Oncol Rev (2008) 2:102–113
DOI 10.1007/s12156-008-0064-2

REVIEW

# Management of radiation therapy-induced mucositis in head and neck cancer patients. Part I: Clinical significance, pathophysiology and prevention

**Wei Cheong Ngeow · Wen Lin Chai · Rosnah Binti Zain**

Received: 20 April 2008 / Accepted: 18 May 2008 / Published online: 11 July 2008
©Springer-Verlag 2008

**Abstract** Oropharyngeal mucositis is the acute inflammatory and ulcerative reaction of the oral mucosa following radiation therapy to the head and neck region. It is such a common problem that nearly all head and neck cancer patients develop some degree of mucositis. This complication is usually transient in nature but it also represents an important clinical problem as it is a painful, debilitating, dose-dependent side effect for which there is no widely acceptable prophylaxis or effective treatment. As several authoritative groups have recently either undertaken systematic reviews or issued guidelines on the management of mucositis, it is the aim of this review to provide instead an overview of all the possible remedies available, as well as highlighting to researchers the gaps that need to be filled. The first part of this review outlines the clinical significance and pathophysiology of radiation-induced mucositis, and looks into some of the preventive approaches available.

**Keywords** Head and neck cancer · Radiation therapy · Mucositis · Management

## Introduction

Radiation therapy (RT) is an important and indispensable mode of treatment for head and neck cancers, given to up to 75% of all head and neck cancer patients [1]. Besides ablating cancer, RT results in a number of biochemical changes, such as damage to membrane structures and cellular DNA, and alterations of the immune system, making it inefficient in resisting the attack of free radicals [2]. As the normal human oral mucosa has a rapid turnover rate, i.e. every 9–16 days, it means that the oral mucosa is very susceptible to the effects of RT [3].

Painful mouth sores described as mucositis/stomatitis is common during RT for head and neck cancer, with nearly all patients developing some degree of mucositis [4–7]. This happens because of the decreased cell renewal in the epithelium exposed to radiation [8]. Mucositis is made worse when concurrent chemotherapy (CT) is administered [4]. Most literature before the early 1980s used the term of stomatitis to describe the oral lesions after CT and RT. However, this was not specific as it included other

W.C. Ngeow (✉)
Department of Oral & Maxillofacial Surgery
Faculty of Dentistry, University of Malaya
50603 Kuala Lumpur, Malaysia
e-mail: ngeowy@um.edu.my

W.L. Chai
Department of General Dental Practice and Oral & Maxillofacial Imaging, Faculty of Dentistry,
University of Malaya, 50603 Kuala Lumpur, Malaysia

R.B. Zain
Department of Oral Pathology, Oral Medicine and Periodontology
Faculty of Dentistry,
University of Malaya, 50603 Kuala Lumpur, Malaysia

complications such as infection and pain in the oral cavity. The terminology of oral mucositis was later increasingly used. This more specific definition refers to cancer therapy-mediated injury to the mucosa that results in mucosal inflammation of the basal epithelial cell layer [3]. However, for the purpose of this review and in line with the treatment provided for head and neck cancer, mucositis in this context will be confined to the oropharyngeal area.

Mucositis is classified as grades I to IV according to severity [7]. Mucositis was first described as a development of four serial phases [9], but was later redefined as a process with five consecutive phases that includes initiation, primary damage response, signal amplification, ulceration and healing [10]. All the phases are interdependent and are the outcomes of a series of actions mediated by cytokines, direct toxicity effect of irradiation, and changes in oral bacterial flora. In cases of concomitant radiochemotherapy (RCT), the status of the patient's blood profile is also an important factor [9]. Clinically mucositis can appear as erythema, mucosal atrophy and ulceration with or without pseudomembranes.

Mucositis is generally associated with pain but is usually transient in nature, irrespective of its grading. However, the pain can be very intense, resulting in the loss of critical functions of the oral cavity, namely speech and swallowing, and requires the administration of opioid analgesics [11]. Swallowing difficulties limit liquid and food intake, leading to dehydration and weight loss; therefore, the need for nutritional support arises [12–14]. Mucositis may be a potential portal for infection with subsequent risk of septicemia [15, 16]. All these complications may lead to delays in administration or limitations in radiation dosage and even permanent cessation of therapy prior to completion of the planned radiation treatment program. There may also be an increase in hospitalization and cost of treatment [12, 17]. Costs generally increase according to the severity of mucositis [12]. Because of the interruption in the treatment of head and neck cancer, there is evidence to confirm that the radiocurability of cancer and patient survival will eventually be affected [18–30].

