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Pathogenesis and Amelioration of Radiation-Induced Oral Mucositis

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Introduction

Cancers of the upper aerodigestive tract account for 66,000 annual cases in the United States [1]. Many of these cancers will receive fractionated radiation and develop oral mucositis, an inflammatory and ulcerative response in irradiated mucosal tissues, during therapy. Severity of mucositis symptoms varies, and depends on treatment and patient-related factors including concurrent chemotherapy (CHT) agents used, total RT dose, treatment volumes, patient comorbidities, and oral hygiene [2, 3]. Definition and Grading of OM severity is based on Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (Table 1).

The impact of mucositis is significant. Acutely, patients can experience pain, anorexia, dehydration, dysphagia, dysgeusia, and generalized malaise. Long term toxicities including permanent dysphagia, dysgeusia, and dental decay may result from severe acute cases. Treatment delays and chemotherapy dose reduction/discontinuation may be indicated for patient safety as a consequence but at the cost of cancer outcomes [4]. Need for additional supportive care and hospitalizations to manage OM increase HNC treatment costs from 10% to 100%. For one HNC patient, this may mean an increase from $20,000 to up to $40,000 dollars [5, 6].

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Strategies for the avoidance of mucositis and its amelioration are critical in the treatment of HNC patients. The ongoing pursuit of toxicity avoidance in HNC therapy has led to RT volume and dose limitation, the investigation of different concurrent systemic therapy agents with RT, and, when appropriate, surgical extirpation in lieu of RT. Agents to reduce the rate and severity of mucositis is an area of research. This has resulted in the novel use of existing pharmacologics and brand new pharmacologics for mitigating mucositis with varying efficacy and safety. In this review, strategies for prevention and management of OM in the HNC setting are discussed, with an emphasis on interventions which are effective and safe.

Pathogenesis

A multiphase process underlies the development of mucositis of the upper aerodigestive tract, beginning with cytotoxicity induced directly by ionizing radiation [7, 8]. Ionizing radiation results in direct DNA damage to cells within the RT field. Double-strand breaks are the most lethal form of damage, which if not correctly repaired, results in induction of programmed cell death [9]. Other effects of ionizing radiation include single strand breaks and elimination of bases at certain sites which contribute to DNA destabilization. Tumor cells with higher cellular turnover rates and mutations in DNA repair genes are killed in greater proportion to healthy mucosal cells which more readily repair double-strand breaks. Nevertheless, repeated insult to DNA inhibits cellular transcription and replication which over a multi-week course of RT, results in death of normal tissues [10].

The second step in RT-mediated OM involves potentiation of cytotoxicity by reactive oxygen species (ROS). Hydrogen peroxide, hydroxyl free radicals, and superoxide anions are released by endothelial cells, fibroblasts, and cells of the innate immune system in response to exposure to ionizing radiation. At normal physiologic levels, ROS are generated through mitochondrial oxidative phosphorylation and play important roles in cellular signaling, proliferation, and metabolic processes [11]. Under exogenous stress, high levels of ROS are produced which overcome cellular antioxidizing capabilities and perpetuates DNA damage. A host of reactions with the bases and phosphate groups in DNA can occur with ROS, resulting in alteration of DNA structure and single and double strand breaks [12]. Outside of the nucleus, oxidation reactions alter protein and lipid membrane functions. Additionally, inflammatory signaling pathways are upregulated during high ROS states which further contribute to cytotoxicity [13].

Subsequently, cellular insult from radiation and ROS lead to the third step in the OM pathway. In this inflammatory phase, cytokines including tissue necrosis factor alpha (TNF-α), prostaglandins, NF-κβ, and interleukin (IL) 1β, are released. These pro-inflammatory cytokines have demonstrated a high degree of correlation with mucosal injury following exposure to RT. It is believed their mechanism of enhancing RT and ROS-mediated mucosal damage is by recruiting additional monocytes and neutrophils and increasing vascular endothelial permeability to these inflammatory cells. In turn, inflammatory cells generate more ROS and attack the healthy mucosal epithelium [14–17]. Anti-inflammatory cytokines including IL-10 and IL-11 are important to regulate the overall inflammation cascade and decreased levels of these cytokines have also been implemented in worsened OM [18].

