therapeutic potential is still controversial and requires further investigation.

4. Transforming growth factor-β inhibits the oral basal cell proliferation. It was shown to reduce the incidence of CT-induced mucositis (194). However, a reliable clinical trial is needed to assess its therapeutic potential with RT.

5. Beta-carotene’s antioxidative effect (195, 196) was implemented in a randomized clinical trial where there was a significant reduction in the incidence of severe OM in CCRT (197).

6. Analgesics are strong candidates for alleviating the pain related to RIOM. A retrospective study showed that opioid therapy remains a cornerstone for OM pain management in CCRT, as suggested by the MASCC/ISOO guidelines (33, 198).

7. Azelastine is a potent second-generation selective histamine antagonist that is used as an anti-inflammatory and antioxidant agent. One clinical trial showed significant reduction in the incidence and the severity of OM with CCRT (199).

8. Propantheline is an anticholinergic agent that reduces the salivary flow. One clinical trial showed that propantheline and oral cryotherapy may be feasible and effective in reducing mucosal toxicity in cancer patients receiving high-dose CT (200). However, studies are needed for RIOM.

9. Immunoglobulins have lower salivary and systemic levels in patient receiving antineoplastic therapy. They have immune-modulating and anti-inflammatory properties. Intravenous or intramuscular immunoglobulins are frequently applied as prophylactic and therapeutic options for RIOM (158, 201).

10. Systemic corticosteroids were used in RIOM management. A double-blind placebo-controlled randomized trial has shown a tendency toward reduced RT interruption in prednisone-treated relative to placebo-treated patient groups without evidence of reduced RIOM incidence or severity (202).

11. Pentoxifylline regulates endotoxin-induced production of TNF-α. Although the preclinical studies showed significant reduction in the severity of RIOM with pentoxifylline (203), the clinical trials show that it is not effective in reducing the antineoplastic oral toxicity (204–208).

12. Salicylic acid derivatives should be avoided due to the increased risk for bleeding (34–36).

13. Sphingomyelinase and ceramide synthase inhibitors can be a potential candidate for RIOM. They inhibit the ceramide pathway-mediated RT-induced apoptosis (209–216). No current clinical trials have been started for them yet.

III Oral microbial load reduction agents

1. Antimicrobial agents showed beneficial effect in prophylaxis and reduction of the severity of RIOM. RT injury leads to a change in the mucosal membrane barrier, salivary flow, and composition which favor the growth and colonization of different bacterial species, mainly Gram-negative bacteria. Many preclinical studies have investigated the therapeutic effect of different antimicrobial agents in RIOM (217–220). The FDA has granted fast track designation for brilacidin-OM, an oral rinse formulation of defensin-mimetic brilacidin (221–223), for the prevention of OM. There is a current phase II clinical trial to evaluate the safety and efficacy of brilacidin oral rinse in patients with head and neck cancer (NCT02324335).

2. Fungal infections are not involved directly in the development in RIOM, rather they can complicate the situation, especially in immunocompromised patients, and that is why the use of antifungal agents have been applied in RIOM treatment. A clinical study has shown that systemic fluconazole prophylaxis caused a significant beneficial effect on the severity of OM and on radiotherapy interruptions (224). The same effect was noted in randomized clinical trials investigating clotrimazole (2). Some oral mouthwashes containing amphotericin B have shown similar effects; however, due to carrier allergy, there might be a limitation in its application (225).

3. Antibacterial agents have been investigated in mucositis depending on a hypothesis stating that aerobic species (e.g., Pseudomonas spp. and Staphylococcus epidermidis), anaerobic bacteria (e.g., Bacteroides spp., and Veillonella spp.), and endotoxin of aerobic Gram-negative bacilli are considered a main contributor in the development of the secondary infection phase in RIOM (2, 226). Antimicrobial lozenges with polymyxin-E and tobramycin have protected against severe mucositis when compared to placebo or chlorhexidine (227). In addition, ciprofloxacin- and ampicillin-containing mouthwashes showed similar effect (228, 229).

4. Antiviral agents against herpes simplex virus (HSV) type I and varicella zoster virus (VZV) were applied topically and systematically. HSV and VZV are the most common viral infections that aggravate RIOM in seropositive and myelo-suppressed patients (230–232). Systemic and topical acyclovir was investigated and applied in RIOM management and caused a reduction in the oral herpetic infections without an evident prophylactic role against OM itself (233–238).

CELLULAR THERAPIES FOR RIOM

Bone marrow-derived mesenchymal stromal cells (bmMSCs) therapy have been applied in fractionated radiation-induced OM where the administration of a systemic single dose of six million MSCs resulted in a significant decrease in ED₉₀ (the RT dose that produces ulcer in 50% of irradiated mice) (239). The first MSCs therapy for RIOM was done in 2014 by Schmidt et al. (239). They concluded that transplantation of BM or bmMSCs could modulate RIOM in fractionated RT, depending on the time of transplantation (239). Nevertheless, in another study, the authors concluded that bmMSCs transplantation had no therapeutic benefits on RIOM in single-dose RT when compared to the therapeutic effect of mobilization of endogenous BM stem
cells (240). More studies are needed in this field building on the initial studies, which showed significant and clinically relevant therapeutic gain of MSCs therapy for RIOM (Table 10).

**Clinical Trials for RIOM**

Table 10 summarizes the clinical trials that were done until 2001 for prevention (P) and treatment (T) of RIOM (2). The current clinical trials for RIOM are summarized in Table 11 and were found when searching the clinical trials website of the National Institute of Health for RIOM. We have documented 40 RIOM treatment and prevention clinical trials.

**CONCLUSION**

Despite its high incidence, RIOM is a self-limited radiotherapy-induced normal tissue injury. It is a dose-limiting toxicity in most cases of head and neck cancer patients. However, in moderately to severely sick patients, it could be a lethal injury. Many preclinical and clinical studies have been conducted for the prevention and treatment of RIOM. Currently, there are numerous prevention and treatment strategies for RIOM. However, there is no single agent or management regimen that has been agreed upon between caregivers that significantly improves RIOM to a clinically relevant and satisfactory standard. Nevertheless, the current guidelines recommend good oral care, IMRT, radiation shields, palifermin, amifostine, and cryotherapy for RIOM prevention. RIOM treatment focuses on palliative measures and symptoms relief; e.g., pain management, nutritional support, good oral hygiene, and reduced oral microbial load. Interestingly, mesenchymal stromal cells therapy for RIOM shows promise for potential therapeutic and clinically relevant benefits. However, more studies are still needed to confirm such therapeutic potential.