The severity of mucositis depends on the type of radiation, fractionation schedule, dosage, target area and irradiated tissue volume, and duration of treatment [4, 19, 31]. It is estimated that approximately 60% of patients receiving standard RT and more than 90% of those receiving experimental modalities that include combined RCT or altered fractionations will develop severe oral mucositis [19]. It has been found that the intensity of oral mucositis was significantly correlated with the intensity and the distress scores of oral dysfunction [32]. Therefore, due attention should be given to the management of this problem even though there are currently no established measures of prevention which are satisfactory in all cases.

This article will attempt to review current management recommended or practised for radiation-induced mucositis (RM), though clinically it may be difficult to distinguish between aspects of oral mucositis that originate from RT alone and those from CT, when cytotoxic drugs are also administered concurrently. One distinction is that radiation damage is anatomically site-specific, unlike the systemic effect of cytotoxic drugs that also cause myelosuppresion. The neutropenia resulting from chemotherapy which predisposes the oral mucosa to bleeding is not commonly seen in RM [33]. Mucositis can become localized in cases of irradiated oral tissues, or generalized, as in the case of mucosal denudation following CT. RT also causes damage to the nearby salivary glands, resulting in a reduction in saliva production and changes in the saliva composition and pH value. This will be followed by changes in the oral microflora, thus enhancing the possible development of infection [34–37]. Lastly, the tissues irradiated remain compromised throughout the life of the patient. The oral mucosa is more easily damaged by subsequent toxic drug or radiation exposures, and normal physiological repair mechanisms are compromised as a result of permanent cellular depopulation [36].

It must be emphasized that several authoritative groups such as the Cochrane Collaboration [38, 39] and the Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) [40, 41] have either continuously undertaken systematic reviews or issued guidelines on the management of oral mucositis. However, these reviews and guidelines were broad-based, covering amongst others all aspects of gastrointestinal mucositis and included amount of analgesia, dysphagia, systemic infection, length of hospitalization, cost, and patient quality of life in both patients receiving RT and/or CT. Furthermore, the recommendations were general in nature and did not discuss specific types of cancer, patients who might benefit from certain agents, or how clinicians might use the agents effectively [42]. There are currently only two meta-analyses that included randomized clinical trials with the prevention of mucositis as primary endpoint in cancer patients treated with head and neck RT or RCT [19, 43]. While not trying to reinvent the wheel, it is our intention to confine this review to an overview on the management of RM, highlighting the gaps in current management, because as clinicians, we are aware that care for oral mucositis continues regardless of whether or not there are comprehensive evidence-based recommendations and/or guidelines.

## Pathology

Evidence has emerged to suggest that mucositis develops as a series of dynamic interactions that begin in the epithelium but then progress to involve other tissue components. Sonis has proposed that this process can be thought of as occuring in five phases: initiation, message generation, signal amplification, ulceration and healing [10]. This can be summarized as a complex biological process involving direct damage to the divided cells of the oral epithelium, with depletion of the basal epithelium, both of which are modulated by the immune system, inflammatory process, and superinfection by oral bacterial flora [10, 19, 44].

The first sign of inflammatory change is seen at the end of the first week after a 2-Gy daily fractioned RT program. It presents first as a white discoloration [45]. This is due to decreased mitotic activity and subsequent longer retention of superficial cells, allowing them to become more highly keratinized. The influence of RT on the maturation and cellular growth explains a lag phase of approximately 1 or 2 weeks between the start of cancer therapy and clinical manifestations on the mucosa [3]. A more subtle mucosal reaction starts in the second week or by the time 20–30 Gy has been given (case dependent), where the reddening of mucosa becomes evident as these superficial cells are lost and are not replaced in sufficient numbers by the underlying epithelium. Ulceration will follow when this thin mucosa breaks. Ulceration involves penetration through the epithelium into the submucosa. These ulcerated areas may be covered by white or yellow fibrinous exudates [46]. This ulcerative phase is primarily responsible for the main clinical symptoms of mucositis, namely pain, inflammation and loss of function.

After an additional 10–20 Gy, small white areas of pseudomembrane begin to appear. In their early development, these patches tend to be scattered throughout the treatment field. As the treatment continues, the patches begin to coalesce, leading to confluent mucositis [47]. The mucosa of the oral cavity does not react in the same manner at all locations. Mucositis is most severe in the soft palate, followed, in order, by the mucosa of the hypopharynx, floor of the mouth, cheek, base of the tongue, lips, and dorsum of the tongue. Patients with compromised oral mucous membranes secondary to alcoholism and/or excessive smoking exhibit the most severe mucosal changes [48–50].

A high concentration of endogenous oral flora may contribute to further mucosal damage [51]. Disruption of the mucosal barrier constitutes an important risk factor for infection. Among patients with febrile septicemia, 25%–50% have been reported to show an oral focus of infection [52]. Mucosal damage also predisposes to colonization with an abnormal bacterial flora as well as yeasts. The incidence of invasive mycosis has increased in line with the intensity of cancer treatment. Almost all cases of systemic candidiasis originate from the oral cavity. There was a clear tendency for patients with positive cultures for aerobic Gram-negative bacteria and yeasts during treatment to have more severe mucositis [53].