Changes in expression of extracellular matrix (ECM) proteins of oral cavity tissues such as fibronectin and collagen in response to tissue injury from RT and CHT further enhance the inflammatory phase [19].

Over the first 1–2 weeks of RT, the cytotoxic effects of ionizing radiation, inflammation, and ROS-mediated DNA damage result in gradual apoptosis of mucosal epithelial cells within the stratified squamous epithelium and lamina propria layers. The outcome is mucosal ulceration and formation of pseudomembranes which marks the characteristic appearance of OM. Ulcerative sites become relatively neutropenic which predisposes them to bacterial and yeast infections. These bacterial toxins further simulate the underlying inflammatory state through release of additional cytokines [16]. The ulceration stage is the most painful due to loss of the epithelium covering the nerve endings in the lamina propria layer [20]. Healing takes place over the course of weeks to months once the initial insult from radiation is removed and cells in the basal layer are signaled to proliferate and differentiate into healthy stratified squamous epithelium. Steps in OM pathogenesis and interventions which target each step are illustrated (Figure 1).

Avoidance and Prophylactic Strategies

Radiotherapy Dose-Volume Limitation

Limiting RT dose to oral mucosa and volume of non-tumor oral mucosa irradiated reduces the impact of the first step in OM pathogenesis, i.e., direct cytotoxicity from ionizing radiation. Numerous dose-volume models for mucositis have documented significant decreases in mucositis with limitations of radiation dose and/or volume to the oral cavity [21]. Tongue deviation with a custom stent is a simple solution to reduce dose to oral mucosa that is readily available in practice [22]. Decreasing both the high-dose and low-dose volumes in RT plans aid in achieving mucosal constraints with significant decreases in G2 mucositis noted with decreases in high-dose PTV volume ($p=0.017$) [23]. This can be achieved with intensity modulated radiotherapy (IMRT) which can lower high dose regions and/or proton beam therapy which can reduce low dose regions [24–27].

Reduction in RT dose prescriptions also lead to lower mucositis rate and severity. Modeling of normal tissue complication probability (NTCP) has suggested greater G3 OM avoidance through lowering total dose prescribed rather than focusing on achieving mean dose constraints [28, 29]. Traditionally, dose prescriptions of 70 Gy in 2 Gy fractions are needed for the definitive treatment of head and neck cancer. Recent studies in HPV-associated oropharynx cancer, which have favorable prognosis and increased radiosensitivity relative to HPV-negative oropharynx cancer, demonstrate comparable local control treated with de-intensified definitive dose of 60 Gy [30, 31]. This decrease in total dose by 10 Gy improves G3 mucositis from historically >50% to 9% which suggest a threshold for severe mucositis development around 60 Gy. Further reduction in total dose to 54 Gy following complete or partial response to induction chemotherapy halved the rate of G2 mucositis from 77% to 36% per Chen et al [32]. A currently accruing phase II/III randomized clinical trial (NCT03952585) is directly comparing 70 Gy vs 60 Gy in the definitive treatment of oropharynx cancer and will further define the OM benefit with reduction in RT prescription dose.

Free Radical and Reactive Oxygen Species Neutralization

Generation of free radicals and reactive oxygen species (ROS) following ionizing radiation potentiates RT-induced cytotoxicity and is the second step in mucositis pathogenesis. Interventional agents which act on this step can dampen the oxidative stress response of mucosal tissues to ionizing radiotherapy. Concerns that supplementation of exogenous antioxidants during RT may confer radioprotective effects to tumor cells have not manifested in clinical studies of topical applications but are a concern with systemic administration [33, 34].

Glutamine has been found to be depleted in mucosal cells during periods of oxidative stress. Chattopadhyay et al. demonstrated that patients randomized to glutamine swish-and-swallow 2 hours prior to each RT fraction had significantly lower rate of G3+ OM compared to placebo (17.2% vs 54.3%, $p<0.05$) [35]. However, a more recent randomized study did not demonstrate a significant mucositis benefit [36]. Currently, the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer (MASCC) recommends against the use of parental glutamine but supports glutamine oral rinse for OM prevention [37].