**AUTHOR CONTRIBUTIONS**

OM: conception and design, collection and/or assembly of data, review writing, and final approval of the review. NE: conception, design, and final approval of the review. TM: conception and design, financial support, and final approval of the review.

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Maria et al.  Radiation-Induced Oral Mucositis

38. Zheng C, Cotrim AP, Sunshine AN, Sugito T, Liu L, Sowers A, et al. Prevention of radiation-induced oral mucositis: a video-capule endoscopy study. *Bone Marrow Transplant* (2008) 42(5):337–43. doi:10.1038/bmt.2008.168

41. Blijlevens N, Sonis S, Palifermin (recombinant keratinocyte growth factor-1): a pleiotropic growth factor with multiple biological activities in preventing chemotherapeutic- and radiotherapy-induced mucositis. *Ann Oncol* (2007) 18(5):817–26. doi:10.1093/annonc/mdl332

45. Beaven AW, Shea TC. Recombinant human keratinocyte growth factor palifermin reduces oral mucositis and improves patient outcomes after stem cell transplant. *Drugs Today (Barc)* (2007) 43(7):461–73. doi:10.1358/dt.2007.43.7.1119723

46. Dorr W, Reichel S, Spekl K. Effects of keratinocyte growth factor (palifermin) administration protocols on oral mucositis (mouse) induced by fractionated irradiation. *Radiother Oncol* (2005) 75(1):99–105. doi:10.1016/j.radonc.2004.12.006

57. Komaki R, Lee JS, Milas L, Lee HK, Fossella FV, Herbst RS, et al. Effect of amifostine on acute toxicity from concurrent chemotherapy and radiotherapy in patients with head and neck squamous cell carcinoma treated with high-dose chemotherapy and autologous hematopoietic stem-cell transplantation. *Clin Cancer Res* (2005) 11(19):7207–14. doi:10.1158/1078-0432.CCR-04-1324

58. Amrein PC, Clark JR, Supko JG, Fabian RL, Wang CC, Colevas AD, et al. Phase II prospective, randomized, phase III trial. *Int J Radiat Oncol Biol Phys* (2011) 79(3):786–94. doi:10.1016/j.ijrobp.2010.09.030

64. Amrein PC, Clark JR, Supko JG, Fabian RL, Wang CC, Colevas AD, et al. Phase III trial and pharmacokinetics of escalating doses of paclitaxel and concurrent hyperfractionated radiotherapy with or without amifostine in patients with advanced head and neck carcinoma. *Cancer* (2005) 104(7):1418–27. doi:10.1002/cncr.21312

65. Komaki R, Lee JS, Milas L, Lee HK, Fossella FV, Herbst RS, et al. Effects of amifostine on acute toxicity from concurrent chemotherapy and radiotherapy for inoperable non-small-cell lung cancer: report of a randomized comparative trial. *Int J Radiat Oncol Biol Phys* (2004) 58(5):1369–77. doi:10.1016/j.ijrobp.2003.10.005

Frontiers in Oncology | www.frontiersin.org May 2017 Volume 7 Article 89 17
58. Karacutin D, Yucel B, Leblebicioglu B, Aksakal O, Marol O, Incekar O. A randomized trial of amifostine as radioprotector in the radiotherapy of head and neck carcinoma. Biol Oncol (2004) 9(1):23–6.

59. Athanassiou H, Antonadou D, Collarakis N, Kouveli A, Synodinou M, Paraskevadis M, et al. Protective effect of amifostine during fractionated radiotherapy in patients with pelvic carcinomas: results of a randomized trial. Int J Radiat Oncol Biol Phys (2003) 56(4):1154–60. doi:10.1016/S0360-3016(03)00187-1

60. Bardet E, Martin L, Calais G, Tuchais C, Bourhis J, Rhein B, et al. Preliminary data of the GORTEC 2000-02 phase III trial comparing intravenous and subcutaneous administration of amifostine for head and neck tumors treated by external radiotherapy. Semin Oncol (2002) 29(6 Suppl 19):57–60. doi:10.1053/sonc.2002.37348

61. Li CJ, Wang SZ, Wang SY, Zhang YP. Assessment of the effect of local application of amifostine on acute radiation-induced oral mucositis in guinea pigs. J Radiat Res (2014) 55(5):847–54. doi:10.1093/jrr/rtr024

62. Praetorius NR, Mandal TK. Alternate delivery route for amifostine as a radio-/chemo-protecting agent. J Pharm Pharmacol (2008) 60(7):809–15. doi:10.1211/jpp.60.7.0001

63. Kouvaris JR, Kouloulas VE, Vlahos IJ. Amifostine: the first selective-target and broad-spectrum radioprotector. Oncologist (2007) 12(6):738–47. doi:10.1634/theoncologist.12-6-738

64. Eisbruch A. Amifostine in the treatment of head and neck cancer: intravenous administration, subcutaneous administration, or none of the above. J Clin Oncol (2011) 29(2):119–21. doi:10.1200/JCO.2010.31.5051

65. Gu J, Zhu S, Li X, Wu H, Li Y, Hua F. Effect of amifostine in head and neck cancer patients treated with radiotherapy: a systematic review and meta-analysis based on randomized controlled trials. PLoS One (2014) 9(5):e95968. doi:10.1371/journal.pone.0095968

66. Keus R, Noach P, de Boer R, Lebesque J. The effect of customized beam shaping on normal tissue complications in radiation therapy of parotid gland tumors. Radiat Oncol (1991) 21(5):211–7. doi:10.1016/S0301-472X(03)00041-9

67. Kaanders JH, Fleming TJ, Ang KK, Maor MH, Peters LJ. Devices valuable in mitigating radiation-induced toxicity in radiation therapy of parotid gland tumors. Int J Radiat Oncol Biol Phys (2002) 53(6):1373–83. doi:10.1016/S0360-3016(01)02520-6

68. Perch SJ, Machtay M, Markiewicz DA, Kligerman MM. Decreased acute radiation-induced toxicity with the use of a novel device. Int J Radiat Oncol Biol Phys (2003) 56(4):1154–60. doi:10.1016/S0360-3016(03)00187-1

69. Rajagopalan MS, Stone B, Wigema J, Salimi U, Epperly MW, Geoff J, et al. Intraoperative manganese superoxide dismutase-plasmid liposomes ameliorates novel total-body and thoracic radiation sensitivity of NOS1−/− mice. Radiat Res (2010) 174(3):297–312. doi:10.1667/RR2019.1