Symptoms usually begin to abate with the completion of RT while most ulceration normally heals completely between 2–6 weeks after the completion of RT [8, 54]. In the mean time, attempts to conserve the necrotic and ulcerated mucosal tissues should be made. Consideration must be given to the possibility of the development of soft tissue radionerosis (and eventual osteoradionecrosis) if the ulceration does not heal 3-6 months following RT [55–57]. Osteoradionecrosis is primarily a non-healing wound secondary to endarteritis that usually presents concurrently with soft tissue radionecrosis [58]. This chronic non-healing wound occurs as a result of failure of the irradiated macrophages to re-organize the wound and the fibroblasts to lay down new collagen [59]. Clinically radionecrosis of the mucosa may require aggressive intervention when hemorrhage may become a major problem due to erosion of major vessels adjacent to the mucosa [55].

## Prevention

Prevention is better than cure; this is a widely accepted philosophy in medicine that is particularly true in the case of RM. Prevention entails preventing normal tissue from being damaged as well as preventing progressive mucositis resulting from poor oral and dental hygiene. However, the prevention (and treatment) of RM is a controversial subject. Up to now, no one effective intervention has been discovered or highly recommended [19, 38, 41]. Most supportive care, at best, has been empirical and anecdoctal. A meta-analysis suggested that most interventions, when chosen on a sound biological basis, are effective in preventing severe oral mucositis [19].

Various means of prevention have been utilized to protect healthy tissue from the effect of RT. These include the use of physical barriers, radioprotectants/cytoprotectants and anti-oxidants. Besides, it is important to ensure that patients have a good oral hygiene prior to RT. It is also essential to provide adequate oral health care throughout the course of cancer treatment as rigorous oral health care has been recognized to be important in preventing progressive mucositis and in the suppression of microbial colonization [60–63]. Table 1 summarises the preventive approaches for the management of RM.

## Physical protection of healthy tissue

The most common technique to reduce the incidence of RM is to protect the unaffected mucosa by lead shields and midline radiation blocks, use of conformation therapy, use of mouth bites, decreasing dose-per-fraction, deliberate use of treatment breaks and use of 3-dimensional RT [64–66]. The panel of the Mucositis Study Section of the MASCC/ISOO in 2004 recommended the use of midline radiation blocks and three-dimensional radiation treatment to reduce mucosal injury [40].

Sodium alginate is used in dentistry as dental impression material. It is a good chelator that reduces the absorption of radioactive toxins, such as radio-strontium [67]. Oshitani et al. (1990) evaluated the effect of sodium alginate on 39 patients with RM (17 study group; 22 control with no administration) and found that sodium alginate reduced the pain and the erosion of oral mucosa significantly. The interval of RT was shortened because of this effect [68]. However, there was no further study to validate this promising outcome.

## Radioprotectants/cytoprotectants

Radioprotectants/cytoprotectants are pharmacological agents or compounds that protect normal cells with limited or no effect on tumor cells. This enhances therapeutic benefits of treatment while promoting repair of irradiated tissues [69, 70].

### *Amifostine*

First reported to selectively protect mucosal cells from the effects of CT, amifostine is the organic thiophosphate that is the only agent recognized by the American Society of Clinical Oncology (ASCO) and approved by the US Food and Drug Administration (FDA) as a radioprotectant for solid tumors [71]. Amifostine has been shown in systematic reviews to present significant preventive effect on the development or severity of oral mucositis [38, 43]. The Cochrane Collaboration [38] concluded that amifostine may prevent or reduce the severity of oral mucositis in adults with head and neck cancer treated with RT. Echoing the same note, the meta-analysis by Stokman [43] found a significant effect of amifostine in the prevention of grades 3 and 4 mucositis in RT patients.

Radiation damages cells by inducing release of DNA free radicals, which leads to breakage or formation of hydroxyl free radicals and electrons that interact with molecules such as DNA. The free thiol metabolite of amifostine binds to and detoxifies these potentially damaging molecules upon entry into the cell. It then scavenges oxygen and hydroxyl free radicals generated by radiation, resulting in normal cell protection and reduced normal tissue toxicity, as well as preventing damage to cellular DNA and RNA [69, 72].