Amifostine, an organic thiophosphate, is a ROS scavenger that has been used in multiple head and neck cancer investigations to limit mucositis and xerostomia [38]. While FDA approval was granted secondary to a study demonstrating reduced xerostomia [39], other studies failed to demonstrate a xerostomia benefit to the compound and none demonstrate a mucositis benefit. Despite the rationale for its use as an ROS scavenger, amifostine is rarely used in clinical practice [40]. No recommendation for or against use of amifostine is made by the MASCC.

Avasopasem manganese (GC4419) is a mimetic of the endogenous metalloenzyme, superoxide dismutase, and neutralizes superoxide free radicals by converting them to hydrogen peroxide. A recent phase IIb study by Anderson et al. demonstrated the duration of G3+ OM was significantly reduced in the 90 mg GG4419 group compared to placebo from 19 to 1.5 days ($p<0.024$). Analysis of disease-specific outcomes including local control, PFS, and OS were statistically identical across all arms at 2-years [41]. A phase III clinical trial (NCT03689712) of GC4419 vs placebo in locally advanced head and neck cancer patients undergoing RT has recently completed accrual and is pending results.

Additional ROS-neutralizing remedies include *propolis* and *zinc*. Propolis is a tough resin found in bee hives which contains high contents of organic aromatic acids with ROS scavenging properties. Zinc participates in crucial cellular metabolic pathways and induces synthesis of metallothionein which is incorporated into metalloenzymes crucial in the endogenous defense against free radicals [42, 43]. No recommendation for or against use of zinc or propolis in OM prevention is made by the MASCC [37].

Anti-Inflammatories

Limiting the inflammatory phase of OM pathogenesis is important in reducing the clinical impact of OM and preventing the progression towards the ulcerative phase. A positive feed-back loop involving pro-inflammatory cytokines that recruit macrophages, neutrophils, and lymphocytes results in more ROS and cytokine release, ultimately propagating the

mucosal damage initiated by RT and ROS. Agents acting on the inflammatory phase dampen the severity of OM.

Benzydamine is an atypical non-steroidal anti-inflammatory drug which inhibits pro-inflammatory cytokine production. Topical application of benzydamine has been shown in randomized controlled trials to prevent OM and reduce its severity [44]. Kazemian et al. found a statistically significant reduction in mucositis with benzydamine most notable starting at 3 weeks into RT. In the placebo group, OM scores did not plateau until the 7th week of RT, but in the benzydamine group, OM scores plateaued at the 3rd week. (p=0.049) [45]. It is a strong recommendation by the MASCC to implement benzydamine mouthwash in patients receiving 50 Gy or more of RT for HNC [37].

Clonidine is an α2-receptor agonist which, in addition to its antihypertensive properties, has been found to decrease pro-inflammatory and increase anti-inflammatory cytokines released from immune cells [46, 47]. For treatment of mucositis, it is typically administered as a mucoadhesive buccal tablet (MBT) [48]. A sequential phase IIb/III, multicenter, randomized clinical trial of clonidine MBT for the prevention of severe OM in oropharynx cancer patients undergoing CRT is currently accruing (NCT04648020).

Photobiomodulation (PBM), also known as low-level laser therapy, utilizes light sources calibrated to visible red and near infrared wavelengths (600–700 nm) and low energy (1 J/cm^2). The anti-inflammatory mechanism is secondary to activation of endogenous chromophores and downregulation of COX-2 signaling. It also decreases levels of profibrotic TGF-β [49, 50]. Studies evaluating PBM are heterogeneous due to differences in irradiance parameters of light sources used and their methods of application but in general demonstrate significant decreases in OM [51–54]. Intraoral PBM is recommended by the MASCC for prevention of OM secondary to RT and CRT. Additionally drugs like celecoxib, misoprostol, and rebamipide have shown efficacy in small studies, but robust evidence supporting their use is lacking [37].