70. Holley AK, Xu Y, St Clair DK, St Clair WH. RelB regulates manganese superoxide dismutase gene and resistance to ionizing radiation of prostate cancer cells. Ann N Y Acad Sci (2010) 1201:129–36. doi:10.1111/j.1749-6632.2010.05613.x

71. dos Santos Montagner GF, Sagrillo M, Machado MM, Almeida RC, Mostardeiro CP, Duarte MM, et al. Toxicological effects of ultraviolet radiation on lymphocyte cells with different manganese superoxide dismutase AlA16Val polymorphism genotypes. Toxicol In Vitro (2010) 24(5):1410–6. doi:10.1016/j.tiv.2010.04.010

72. Holley AK, St Clair DK. Preventing Dr. Jekyll from becoming Mr. Hyde: is manganese superoxide dismutase the key to prevent radiation-induced neo-plastic transformation? Cancer Biol Ther (2009) 8(20):1972–3. doi:10.4161/cbt.8.20.9941

73. Josson S, Xu Y, Fang F, Dhar SK, St Clair DK, St Clair WH. RelB regulates manganese superoxide dismutase gene and resistance to ionizing radiation of prostate cancer cells. Oncogene (2006) 25(10):1554–9. doi:10.1038/sj.onc.1201986

74. Guo HH, Zhao HW, Xu ZF, Ma H, Song XL, Guan J, et al. Manganese superoxide dismutase gene transfection of mouse small intestinal epithelial cells protects them from radiation injury. Zhonghua Zhong Liu Za Zhi (2005) 27(11):672–5.

75. Guo HH, Wolfe D, Epperly MW, Huang S, Liu K, Glorioso JC, et al. Gene transfer of human manganese superoxide dismutase protects small intestinal villi from radiation injury. J Gastrointest Surg (2003) 7(2):229–35; discussion 235–6.

76. Guo H, Seixas-Silva JA Jr, Epperly MW, Grettom JF, Shin DM, Bar-Sagi D, et al. Prevention of radiation-induced oral cavity mucositis by plasmid/liposome delivery of the human manganese superoxide dismutase (SOD2) transgene. Radiat Res (2003) 159(3):361–70. doi:10.1667/0033-7587(2003)159[361:PORIOC]2.0.CO;2

77. Guo G, Yan-Sanders Y, Lyn-Cook BD, Wang T, Tamae D, Ogi J, et al. Manganese superoxide dismutase-mediated gene expression in radiation-induced adaptive responses. Mol Cell Biol (2003) 23(7):2362–78. doi:10.1128/MCB.23.7.2362-2378.2003

78. Epperly MW, Bernarding M, Grettom J, Jefferson M, Nie S, Greenberger JS. Overexpression of the transgene for manganese superoxide dismutase (MnSOD) in 3D2 cl 3 cells prevents apoptosis induction by TNF-alpha, IL-3 withdrawal, and ionizing radiation. Exp Hematol (2003) 31(6):465–74. doi:10.1016/S0301-472X(03)00041-9

79. Epperly MW, Sikora CA, DeFilippis SJ, Grettom JA, Zhan Q, Kufe DW, et al. Manganese superoxide dismutase (SOD2) inhibits radiation-induced apoptosis by stabilization of the mitochondrial membrane. Radiat Res (2002) 157(5):568–77. doi:10.1667/0033-7587(2002)157[568:MSDSIR]2.0.CO;2

80. Motoori S, Majima HJ, Ebara M, Kato H, Hirai F, Kakinuma S, et al. Overexpression of mitochondrial manganese superoxide dismutase protects against radiation-induced cell death in the human hepatocellular carcinoma cell line HLE. Cancer Res (2001) 61(14):5382–8.

81. Epperly MW, Kagan VE, Sikora CA, Grettom JE, DeFilippis SJ, Bar-Sagi D, et al. Manganese superoxide dismutase-plasmid/liposome (MnSOD-PL) administration protects mice from esophagitis associated with fractionated radiation. Int J Cancer (2001) 96(4):221–31. doi:10.1002/ijc.1023

82. Epperly MW, Grettom JA, DeFilippis SJ, Greenberger JS, Sikora CA, Liggitt D, et al. Modulation of radiation-induced cytokine elevation associated with esophagitis and esophageal stricture by manganese superoxide dismutase-plasmid/liposome (SOD2-PL) gene therapy. Radiat Res (2001) 155(1 Pt 1):2–14. doi:10.1667/0033-7587(2001)155[0002:MORIC2]2.0.CO;2

83. Kuninaka S, Ichinose Y, Koja K, Toh Y. Suppression of manganese superoxide dismutase augments sensitivity to radiation, hyperthermia and the microvilli of rabbit eyes exposed to UV radiation. Biomed Res Int (2015) 2015:973197. doi:10.1155/2015/973197

84. Eldridge A, Faut M, Wohoshaecl, Grindal DJ, Chromy BA, Li J. Manganese superoxide dismutase interacts with a large scale of cellular and mitochondrial proteins in low-dose radiation-induced adaptive radio-protection. Free Radiol Med Biol (2012) 53(10):1838–47. doi:10.1016/j.freeradiobiomed.2012.08.589

85. Rajagopalan MS, Stone B, Wigema J, Salimi U, Epperly MW, Geoff J, et al. Intraoperative manganese superoxide dismutase-plasmid liposomes ameliorates novel total-body and thoracic radiation sensitivity of NOS1−/− mice. Radiat Res (2010) 174(3):297–312. doi:10.1667/RR2019.1

86. Holley AK, Xu Y, St Clair DK, St Clair WH. RelB regulates manganese superoxide dismutase gene and resistance to ionizing radiation of prostate cancer cells. Ann N Y Acad Sci (2010) 1201:129–36. doi:10.1111/j.1749-6632.2010.05613.x
doxorubicin in colon cancer cell lines by inducing apoptosis. Br J Cancer (2000) 83(7):928–34. doi:10.1054/bjoc.2000.1367

92. Epperly MW, Epstein CJ, Travis EL, Greenberger JS. Decreased pulmonary radiation resistance of manganese superoxide dismutase (MnSOD)-deficient mice is corrected by human manganese superoxide dismutase-plasmid/ liposome (SOD2-PL) intratracheal gene therapy. Radiat Res (2000) 154(4):365–74. doi:10.1667/0033-7587(2000)154[0365:DPSRPM]2.0.CO;2

93. Sasaki H, Akamatsu H, Horio T. Effects of a single exposure to UBV radiation on the activities and protein levels of copper-zinc and manganese superoxide dismutase in cultured human keratinocytes. Photochem Photobiol (1997) 65(4):707–13. doi:10.1111/j.1754-1097.1997.tb01914.x

94. Otero G, Avila MA, Emfietzoglou D, Clerch LB, Massaro D, Notario V. Increased manganese superoxide dismutase activity, protein, and mRNA levels and concurrent induction of tumor necrosis factor alpha in radiation-initiated Syrian hamster cells. Mol Carcinog (1996) 17(4):715–80. doi:10.1002/(SICI)1098-2744(19961217):14<175::AID-MC13.0.CO;2-D

95. Nakano T, Oka K, Taniguchi N. Manganese superoxide dismutase expression correlates with p53 status and local recurrence of cervical carcinoma treated with radiation therapy. Cancer Res (1996) 56(12):2771–5.