Amifostine can be given intravenously as a short 3-minute infusion 15–30 minutes before RT or as a slow subcutaneous injection 20–60 minutes before RT. At doses that

**Table 1** Summary of preventive approaches for the management of radiation-induced mucositis

| Approaches | Therapy used | Route |
|---|---|---|
| Physical protection of healthy tissue | Lead shields | Physical protection |
| | Midline radiation blocks | Physical protection |
| Radioprotectants / cytoprotectants | Amifostine | Intravenous / Subcutaneous |
| | Glutamine | Topical (mouthwash) / Oral / Intravenous |
| | Prostaglandins | Topical (mouthwash) |
| Anti-oxidants | β-carotene / vitamin A | Oral |
| | α-tocopherol / vitamin E | Topical (mouthwash) and swallow |
| | Combination of vitamins, azelastine and glutathione | Oral |
| | Allopurinol | Topical (mouthwash) |
| | Zinc | Oral |
| Oral health care | Plaque control | - |
| | Moisturize oral mucosa | |
| | Avoid irritants | |
| | Saliva substitutes | |

vary between 150–300 mg/m²/day for intravenous infusion and 500 mg/day for subcutaneous administration, amifostine has been reported to reduce the radiation-induced toxicities in patients with head and neck cancer with no negative impact on antitumor efficacy [73–80]. Antonadou et al. [78] suggested that the prophylactic effect of amifostine is more potent if given throughout the course of RT rather than with the administration of CT at weekly intervals, as practised in some studies [75, 78]. Some studies also suggested that the effect of amifostine may be dose dependent [81, 82]. Two studies suggested that daily doses of more than 300 mg/m² are needed to alleviate mucositis [75, 78].

Because amifositine and its active metabolite, WR-1065, accumulate with high concentrations in the salivary glands, it is also indicated to reduce the incidence of moderate to severe xerostomia in patients undergoing RT for head and neck cancer [78, 83–85]. It has been claimed that amifostine reduced both the acute and late phase of xerostomia that results from RT [82, 84–86]. In fact, its use has been recommended by the American Society of Clinical Oncology since 1999 [87]. This is, of course, an added advantage as its effect is akin to killing two birds with one stone.

The major toxic effect of amifostine is hypotension, severe nausea and vomiting and allergic reaction, especially when used intravenously [79, 85, 88]. Generally, higher intravenous dosage of amifostine is badly tolerated. Bourhis et al. reported that twice daily dosage of 150 mg/m² resulted in 38% discontinuation while Rades et al. reported a discontinuation rate of 38% and 44% for doses of 200 mg/m² and 300 mg/m² respectively (average of 41% for both groups combined) [79, 88]. Worse, when concurrent CT is administered, the discontinuation rate increased to 78%, probably due to increased acute toxicity [88]. In contrast, subcutaneous administration of amifostine is simpler and has been reported to be better tolerated [89–91]. Subcutaneously administered amifostine has the same bioavailability as its intravenous route [92]. The major adverse effect of subcutaneous administration is nausea. Others include local erythema at the injection site, asthenia, fever and allergic reaction [91].

*Glutamine*

Glutamine, a naturally occurring amino acid is known to have a role in the maintenance and healing of tissues, especially in the gastrointestinal mucosa. It has been used in topical (oral rinses), oral and parenteral formulations as a mucosal cytoprotectant and healing accelerant [93].

Studies on the prevention of oral mucositis in head and neck cancer patients undergoing RT with or without concurrent CT have been promising. The administration of intravenous glutamine 0.4 g/kg weight/day during CT days resulted in a significant difference in incidence of mucositis, the number of patients with severe objective mucositis, and the experience of pain and need for feeding tubes; all these findings favor the study group [94]. Huang et al. evaluated the influence of oral glutamine on RM in the RT of head and neck cancer and found that it significantly reduced the duration and severity of objective mucositis. The 2 g glutamine in 30 mL normal saline suspension, to be rinsed around the mouth for three minutes and expectorated before the start of RT, meals and at bedtime daily also shortened the duration of ≥ grade 3 subjective mucositis [95]. However, patients from both study and control groups required similar doses of analgesics for pain relief. Topical usage of glutamine allowed a higher daily dosage of 8 g to be used. Anderson et al. suggested that glutamine be provided not only during treatment for the amelioration of mucositis associated with CT or RT, but for at least two weeks after the completion of treatment [96].

While the finding on the topical use by Huang et al. was promising, the trial was unfortunately a single-blind randomized study. There are currently no reports of follow-up to either study. A meta-analysis [43] found glutamine had no effect on the prevention of mucositis in RT patients. The Cochrane Collaboration [38] found insufficient evidence to support or refute that glutamine was more or less effective than placebo for the prevention of mucositis formation at any level of severity.

*Prostaglandins (PGE-1 and PGE-2)*

Prostaglandins are mediators that have a variety of potent physiological effects, including effects on the inflammatory and immune response. They belong to a subclass of lipids known as the eicosanoids. Topical prostaglandins are believed to possess anti-inflammatory and cytoprotective properties. Both prostaglandin E1 (misoprostol) and prostaglandin E2 have been evaluated in a small series of RT or CT patients, with conflicting outcomes [97–102].