Oral Hygiene and Antimicrobials

Implementation of a comprehensive patient education program with specific instructions on maintaining oral health alleviates the impact of OM in HNC patients [55, 56]. As OM progresses to the ulcerative phase, bacterial and yeast overgrowth in the relatively neutropenic ulcerative sites further simulate the underlying inflammatory state [57, 58]. Positive cultures of these microbes have been associated with severity of mucositis and in severe cases, bacteremia and sepsis [59]. Antiseptic mouth rinses and pastes are thus commonly integrated into oral hygiene programs for patients receiving treatment for HNC [60, 61].

Chlorhexidine is the most frequently studied antiseptic mouth rinse for preventing OM, and strengths range from 0.12% to 0.20% [62]. Multiple negative randomized and blinded clinical trials have investigated its role in preventing chemotherapy and RT-induced OM compared to placebo and other solutions [63–65]. Other antimicrobials such as *iseganan* rinse, a protegin analog with broad spectrum microbicidal activity, and *polymixin E-tobramycin-amphotericin B (PTA)* lozenges have shown mixed results in translational

studies and clinical trials as well [58, 66–68]. Overall, antiseptics are not recommended to be used alone but may have utility in improving oral hygiene and eliminating bacteriogenic food residues from the oral cavity.

Honey has been used for its antimicrobial and anti-inflammatory properties by ancient cultures. It has been shown to promote wound healing by accelerating the epithelization process, and has been used effectively for burns, post-surgical wound infections, and inflammatory skin conditions [69, 70]. Several small studies of oral honey application prior to and after each RT fraction have demonstrated decreased G3+ mucositis incidence [71, 72]. MASCC suggests honey be used in patients undergoing RT or CRT for HNC but variability of sources of honey and heterogeneity of these small studies preclude a stronger recommendation [37].

Doxepin and *diphenhydramine-lidocaine-antacid (DLA)* mouth rinses are not used in OM prophylaxis but are effective in alleviating pain once OM has manifested. A phase 3 randomized trial of doxepin, DLA, and placebo in patients with established OM pain demonstrated that doxepin and DLA reduced total OM pain by 2.9 and 3.0 points, respectively, compared to placebo. While pain reduction was significant, this reduction did not meet the pre-specific threshold for clinical significance [73]. On the other hand, 0.2% topical morphine gel or 2% morphine mouthwash has demonstrated safe, fast-acting, and significant pain improvement compared to both placebo and DLA solutions [74, 75]. The MASCC suggests that morphine be considered in patients with significant OM-related pain, while no recommendations for doxepin or DLA solutions are made [37].

Growth Factors

Stimulation of mucosal endothelial cell and keratinocyte growth may protect the upper aerodigestive tract against RT and chemotherapy-induced OM. Granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) are the most studied growth factors for mucositis prevention. They are known to upregulate neutrophils which then stimulate endothelial cell and keratinocytes. Systemically administered forms have been tested in phase III clinical trials with positive results in the chemotherapy alone and bone marrow transplant settings [76, 77]. Mouth-rinse forms have generally not been as successful in preventing OM [78]. In the RT setting, Schneider et al. evaluated the efficacy of subcutaneous filgrastim (G-CSF) in reducing OM. Fourteen patients were randomized to daily injections with dosing titrated to 10,000 to 30,000 neutrophils per liter. Despite small sample size, incidence of G3+ OM was significantly lower in the filgrastim group [79].

Palifermin is a growth factor for OM prevention. Unlike earlier growth factors used for OM, palifermin is a recombinant human keratinocyte growth factor which stimulates proliferation of epithelial cells and increases mucosal thickness. After efficacy was demonstrated in the bone marrow transplant setting [80] head and neck placebo controlled trials similarly demonstrated significant lowering of the incidence of G3+ OM among patients treated with CRT. However this was accompanied by no difference in narcotic use or patient reported pain, thus, tempering enthusiasm [81].