96. Lin PS, Ho KC, Sung SJ, Tsai S. Cytotoxicity and manganese superoxide dismutase in cultured human keratinocytes. Lymphokine Cytokine Res (1993) 154(4):365–74. doi:10.1667/0033-7587(2000)154[0365:DPRROM]2.0.CO;2

97. Miller MM, Donald DV, Hagemann TM. Prevention and treatment of radiation-related mucositis. J Laryngol Otol (1994) 108(8):663–5. doi:10.1007/s00520-000-2072-7

98. Ps SK, Balan A, Sankar A, Bose T. Radiation induced oral mucositis. Oral Surg Oral Med Oral Pathol (1992) 10(12):1963–8. doi:10.1200/JCO.1992.10.12.1963

99. Barker G, Loftus L, Cuddy P, Barker B. The effects of sucralfate suspension in irradiated salivary glands. Oral Surg Oral Med Oral Pathol (1990) 71(3):288–93. doi:10.1016/0022-2151(90)90301-R

100. den Dertom J, van Steenbergen WM, Hekkert PM. Effect of topically applied lidocaine and prilocaine on pain induced by thermal and mechanical stimuli in oral mucosa. J Oral Rehabil (2010) 37(1):32–8. doi:10.1111/j.1365-2842.2009.02259.x

101. Maruta Y, Kofuji K, Nishida N, Kamaguchi R. Development of film dosage form containing allopurinol for prevention and treatment of oral mucositis. Invest New Drugs (2012) 30(5):433–9. doi:10.1007/s10637-012-9727-2

102. van den Wyngaert T. Topical honey application to reduce radiation-induced oral mucositis: a therapy too sweet to ignore? J Evid Based Dent Pract (2012) 12(4):203–5. doi:10.1016/j.jebdp.2012.09.011
128. Song JJ, Twumasi-Ankrah P, Salcido R. Systematic review and meta-analysis on the use of honey to protect from the effects of radiation-induced oral mucositis. *Adv Skin Wound Care* (2012) 25(1):23–8. doi:10.1097/01.ASW.0000410867.14586.33

129. Khanal B, Baliga M, Uppal N. Effect of topical honey on limitation of radiation-induced oral mucositis: an intervention study. *Int J Oral Maxillofac Surg* (2010) 39(12):1181–5. doi:10.1016/j.ijom.2010.05.014

130. Bardy J, Molassiotis A, Ryder WD, Mais K, Sykes A, Yap B, et al. A double-blind, placebo-controlled, randomised trial of active manuka honey and standard oral care for radiation-induced oral mucositis. *Br J Oral Surg* (2012) 50(3):221–6. doi:10.1016/j.bjoms.2011.03.005

131. Santos-Silva AR, Rosa GB, Eduardo CP, Dias RB, Brandao TB. Increased risk for radiation-related caries in cancer patients using topical honey for the prevention of oral mucositis. *Int J Oral Maxillofac Surg* (2011) 40(11):1335–6; author reply 1235. doi:10.1016/j.ijom.2011.05.006

132. Arora H, Pai KM, Majia A, Vidyasagar MS, Rajeev A. Efficacy of He-Ne granulocyte macrophage-colony stimulating factor (GM-CSF) and sucralfate in prevention of radiation-induced mucositis: a randomized, placebo-controlled study. *Support Care Cancer* (2012) 20(5):1373–4. doi:10.1007/s00520-011-1587-9

133. High KP, Legault C, Sinclair JA, Cruz J, Hill K, Hurd DD. Low plasma concentrations of retinol and alpha-tocopherol in hematopoietic stem cell transplant recipients: the effect of mucositis and the risk of infection. *Am J Hematol* (2002) 69(3):158–63. doi:10.1002/ajh.10153

134. Nottage M, McLachlan SA, Brittain MA, Oza A, Hedley D, Feld R, et al. Efficacy of sucralfa in prevention of radiation-induced oral mucositis. *Int J Oral Maxillofac Surg* (2003) 32(8):683–9. doi:10.1016/S0901-5027(03)00220-5

135. Epstein JB, Stevenson-Moore P, Jackson S, Mohamed JH, Spinelli JJ. Oral sucralfate suspension for mucositis. *Cancer Invest* (2002) 20(11):1078–84. doi:10.1080/07357900290102761

136. Epstein JB, Stevenson-Moore P, Jackson S, Mohamed JH, Spinelli JJ. Prevention of oral mucositis in bone marrow transplantation: a double-blind, randomised controlled trial of sucralfate. *Ann Oncol* (2001) 12(7):953–5. doi:10.1093/annonc/12.7.953

137. Epstein JB, Stevenson-Moore P, Jackson S, Mohamed JH, Spinelli JJ. Protective effect of alpha-tocopherol in head and neck cancer radiation-induced mucositis: a double-blind randomized trial. *Head Neck* (2004) 26(4):313–21. doi:10.1002/hed.10382

138. Rahn R, Adamietz IA, Böttcher HD, Schafer V, Reimer K, Fleischer W. Povidone-iodine to prevent mucositis in patients during antineoplastic radiochemotherapy. *Dermatology* (1997) 195(Suppl 2):57–61. doi:10.1159/000246032

139. Adamietz IA, Rahn R, Böttcher HD, Schäfer V, Reimer K, Fleischer W. Prophylaxis with povidone-iodine against induction of oral mucositis by radiochemotherapy. *Support Care Cancer* (1998) 6(4):373–7. doi:10.1007/s005200050179