Misoprostol, a synthetic prostaglandin E1 (PGE1) analog has been discovered to have mucosal cytoprotectant properties in animal studies. Pilot studies suggested that the 200 mg tablet, dissolved in water and administered as a daily oral rinse for about 20 minutes before irradiation, may protect the oropharyngeal mucosa from RM in humans [98, 103]. However, the study by Hanson was plagued by several problems, including adherence to the protocol design [103]. In comparison, a recent randomized, double-blind, placebo-controlled trial in head and neck cancer patients receiving radical dose RT was found to offer no reduction in mucositis. What was worse, patients allocated to misoprostol reported slightly increased sore-

ness and a greater use of analgesics [104].

Similarly, 0.5 mg topical prostaglandin E2 (PGE2) tablets, given four times a day at 4-hour intervals have been suggested to be of some benefit in uncontrolled studies [100, 102]. In addition, Porteder et al. found that their patients reported experiencing less pain than the control group [105]. However, a randomized double-blind trial on patients undergoing bone marrow transplant provided opposite results [99].

## Anti-oxidants

Radiation is known to generate reactive oxygen species, such as superoxide radicals, hydrogen peroxides and hydroxyl radicals. These products have been found to injure cells, leading to mucositis [106]. Radical scavenging by anti-oxidants and hence, a reduction of radiation effects at their onset have been suggested to prevent the side effects of RT [107].

Various drugs, vitamins, enzymes and chemicals are known to have anti-oxidant effects. This includes vitamins A (especially β-carotene), C (ascorbic acid), and E (α-tocopherol), allopurinol, azelastine, glutathione and the supplements zinc and selenium. Two recent reviews on the use of anti-oxidants during CT and RT suggested that they enhance the killing of therapeutic modalities for cancer and at the same time decrease their side effects, protect normal tissue and increase survival [108, 109].

### *β-carotene/ Vitamin A*

β-carotene is an anti-oxidant from plants that the body converts into vitamin A. In the only study of the effect of systemic β-carotene in head and neck cancer patients undergoing RT, Mills found that patients who took a daily dosage of 250 mg β-carotene for 21 days followed by 75 mg daily during the course of treatment, reported less severe mucosal reaction and later manifestation of severe mucositis than the control group [110]. However, there is no follow-up study to confirm this encouraging outcome.

### *α-tocopherol/Vitamin E*

Vitamin E is a fat soluble vitamin with anti-oxidant properties that is available in 8 different forms. It is the most important natural antioxidant present in the human blood with a main biological function of scavenging peroxyl free radicals in the cell membrane [111].

Various studies on patients with chemotherapy-induced mucositis (CM) suggested that vitamin E or its main constituent, α-tocopherol may be an effective agent for prevention, though a recent report on children undergoing doxorubicin CT suggested otherwise [112–115]. In the recent doxorubicin CT study, non-compliance was reported to be twice as high in the study group than the control, and this may perhaps influence the outcome [115]. In the only study on patients with RM, topical rinsing of 400 mg vitamin E before every conventional fraction and 8–12 hours later during the 5–7 weeks of RT was found to decrease the incidence of symptomatic mucositis [116]. As α-tocopherol was available as an oil solution enclosed in a capsule, patients needed to dissolve it in saliva, rinse for five minutes, and swallow it immediately before every session of RT. Its use as a topical agent was based on its anti-oxidant and membrane-stabilizing effect [54].

### *Combination of vitamins, azelastine & glutathione*

Vitamin C and E have been used together with azelastine and gluthatione to alleviate the severity of mucositis due to RCT [117]. Azelastine is an anti-histamine. It acts against histamine, a chemical that is released in inflammatory reaction. Glutathione, on the other hand, is a tripeptide that is an antioxidant. Daily doses of 2 mg azelastine, 500 mg vitamin C, 200 mg vitamin E and 200 mg glutathione were found to be useful for the prophylaxis of mucositis [117]. However, there was no follow-up in a randomized, double-blind, placebo-controlled study to substantiate this encouraging finding.

### *Allopurinol*

Allopurinol is in a class of medications called xanthine oxidase inhibitors. It is known to inhibit xanthine oxidase, orotidylate decarboxylase and proteases, as well as showing an antioxidant effect that reduces the production of active oxygen [11, 118, 119]. It is generally regarded as an efficient remedy against oral mucositis, with studies of its effects being mostly based on the reduction in CM [117, 118, 120–129].

One randomized, double blind, placebo-controlled study recently confirmed its promising preventive potential in RM. In this study, significant differences were found in the lengthy use (between three and six weeks) of allopurinol mouthwash [130].