Alternative Systemic Therapies

Cisplatin is efficacious in both the definitive and adjuvant concurrent settings and is the most common head and neck radiation sensitizer. The application of concurrent cisplatin significantly increases acute mucositis [82]. In one of the largest endeavors to replace cisplatin, cetuximab, an inhibitor of epidermal growth factor receptor, was demonstrated to cause a statistically similar rate of OM in the management of oropharynx cancer [83]. Immuno-oncologics (IO), particularly inhibitors of programed cell death protein 1 (PD-1) are potential candidate radiosensitizers to replace cisplatin with (hopefully) less mucositis. Results from currently accruing studies will determine how much or how little RT + immunotherapy is ultimately recommended.

Emerging Therapeutics

An abundance of interventions designed or repurposed to prevent OM exist. As described in this text, the efficacy, safety, and ease of use of these interventions vary drastically. Thus, there is an ongoing pursuit of more effective and practical remedies with potential to revolutionize the toxicity profile of HNC therapy. Described below are several promising novel agents being evaluated in clinical trials which are currently accruing or closed to accrual and pending results.

EC-18 is a first-in-class immunomodulatory agent with anti-inflammatory properties and promotes anti-infective and tissue-healing pathways of the immune system. A Phase 2, randomized, double-blind, placebo-controlled trial is ongoing (NCT03200340) in patients with SCC of the head and neck receiving CRT with cisplatin and a minimum RT dose of 60 Gy. EC-18 has received fast track designation by the U.S. Food and Drug Administration (FDA).

Dusquetide (SGX942) is also a first-in-class immunomodulatory agent labeled as an innate defense regulator which promotes anti-inflammatory, anti-infective, and tissue-healing pathways of the innate-immune system. A Phase 3 randomized, double-blind, placebo-controlled, multi-national trial is currently taking place (NCT03237325) to evaluate the efficacy of SGX942 in patients with SCC of the oral cavity and oropharynx receiving CRT with cisplatin and a minimum RT dose of 55 Gy.

IL-11 is an anti-inflammatory cytokine which counteracts the pro-inflammatory cytokines IL-1 and IL-2 and down-regulates the inflammatory cascade. It is currently being studied in a Phase 3, randomized, placebo-controlled, open-label study (NCT03720340) in early and locally advanced nasopharynx cancer patients undergoing neo-adjuvant chemotherapy and CRT.

Ulinastatin is a naturally derived protease inhibitor which has anti-inflammatory properties. It has been found that ulinastatin is down-regulated under inflammatory stress, and when administered exogenously, can reduce the severity of OM. A Phase 3, randomized, open-label study (NCT03387774) is ongoing in patients with locally advanced nasopharynx cancer undergoing concurrent CRT with cisplatin and a minimum RT dose of 68 Gy.

MucoLox is a mucoadhesive polymer administered prophylactically to ameliorate OM symptoms. A Phase 2, randomized, single-blinded clinical trial (NCT03461354) is ongoing to compare MucoLox to sodium bicarbonate mouth rinse in patients undergoing RT with or without concurrent chemotherapy for HNC.

Maxillofacial and Oral Cavity Massage has emerged as a technique to reduce OM secondary to RT. A randomized, open-label clinical trial is currently ongoing comparing massage plus routine oral care to routine oral care alone (NCT03788499) in patients with nasopharynx cancer undergoing RT. The massage technique consists of manual massaging of the left and right cheeks, the upper jaw, the lower jaw, peri-oral region, tongue, hard palate, gums, and buccal mucosa.

Additional Considerations and Summary

Severe, G3+ OM has significant consequences in terms of patient quality of life, disease outcomes, and economic burden. Many effective strategies exist, but they range broadly in their practicality and supporting evidence. Some therapeutics are affordable and easy to comply with but have low-quality of evidence supporting their efficacy in reducing incidence of G3+ OM. Other strategies may be touted as highly effective, but are expensive and time consuming to use, or cause additional toxicity that limit their benefit. Striking a balance among efficacy, practicality, and the support of high-quality evidence, is an elusive target.