140. Vokurka S, Bystricka E, Koza V, Scudlara J, Pavlicova V, Valenta D, et al. The comparative effects of povidone-iodine and normal saline mouthwashes on oral mucositis in patients after high-dose chemotherapy and APBSCT – results of a randomized multicentre study. *Support Care Cancer* (2005) 13(7):554–8. doi:10.1007/s00520-005-0792-9

141. Berger A, Henderson M, Nadolman W, Duffy V, Cooper D, Saberski L, et al. Oral capsaicin provides temporary relief for oral mucositis pain secondary to chemotherapy/radiation therapy. *J Pain Symptom Manage* (1995) 10(3):243–8. doi:10.1016/0885-3924(95)00130-0

142. Lalla RV, Pilbeam CC, Walsh SJ, Sonis ST, Keefe DM, Peterson DE. Role of the cyclooxygenase pathway in chemotherapy-induced oral mucositis: a pilot study. *Support Care Cancer* (2010) 18(1):95–103. doi:10.1007/s00520-009-0635-1

143. Lopes NN, Flapler H, Chavantes MC, Lalla RV, Yoshimura EM, Alves MT. Cyclooxygenase-2 and vascular endothelial growth factor expression in 5-fluorouracil-induced oral mucositis in hamsters: evaluation of two low-intensity laser protocols. *Support Care Cancer* (2009) 17(11):409–15. doi:10.1007/s00520-009-0603-9
164. Sonis ST, O’Donnell KE, Popat R, Bragdon C, Phekan S, Cocks D, et al. The relationship between mucosal cyclooxygenase-2 (COX-2) expression and experimental radiation-induced mucositis. Oral Oncol (2004) 40(2):170–6. doi:10.1016/j.oraloncology.2003.03.048

165. Pillsbury HC III, Webster WP, Rosenman J. Prostaglandin inhibitor and radiation in advanced head and neck cancers. Arch Otolaryngol Head Neck Surg (1986) 112(5):552–3. doi:10.1001/archotol.1986.03780050070013

166. Kono T, Kaneko A, Matsumoto C, Miyagi C, Ohbuchi K, Mizuhara Y, et al. Multitargeted effects of hangeshatshi for treatment of chemotherapy-induced oral mucositis on inducible prostaglandin E2 production in human oral keratinocytes. Int J Cancer Ther (2014) 13(5):435–45. doi:10.11751/15343754.113520035

167. Hanson WR, Marks JE, Reddy SP, Simon S, Mihalo WE, Tova Y. Protection from radiation-induced oral mucositis by a mouse riming contains the prostaglandin E1 analog, misoprostol: a placebo controlled double blind clinical trial. Adv Exp Med Biol (1997) 406B:811–8.

168. Maltoni M, Sansonni E, Derni S, Milandri C, Martini F, Nanni O, et al. Topical treatment of radiation-induced oral mucositis. Oncol Rep (1996) 3(1):205–8.

169. Hanson WR, Marks JE, Reddy SP, Simon S, Mihalo WE, Tova Y. Protection from radiation-induced oral mucositis by misoprostol, a prostaglandin E1(1) analog: a placebo-controlled, double-blind clinical trial. Am J Ther (1995) 2(11):850–7. doi:10.1097/00045391-199511000-00005

170. Labar B, Mrská M, Pavletič Z, Bogdančík V, Nemeth D, Aurer I, et al. Prostaglandin E2 for prophylaxis of oral mucositis following BMT. Bone Marrow Transplant (1993) 11(5):379–82.

171. Matejka M, Nell A, Kment G, Schein A, Leukauf M, Porteder H, et al. Local benefit of prostaglandin E2 in radiochemotherapy-induced oral mucositis. Br J Oral Maxillofac Surg (1990) 28(2):89–91. doi:10.1016/0266-4356(90)90928-8

172. Pretnar J, Glazar D, Mlakar U, Modic M. Prostaglandin E2 in the treatment of oral mucositis due to radiochemotherapy in patients with haematological malignancies. Bone Marrow Transplant (1989) 4(Suppl):306.

173. He D, Behar S, Roberts JE, Lim HW. The effect of t-cysteine and N-acetylcysteine on porphyrin/heme biosynthetic pathway in cells treated with 5-aminolevulinic acid and exposed to radiation. Photodermatol Photoimmunol Photomed (1996) 12(5):194–9. doi:10.1111/j.1600-0781.1996.tb00199.x

174. Baier JE, Neumann HA, Moeller T, Kissler M, Borchardt D, Ricken D. [Radiation protection through cytokine release by N-acetylcysteine]. Strahlenther Onkol (1996) 172(2):91–8.

175. Ozgur E, Sahin D, Tomruk A, Uducu M, Oktar D, Guler K, Sempici Dinçel A, Altan N, et al. The effects of N-acetylcysteine and epigallocatechin-3-gallate on liver tissue modifications and cell death in the treatment of methotrexate-induced hepatic toxicity. Int J Radiat Biol (2005) 81(9):877–86. doi:10.1080/095530004200023760

176. Li F, Meng Z, Zhang G, Xing Y, Feng L, Fan S, et al. N-acetylcysteine relieves oxidative stress and protects hippocampus of rat from radiation-induced apoptosis by inhibiting caspase-3. Biomed Pharmacother (2015) 70:1–6. doi:10.1016/j.biopharm.2014.12.029

177. Kilciksiz S, Demirel C, Evirgen Ayhan S, Erdal N, Gurgül S, Tamer L, et al. The effect of N-acetylcysteine on radiation-induced oral mucositis by oral propantheline and cryotherapy. J BUON (2010) 15(3):577–82.

178. Demirel C, Kilciksiz S, Evirgen-Ayhan S, Gurgül S, Erdal N. The preventive effect of N-acetylcysteine on radiation-induced dermatitis in a rat model. J BUON (2010) 15(3):577–82.

179. Demirel C, Kilciksiz S, Ay Ol, Gürögül S, Ay ME, Erdal N. Effect of N-acetylcysteine on radiation-induced genotoxicity and cytotoxicity in rat bone marrow. J Radiat Res (2009) 50(1):43–50. doi:10.1269/jrr.080066

180. Wu W, Abraham L, Ojyo G, Matthews R, Goldstein G, Erkal N. Effects of N-acetylcysteine amide (NACA), a thiol antioxidant on radiation-induced cytotoxicity in Chinese hamster ovary cells. Life Sci (2008) 82(21–22):1122–30. doi:10.1016/j.lfs.2008.03.016

181. Kilciksiz S, Demirel C, Erdal N, Gürögül S, Tamer L, Ayaz L, et al. The effect of N-acetylcysteine on biomarkers for radiation-induced oxidative damage in a rat model. Acta Med Okayama (2008) 62(6):403–9.