The effect of allopurinol mouthwash may be dose-dependent. One randomized, double-blind, placebo-controlled, crossover study suggested that it did not offer any protective effect against CM at a concentration of 1 mg/mL [131]. However, at higher concentrations of 3–6 mg/mL, allopurinol mouthwash has been claimed to have a preventive effect for both CM and RM [127, 130].

More recently, a mixture of allopurinol and carrageenam gel (allopurinol gel) was tested for the management of RM

in rats. It was found to be very effective in mitigating RM and facial dermatitis as well as dermatitis-related pain, especially if used topically two days before starting radiation therapy. The authors argued that this topical gel is a better preparation because of the potential for the release of allopurinol over eight hours [124]. We are awaiting its results in human trials.

*Zinc*

Zinc, a group IIb metal, has been discovered to have important roles in diverse physiological processes that include growth and development, maintenance and priming of the immune system, and tissue repair [132]. One of the major biochemical functions of zinc is the maintenance of membrane structure and function. Hence it is essential for wound healing and maintaining healthy epithelial tissue [133]. Studies have demonstrated that the anti-oxidant role of zinc [133–135] works on two mechanisms: the protection of sulfhydryl groups against oxidation, and the inhibition of the production of reactive oxygens by transition metals [135]. Thus, it protects against free radical damage released during inflammatory responses, as in RM.

Ertekin et al. found that 50 mg zinc sulphate taken 3 times daily beginning on the first day of RT and ending at six weeks after treatment is beneficial in decreasing oral discomfort and the severity of mucositis [136]. Patients given zinc sulphate were reported to suffer a lower degree of mucositis compared to placebo. Moreover, confluent mucositis developed later in those given zinc sulfate but started to improve sooner than the placebo group. This finding is confirmed by another study undertaken in Taiwan two years later using 25 mg zinc 3 times daily [137]. Lin et al. also found that zinc supplementation improved the healing process in RM [137]. They claimed that zinc at this trial dosage provided similar benefit while minimizing the adverse effects of vomiting and nausea. However, they found that zinc supplementation did not show much benefit in patients receiving concurrent CT, i.e. patients in the experiment group were unable to tolerate more courses of CT than control.

Oral healthcare

Current care for patients with RM is essentially preventive and palliative, with the application of appropriate oral hygiene care to eliminate potential dental foci of pathological conditions as one of the standard protocols [41, 61–63]. Dietary modifications are also suggested.

It is now standard care that patients are evaluated by the dentist prior to beginning RT [60]. Patients with good previous oral hygiene should be identified to ensure that they continue to maintain this standard, while those in whom the risk of hemorrhage and infection excludes any brushing should be monitored closely. This is essential as mucositis should be treated conservatively to avoid further tissue irritation and damage to the remaining cells from which the epithelium will regenerate [11]. The panel of the Mucositis Study Section of MASCC/ISOO also recommended regular assessment for oral pain using validated instruments by self-report and clinician or professional examination [41].

Special attention should be given to plaque control and oral hygiene [11]. These should be maintained with careful tooth brushing and flossing [62]. Patients should brush their teeth after each meal with a soft toothbrush and a mild dentrifice. A soft toothbrush or foam swab (toothette) cleans teeth effectively and without trauma. A special mild-dentrifice is recommended as mucositis, coupled with the lack of saliva due to salivary gland involvement following RT, will result in an increased sensitivity to strong flavors in the flavoring agents used in ordinary dentrifices [45]. Commercial dentrifices and mouthwashes contain chemicals which can cause irritation, such as alcohol, phenol, aromatics and glycerin oils that prolong mucositis and should, therefore, be avoided [55]. For daily use, toothpastes designed for children or people with xerostomia are recommended, such as Biotène which uses a natural salivary hypothiocyanite-lactoperoxidaselysozyme system. These products have a mild taste and do not contain any of the detergents such as sodium lauryl sulfate that is present in other dentifrices. Sodium lauryl sulfate-containing dentifrices are less suitable because they can be too harsh for the frail mucosal surfaces [138, 139].

Frequent rinsing cleans and lubricates tissues, prevents crusting, and soothes the oral mucosa. Frequent rinsing also removes debris, and prevents debris and bacteria from accumulating. Oral and lip moisturizers can also be helpful. Options for rinsing and debriding agents include sterile water, normal saline, sodium bicarbonate (1 teaspoon in 240 mL of water), salt and soda (one-half teaspoon each of salt and sodium bicarbonate in 240 mL of water) and chlorhexidine. Other newer mouthwashes that may be useful are Biotène®, Oral Balance® or Zendium®; they are formulated for patients suffering from xerostomia [139]. It is of interest to note that Trotti et al. found that patients randomized to receive a study agent or placebo had improved outcomes compared with patients randomized to standard oral care alone. These findings suggested that an emphasis on oral rinsing or the vehicle solution used may significantly reduce the incidence and severity of RM and its associated clinical outcomes [63].