Radiotherapy dose-volume limitation via application of oral cavity dose constraints, reduction of high-dose and low-dose volumes, and transition from 3D-CRT to IMRT is the first step in reducing the impact of OM. Some recommended dose constraints include mean oral cavity dose < 41.8Gy and V30 < 73% [84, 85]. Achieving these constraints and reduction of high dose volumes is made possible by adopting IMRT techniques, although statistically significant reduction in OM incidence with IMRT compared to 3D-CRT have not been seen. Regardless, clinicians must be prudent in their treatment plan evaluation to assure dose to mucosal surfaces is as low as practically achievable without sacrificing target coverage. Tongue deviation, utilization of proton therapy, and deintensification of RT dose in oropharynx cancer patients (when enrolled on clinical studies) are additional RT-specific strategies to achieve this end.

Over-the-counter interventions which are safe, effective, and practical for patient compliance are elusive. Education on good oral hygiene is an essential component in HNC treatment. Clinical trials evaluating the efficacy of different oral hygiene regimens which implement various antiseptic mouth rinse combinations have shown mixed results. There is potential for reduction in OM incidence by over 2-fold [86], whereas other studies have shown no benefit at all [87]. Honey and probiotic lozenges, on the other hand, are potential candidates for safe, effective, and practical OM prevention. Zinc and glutamine supplementation have also been shown in moderately sized clinical trials to reduce OM severity and delays its onset without causing more side effects [35, 43, 71, 72, 88]. Herbal extracts such as propolis and hangeshashinto reduce incidence of G3+ by close to 80% in animal studies and have translated into small but positive human trials [42, 89]. Benzydamine mouth rinse available

without a prescription has also gained a recommendation by the MASCC for OM prevention [37]. Additional validation studies are needed but existing evidence is indicative that these natural remedies are convenient to adhere to treatments are promising solutions for OM.

Novel and efficacious pharmacologic interventions can be difficult to implement or cumbersome to use. The free radical neutralizer, GC4419, is a groundbreaking agent which is safe and effective in reducing severity and duration of G3+ OM. However, it is difficult to clinically administer since it requires daily IV infusions lasting at least 60 minutes [90]. This may be time prohibitive especially for younger, working patients due to the pre-existing inconvenience of daily RT treatments and long chemotherapy infusion sessions. The keratinocyte growth factor, palifermin, may be more practical to use since it requires only once weekly infusions. A robust phase III study demonstrated its efficacy in reducing OM severity and duration in the bone marrow transplant setting, but studies in HNC have shown a smaller degree of benefit [80, 81]. Photobiomodulation is also a safe and effective modality, but cost of devices are high, and daily treatments are time-consuming for both patients and providers.

At the current state, the amelioration of OM should begin with RT plan optimization. Education on good oral hygiene should be reinforced, but not with the expectation of OM avoidance. Honey, probiotics, and benzydamine are additional simple, obtainable, and effective ways of reducing the severity and consequences of OM, and patients should be counseled on their use. Aggressive interventions requiring IV infusions of novel pharmacologic agents or application of cumbersome, light-emitting instruments may be considered on an individual level based on severity of OM expected from RT treatment planning.

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Opinion Statement

Oral mucositis (OM) causes significant detriment to patient quality of life. Despite advances in RT, chemotherapy, and surgery for HNC which have led to improved local control and survival, management of certain toxicities such as OM have not kept pace. Numerous strategies have emerged with demonstrable benefit in preventing severe OM. However, ones which are not only effective, but practical and affordable to implement are rare. For example, infusion of growth factors or free radical scavengers, and daily treatment of intra-oral sites with lasers are supported by high-quality evidence but have not become widely adopted. It falls to familiarity of the physician with the available preventative measures and ultimately, patient preference in accepting which strategies for OM amelioration are used. In this review, we present a pathophysiological-based review of prevention techniques available for reducing the incidence and duration of severe OM.