182. Kilciksiz S, Demirel C, Erdal N, Gürögül S, Tamer L, Ayaz L, et al. The effect of N-acetylcysteine on biomarkers for radiation-induced oxidative damage in a rat model. Acta Med Okayama (2008) 62(6):403–9.

183. Mansour HH, Hafez HF, Fahmy NM, Hanañ N. Protective effect of N-acetylcysteine against radiation induced DNA damage and hepatic toxicity in rats. Biochem Pharmacol (2008) 75(3):773–80. doi:10.1016/j.bcp.2007.09.018

184. Low WK, Sun L, Tan MG, Chua AW, Wang DY. t-N-acetylcysteine protects against radiation-induced apoptosis in a cochlear cell line. Acta Otolaryngol (2008) 128(4):440–5. doi:10.1080/1648071762490

185. Kilciksiz S, Demirel C, Erdal N, Gürögül S, Tamer L, Ayaz L, et al. The effect of N-acetylcysteine on biomarkers for radiation-induced oxidative damage in a rat model. Acta Med Okayama (2008) 62(6):403–9.

186. Lieschke GJ, Ramenghi U, O’Connor MP, Sheridan W, Szer J, Morstyn G. Study of oral neutrophil levels in patients receiving G-CSF after autologous marrow transplantation. Br J Haematol (1992) 82(3):595–9. doi:10.1111/j.1365-2141.1992.tb08996.x

187. Kilciksiz S, Demirel C, Gurgül S, Tamer L, Erdal N, Ayaz L, et al. The effect of N-acetylcysteine on oral mucositis induced by a mouse riming contains the prostaglandin E1 analog, misoprostol: a placebo controlled double blind clinical trial. Adv Exp Med Biol (1997) 406B:811–8.

188. Kim JA, Baker DG, Hahn SS, Goodchild WC. Topical use of N-acetylcysteine for reduction of skin reaction to radiation therapy. Semin Oncol (1983) 10(1 Suppl):86–92.

189. Lieschke GJ, Ramenghi U, O’Connor MP, Sheridan W, Szer J, Morstyn G. Study of oral neutrophil levels in patients receiving G-CSF after autologous marrow transplantation. Br J Haematol (1992) 82(3):595–9. doi:10.1111/j.1365-2141.1992.tb08996.x

190. Kilciksiz S, Demirel C, Gurgül S, Tamer L, Erdal N, Ayaz L, et al. The effect of N-acetylcysteine on biomarkers for radiation-induced oxidative damage in a rat model. Acta Med Okayama (2008) 62(6):403–9.

191. Lieschke GJ, Back B, O’Connor MP, Sheridan W, Szer J, Morstyn G. Study of oral neutrophil levels in patients receiving G-CSF after autologous marrow transplantation. Br J Haematol (1992) 82(3):595–9. doi:10.1111/j.1365-2141.1992.tb08996.x

192. Lieschke GJ, Back B, O’Connor MP, Sheridan W, Szer J, Morstyn G. Study of oral neutrophil levels in patients receiving G-CSF after autologous marrow transplantation. Br J Haematol (1992) 82(3):595–9. doi:10.1111/j.1365-2141.1992.tb08996.x

193. Kilciksiz S, Demirel C, Ender N, Gürögül S, Tamer L, Ayaz L, et al. The effect of N-acetylcysteine on biomarkers for radiation-induced oxidative damage in a rat model. Acta Med Okayama (2008) 62(6):403–9.
radiotherapy-induced oral mucositis? Am J Clin Oncol (1997) 20(4):407–11. doi:10.1097/00000421-199708000-00018

202. Leborgne JH, Leborgne F, Zulianezza E, Ortega B, Mezera J. Corticosteroids and radiation mucositis in head and neck cancer. A double-blind placebo-controlled randomized trial. Radiother Oncol (1998) 47(2):145–8. doi:10.1016/S0167-8140(97)00174-6

203. Gruber S, Schmidt M, Bozaksy E, Wofram K, Haagen J, Habelt B et al. Modulation of radiation-induced oral mucositis by pentoxifylline: preclinical studies. Strahlenther Oncol (1995) 171(3):242–7. doi:10.1007/BF00061475

204. Verdi CJ, Garewal HS, Koenig LM, Vaughn B, Burkhead T. A double-blind, randomized, placebo-controlled, crossover trial of pentoxifylline for the prevention of chemotherapy-induced oral mucositis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod (1995) 80(1):36–42. doi:10.1016/S0709-2104(95)00014-X

205. Ferrá C, de Sanjósé S, Lastra CF, Martí F, Mariño EL, Sureda A et al. Pentoxifylline, ciprofloxacin and prednisone failed to prevent transplant-related toxicities in bone marrow transplant recipients and were associated with an increased incidence of infectious complications. Bone Marrow Transplant (1997) 20(12):1075–80. doi:10.1038/sj.bmt.1701023

206. Lopez-Jimenez J, Cancelas JA, Valino JM, Garcia-Larana J, Garcia-Avello A, Kalhs P et al. Interindividual heterogeneity with an increased incidence of infectious complications. Bone Marrow Transplant (1997) 20(12):1075–80. doi:10.1038/sj.bmt.1701023

207. Stockschläder M, Kalhs P, Bozaksy E, Wolfram K, Haagen J, Habelt B et al. Modulation of radiation-induced oral mucositis by pentoxifylline: preclinical studies. Strahlenther Oncol (1998) 171(3):242–7. doi:10.1007/BF00061475

208. Kalhs P, Lechner K, Stockschlader M, Kruger W, Peters S, Zander A. Radiation-induced oral mucositis: a double-blind, randomized, placebo-controlled, crossover trial of pentoxifylline for the prevention of chemotherapy-induced oral mucositis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod (1995) 80(1):36–42. doi:10.1016/S0709-2104(95)00014-X

209. Verdi CJ, Garewal HS, Koenig LM, Vaughn B, Burkhead T. A double-blind, randomized, placebo-controlled, crossover trial of pentoxifylline for the prevention of chemotherapy-induced oral mucositis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod (1998) 87(5):544–51. doi:10.1016/S1079-2104(98)70013-9

210. Bondi E, Baroni C, Prete A, Gatti M, Carrassi A, Lodi G et al. Local antimicrobial therapy of oral mucositis in paediatric patients undergoing bone marrow transplantation. Oral Oncol (1997) 33(5):322–6. doi:10.1016/S0181-9197(97)00359-0

211. Kuroda K, Caputo GA. Antimicrobial polymers as synthetic mimics of host-defense peptides. Wiley Interdiscip Rev Nanomed Nanobiotechnol (2013) 5(1):49–66. doi:10.1002/wan.1199

212. Takahashi H, Palermo EF, Yasuhara K, Caputo GA, Kuroda K. Molecular design, structures, and activity of antimicrobial peptide-mimetic polymers. Macromol Biosci (2013) 13(1):1285–99. doi:10.1002/mabi.201300126

213. Scott RW, Tew GN. Mimics of host defense proteins; strategies for translation to therapeutic applications. Carr Top Med Chem (2017) 17(5):576–89.