Simple mechanical cleansing by saline is often viewed as the most effective traditional measure [140]. Saline solution is thought to help in the formation of granulation tis-

sue and to promote healing [141]. Saline mouthwash is safe and economical and has been used regularly in cancer populations [142].

While sodium bicarbonate is frequently used for mouth care, a literature search reveals no study of its efficacy. Its recommendation is based on anecdotal evidence. Sodium bicarbonate has been used as a cleansing agent because of its mucolytic action [143].

The combination of salt and soda raises oral pH and is suggested to prevent overgrowth of aciduric bacteria [144]. Dodd et al. in comparing the efficacy of salt and soda against 2 other commonly used mouthwashes (chlorhexidine and "magic" mouthwash), found that salt and soda was as effective as their more expensive counterparts. They suggested that these mouthwashes provide no added value beyond the benefit of performing a systematic oral hygiene protocol [145]. Given the comparable effectiveness of these 3 mouthwashes, it would cost less to use salt and soda mouthwash versus chlorhexidine or "magic" mouthwash. Salt and soda mouthwash has an advantage in that it does not require a prescription and patients can prepare it at home whenever they need it [145].

The use of chlorhexidine in patients with RM has been controversial (see Part II: Supportive treatments. Section A. Pharmaceutical products. 3. Antimicrobials (i) antiseptic mouthwash). The potential benefit of prophylactic rinses with chlorhexidine may be to control plaque levels, gingivitis, reduce the risk of caries and oropharyngeal candidosis, rather than any direct effect upon oral mucositis [11]. Since the intention of using chlorhexidine is more for plaque control, this can be done best by using a soaked foam brush over the tooth surface [146].

Saliva substitutes are indicated, as they moisten the dry oral mucosa that results from RT. Different types of saliva substitutes are now commercially available, containing different polymers as thickening agents, e.g. carboxymethylcellulose, polyacrylic acid, and xanthan gum [139].

Lastly, patients should be advised to follow a light, bland diet, avoiding irritants such as tobacco, alcoholic beverages, very hot, cold, or spicy foods, acidic foods, fruit drinks, and coarse foods [48–50, 54] .

## Conclusions

While our understanding of the pathophysiology of radiation-induced mucositis has improved tremendously over the last two decades, its prevention (and treatment) remains a major and unsolved problem. The results reported from different research centers are often contradictory and, perhaps, confusing. As for preventive measures, the only recommended protocol is the use of midline radiation blocks and 3-dimensional radiation treatment to reduce mucosal injury. Various systematic reviews also found amifostine to be a useful radioprotectant/cytoprotectant while the importance of good oral healthcare cannot be underestimated.

## References


1. Patni N, Patni S and Bapna A (2005) The optimal use of granulocyte macrophage colony stimulating factor in radiation induced mucositis in head and neck squamous cell carcinoma. J Cancer Res Ther 1:136–141
2. Sabitha KE and Shyamaladevi CS (1999) Oxidant and antioxidant activity changes in patients with oral cancer and treated with radiotherapy. Oral Oncol 35:273–277
3. Peterson DE (1999) Research advances in oral mucositis. Curr Opin Oncol 11:261–266
4. Trotti A, Bellm LA, Epstein JB et al (2003) Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. Radiother Oncol 66:253–262
5. Rothwell BR (1987) Prevention and treatment of the orofacial complications of radiotherapy. J Am Dent Assoc 114:316–322
6. Baker DG (1982) The radiobiological basis for tissue reactions in the oral cavity following therapeutic x-irradiation. A review. Arch Otolaryngol 108:21–24
7. Spijkervet FK, van Saene HK, Panders AK et al (1989) Scoring irradiation mucositis in head and neck cancer patients. J Oral Pathol Med 18:167–171
8. Dorr W, Hamilton CS, Boyd T et al (2002) Radiation-induced changes in cellularity and proliferation in human oral mucosa. Int J Radiat Oncol Biol Phys 52:911–917
9. Sonis ST (1998) Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. Oral Oncol 34:39–43
10. Sonis ST (2004) The pathobiology of mucositis. Nat Rev Cancer 4:277–284
11. Scully C, Sonis S and Diz PD (2006) Oral mucositis. Oral Dis 12:229–241
12. Murphy BA (2007) Clinical and economic consequences of mucositis induced by chemotherapy and/or radiation therapy. J Support Oncol 5:13–21
13. Bartelink H, Van den Bogaert W, Horiot JC et al (2002) Concomitant cisplatin and radiotherapy in a conventional and modified fractionation schedule in locally advanced head and neck cancer: a randomised phase II EORTC trial. Eur J Cancer 38:667–673
14. Chan AT, Teo PM, Ngan RK et al (2002) Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. J Clin Oncol 20:2038–2044
15. Epstein JB, Stevenson-Moore P, Jackson S et al (1989) Prevention of oral mucositis in radiation therapy: a controlled study with benzydamine hydrochloride rinse. Int J Radiat Oncol Biol Phys 16:1571–1575
16. Dazzi C, Cariello A, Giovanis P et al (2003) Prophylaxis with GM-CSF mouthwashes does not reduce frequency and duration of severe oral mucositis in patients with solid tumors undergoing high-dose chemotherapy with autologous peripheral blood stem cell transplantation rescue: a double blind, randomized, placebo-controlled study. Ann Oncol 14:559–563