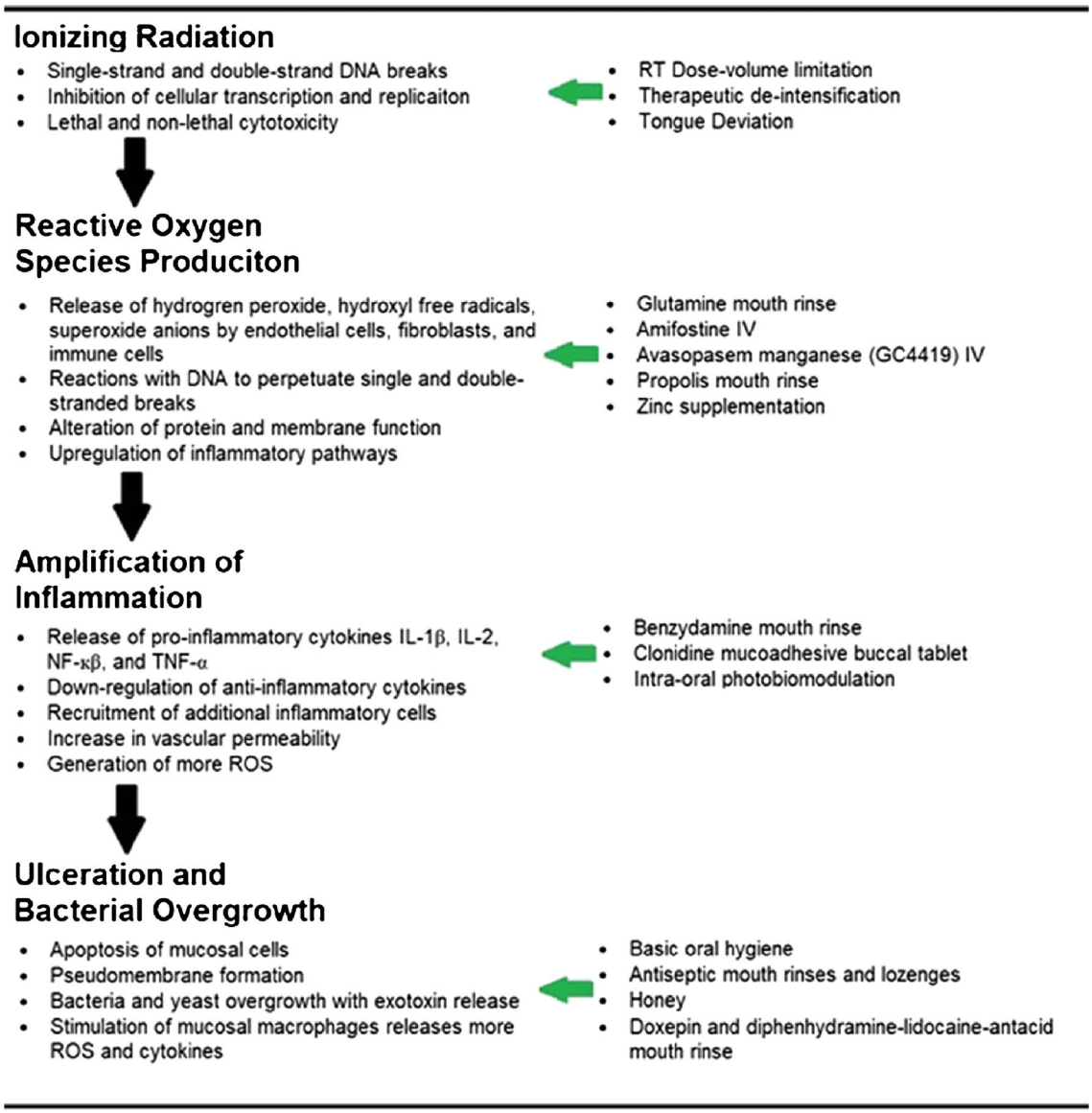

Figure 1.

Steps in oral mucositis pathogenesis and the interventional strategies which target them are summarized in this figure. Growth factors and alternate systemic therapies are not shown.

Table 1.

Grading of oral mucositis per Common Terminology Criteria for Adverse Events Version 5.0

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain, interfering with oral intake	Life-threatening, urgent intervention indicated	Death

Definition: A disorder characterized by ulceration or inflammation of the oral mucosa