214. Nicolato-Galitis O, Velegraki A, Sotiropoulou-Lontou A, Dardoufas K, Kouloulas V, Kyprianou K et al. Effect of fluconazole antifungal prophylaxis on oral mucositis in head and neck cancer patients receiving radiotherapy. Support Care Cancer (2006) 14(1):44–51. doi:10.1007/s00520-005-0385-2

215. Levévre JL, Domenge C, Study Group of Mucositis. A comparative study of the efficacy and safety of fluconazole oral suspension and amphoterin B oral suspension in cancer patients with mucositis. Oral Oncol (2002) 38(4):337–42. doi:10.1016/S1388-8375(01)00063-X

216. Shenev JL. Combination and single-agent empirical antibacterial therapy for febrile cancer patients with neutropenia and mucositis. NCI Monogr (1990) 9:117–22.

217. Spijkervet FK, Van Saene HK, Van Saene JJ, Panders AK, Vermey A, Mehta DM et al. Acyclovir on the radiation-induced oral mucositis in irradiated head and neck cancer patients. J Exp Ther Oncol (1996) 12(2):135–8.

218. Spijkervet FK, Van Saene HK, Van Saene JJ, Panders AK, Vermeulen A, Mehta DA et al. Mucositis prevention by selective elimination of the oral flora on mucositis in irradiated head and neck cancer patients. J Exp Ther Oncol (1996) 1(6):173–7. doi:10.1002/jso.2930460309

219. Matthews RH, McNal R. Prevention of mucositis in irradiated head and neck cancer patients. J Exp Ther Oncol (1996) 12(2):135–8.

220. Spijkervet FK, Van Saene HK, Van Saene JJ, Panders AK, Vermeulen A, Mehta DA et al. Mucositis prevention by selective elimination of the oral flora on mucositis in irradiated head and neck cancer patients. J Exp Ther Oncol (1996) 12(2):135–8.

221. Spijkervet FK, Van Saene HK, Van Saene JJ, Panders AK, Vermeulen A, Mehta DA et al. Mucositis prevention by selective elimination of the oral flora on mucositis in irradiated head and neck cancer patients. J Exp Ther Oncol (1996) 12(2):135–8.

222. Spijkervet FK, Van Saene HK, Van Saene JJ, Panders AK, Vermeulen A, Mehta DA et al. Mucositis prevention by selective elimination of the oral flora on mucositis in irradiated head and neck cancer patients. J Exp Ther Oncol (1996) 12(2):135–8.

223. Spijkervet FK, Van Saene HK, Van Saene JJ, Panders AK, Vermeulen A, Mehta DA et al. Mucositis prevention by selective elimination of the oral flora on mucositis in irradiated head and neck cancer patients. J Exp Ther Oncol (1996) 12(2):135–8.

224. Nicolato-Galitis O, Velegraki A, Sotiropoulou-Lontou A, Dardoufas K, Kouloulas V, Kyprianou K et al. Effect of fluconazole antifungal prophylaxis on oral mucositis in head and neck cancer patients receiving radiotherapy. Support Care Cancer (2006) 14(1):44–51. doi:10.1007/s00520-005-0385-2

225. Lefebvre JL, Domenge C. Study Group of Mucositis. A comparative study of the efficacy and safety of fluconazole oral suspension and amphoterin B oral suspension in cancer patients with mucositis. Oral Oncol (2002) 38(4):337–42. doi:10.1016/S1388-8375(01)00063-X

226. Shenev JL. Combination and single-agent empirical antibacterial therapy for febrile cancer patients with neutropenia and mucositis. NCI Monogr (1990) 9:117–22.

227. Spijkervet FK, Van Saene HK, Van Saene JJ, Panders AK, Vermeulen A, Mehta DA et al. Mucositis prevention by selective elimination of the oral flora on mucositis in irradiated head and neck cancer patients. J Exp Ther Oncol (1996) 12(2):135–8.

228. Spijkervet FK, Van Saene HK, Van Saene JJ, Panders AK, Vermeulen A, Mehta DA et al. Mucositis prevention by selective elimination of the oral flora on mucositis in irradiated head and neck cancer patients. J Exp Ther Oncol (1996) 12(2):135–8.
237. Spruance SL. Cutaneous herpes simplex virus lesions induced by ultraviolet radiation. A review of model systems and prophylactic therapy with oral acyclovir. Am J Med (1988) 85(2A):43–5.

238. Sogowa M, Akagi K, Murata T, Kawasaka S, Sawada S, Yoshii G, et al. Enhancement of radiation effects by acyclovir. Int J Radiat Oncol Biol Phys (1986) 12(8):1537–40. doi:10.1016/0360-3016(86)90211-7

239. Schmidt M, Haagen J, Noack R, Siegemund A, Gabriel P, Dörr W. Effects of bone marrow or mesenchymal stem cell transplantation on oral mucositis (mouse) induced by fractionated irradiation. Strahlenther Onkol (2014) 190(4):399–404. doi:10.1007/s00066-013-0510-3

240. Schmidt M, Piro-Hussong A, Siegemund A, Gabriel P, Dörr W. Modification of radiation-induced oral mucositis (mouse) by adult stem cell therapy: single-dose irradiation. Radiat Environ Biophys (2014) 53(4):629–34. doi:10.1007/s00411-014-0552-7

241. Shieh SH, Wang ST, Tsai ST, Tseng CC. Mouth care for nasopharyngeal cancer patients undergoing radiotherapy. Oral Oncol (1997) 33(1):36–41.

242. Rugg T, Saunders MI, Dische S. Smoking and mucosal reactions to radiotherapy. Br J Radiol (1990) 63(751):554–6. doi:10.1259/0007-1285-63-751-554

243. Scherlacher A, Beaufort-Spontin F. [Radiotherapy of head-neck neoplasms: prevention of inflammation of the mucosa by sucralfate treatment]. HNO (1990) 38(1):24–8.

244. Carter DL, Hebert ME, Smink K, Leopold KA, Clough RL, Brizel DM. Double blind randomized trial of sucralfate vs placebo during radical radiotherapy for head and neck cancers. Head Neck (1999) 21(8):760–6.

245. Feber T. Management of mucositis in oral irradiation. Clin Oncol (R Coll Radiol) (1996) 8(2):106–11.

246. Spijkervet FK, van Saene HK, Panders AK, Vermyen A, van Saene JH, Mehta DM, et al. Effect of chlorhexidine rinsing on the oropharyngeal ecology in patients with head and neck cancer who have irradiation mucositis. Oral Surg Oral Med Oral Pathol (1989) 67(2):154–61.

247. Ferretti GA, Raybould TP, Brown AT, Macdonald JS, Greenwood M, Maruyama Y, et al. Chlorhexidine prophylaxis for chemotherapy- and radiotherapy-induced stomatitis: a randomized double-blind trial. Oral Surg Oral Med Oral Pathol (1990) 69(3):331–8.

248. Hasenauer C, Clasen BP, Roettger D. [Use of standardized oral hygiene in the prevention and therapy of mucositis in patients treated with radiochemotherapy of head and neck neoplasms]. Laryngol Rhinol Otol (Stuttg) (1988) 67(11):576–9.

249. Symonds RP, McIroy P, Khorrari J, Paul J, Pyper E, Alcock SR, et al. The reduction of radiation mucositis by selective decontamination antibiotic pastilles: a placebo-controlled double-blind trial. Br J Cancer (1996) 74(2):312–7.

250. Okuno SH, Foote RL, Loprinzi CL, Gulavita S, Sloan JA, Earle J, et al. A randomized trial of a nonabsorbable antibiotic lozenge given to alleviate radiation-induced mucositis. Cancer (1997) 79(11):2193–9.

251. Carl W, Emrich LS. Management of oral mucositis during local radiation and systemic chemotherapy: a study of 98 patients. J Prosthet Dent (1991) 66(3):361–9.

252. Abdelaal AS, Barker DS, Ferguson MM. Treatment for irradiation-induced mucositis. Lancet (1989) 1(8629):97.

253. Kim JH, Chu FC, Lakshmi V, Houde R. Benzoylamine HCl, a new agent for the treatment of radiation mucositis of the oropharynx. Am J Clin Oncol (1986) 9(2):132–4.

254. Samaranayake LP, Robertson AG, MacFarlane TW, Hunter IP, MacFarlane G, Soutar DS, et al. The effect of chlorhexidine and benzoylamine mouth-washes on mucositis induced by therapeutic irradiation. Clin Radiol (1988) 39(3):291–4.

255. Prada A, Chiesa F. Effects of benzoylamine on the oral mucositis during antineoplastic radiotherapy and/or intra-arterial chemotherapy. Int J Tissue React (1987) 9(2):115–9.

256. Porteder H, Rausch E, Kment G, Watzek G, Matejka M, Sinzinger H. Local prostaglandin E2 in patients with oral malignancies undergoing chemother- and radiotherapy. J Gastrointest Oncol Surg (1988) 16(8):371–4.

257. Macciolesi B, Zajusz A, Pilecki B, Szwatnicka J, Skadowski K, Dorr W, et al. Acute mucositis in the stimulated oral mucosa of patients during radiotherapy for head and neck cancer. Radiother Oncol (1991) 22(1):7–11.

258. Bourhis J, De Crevoisier R, Abdulkarim B, Deutsch E, Lusinchi A, Luboinski B, et al. A randomized study of very accelerated radiotherapy with and without amifostine in head and neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys (2000) 46(3):1105–8.

259. Koukourakis MI, Kyriaz G, Kakolyris S, Kouroussis C, Frangiadaki C, Giatromanolaki A, et al. Subcutaneous administration of amifostine during fractionated radiotherapy: a randomized phase II study. J Clin Oncol (2000) 18(11):2226–33. doi:10.1200/JCO.2000.18.11.2226

260. Schonekas KG, Wagner W, Prott FJ. Amifostine—a radioprotector in locally advanced head and neck tumors. Strahlenther Onkol (1999) 175(Suppl 4):27–9.

261. Wagner W, Prott FJ, Schonekas KG. Amifostine: a radioprotector in locally advanced head and neck tumors. Oncol Rep (1998) 5(3):1255–7.

262. Buntzel J, Kuttner K, Frohlich D, Glatzel M. Selective cytotoxic protection with amifostine in concurrent radiochemotherapy for head and neck cancer. Ann Oncol (1998) 9(5):305–9.

263. Peters K, Alaczi R, Hamzann D, Ziegler PG, Fietkau R. Supportive use of amifostine in patients with head and neck tumors undergoing radio-chemotherapy. Is it possible to limit the duration of the application of amifostine? Strahlenther Onkol (1999) 175(Suppl 4):23–6.

264. Vacha P, Marx M, Engel A, Richter E, Feyerabend T. [Side effects of postoperative radiotherapy with amifostine versus radiochemotherapy alone in head and neck tumors. Preliminary results of a prospective randomized trial]. Strahlenther Onkol (1999) 175(Suppl 4):18–22.

265. Wagner W, Alfrink M, Haus U, Matt J. Treatment of irradiation-induced mucositis with growth factors (rhGM-CSF) in patients with head and neck cancer. Anticancer Res (1999) 19(B):799–803.

266. Rosso M, Blasi G, Gherlone E, Rosso R. Effect of granulocyte-macrophage colony-stimulating factor on prevention of mucositis in head and neck cancer patients treated with chemo-radiotherapy. J Chemother (1997) 9(5):382–5. doi:10.1179/joc.1997.9.5.382

267. Mascarin M, Franchin G, Minatel E, Gobitti C, Talambini R, De Maria D, et al. The effect of granulocyte colony-stimulating factor on oral mucositis in head and neck cancer patients treated with hyperfractionated radiotherapy. Oral Oncol (1999) 35(2):203–8.

268. Schneider SB, Nishimura RD, Zimmerman RP, Tran L, Shiplack J, Tormey D, et al. Filgrastim (r-metHuG-CSF) and its potential use in the reduction of radiation-induced oropharyngeal mucositis: an interim look at a randomized, double-blind, placebo-controlled trial. Cytokines Cell Mol Ther (1999) 5(3):175–80.

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