17. Ferretti GA, Raybould TP, Brown AT et al (1990) Chlorhexidine prophylaxis for chemotherapy- and radiotherapy-induced stomatitis: a randomized double-blind trial. Oral Surg Oral Med Oral Pathol 69:331–338
18. Makkonen TA, Minn H, Jekunen A et al (2000) Granulocyte macrophage-colony stimulating factor (GM-CSF) and sucralfate in prevention of radiation-induced mucositis: a prospective randomized study. Int J Radiat Oncol Biol Phys 46:525–534
19. Sutherland SE and Browman GP (2001) Prophylaxis of oral mucositis in irradiated head-and-neck cancer patients: a proposed classification scheme of interventions and meta-analysis of randomized controlled trials. Int J Radiat Oncol Biol Phys 49:917–930
20. Budihna M, Skrk J, Smid L et al (1980) Tumor cell repopulation in the rest interval of split-course radiation treatment. Strahlentherapie 156:402–408
21. Trott KR (1990) Cell repopulation and overall treatment time. Int J Radiat Oncol Biol Phys 19:1071–1075
22. Withers HR, Taylor JM and Maciejewski B (1988) The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol 27:131–146
23. Parsons JT, Bova FJ and Million RR (1980) A re-evaluation of split-course technique for squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 6:1645–1652
24. Awwad HK, Khafagy Y, Barsoum M et al (1992) Accelerated versus conventional fractionation in the postoperative irradiation of locally advanced head and neck cancer: influence of tumour proliferation. Radiother Oncol 25:261–266
25. Amdur RJ, Parsons JT, Mendenhall WM et al (1989) Split-course versus continuous-course irradiation in the postoperative setting for squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 17:279–285
26. Cox JD, Pajak TF, Marcial VA et al (1992) Interruptions adversely affect local control and survival with hyperfractionated radiation therapy of carcinomas of the upper respiratory and digestive tracts. New evidence for accelerated proliferation from Radiation Therapy Oncology Group Protocol 8313. Cancer 69:2744–2748
27. Overgaard J, Hjelm-Hansen M, Johansen LV et al (1988) Comparison of conventional and split-course radiotherapy as primary treatment in carcinoma of the larynx. Acta Oncol 27:147–152
28. Fowler JF and Lindstrom MJ (1992) Loss of local control with prolongation in radiotherapy. Int J Radiat Oncol Biol Phys 23:457–467
29. Pajak TF, Laramore GE, Marcial VA et al (1991) Elapsed treatment days-a critical item for radiotherapy quality control review in head and neck trials: RTOG report. Int J Radiat Oncol Biol Phys 20:13–20
30. Maciejewski B, Preuss-Bayer G and Trott KR (1983) The influence of the number of fractions and of overall treatment time on local control and late complication rate in squamous cell carcinoma of the larynx. Int J Radiat Oncol Biol Phys 9:321–328
31. Miralbell R, Allal AS, Mermillod B et al (1999) The influence of field size and other radiotherapy parameters on acute toxicity in pharyngolaryngeal cancers. Strahlenther Onkol 175:74–77
32. Cheng KK (2007) Oral mucositis, dysfunction, and distress in patients undergoing cancer therapy. J Clin Nurs 16:2114–2121
33. Madeya ML (1996) Oral complications from cancer therapy: Part 2--Nursing implications for assessment and treatment. Oncol Nurs Forum 23:808–819
34. Abdelaal AS, Barker DS and Fergusson MM (1989) Treatment for irradiation-induced mucositis. Lancet 1:97
35. Brown LR, Dreizen S, Handler S et al (1975) Effect of radiation-induced xerostomia on human oral microflora. J Dent Res 54:740–750
36. Dudjak LA (1987) Mouth care for mucositis due to radiation therapy. Cancer Nurs 10:131–140
37. Tsuzura Y, Okabe I, Shimono I et al (1992) [Prevention of stomatitis in patients with acute myelogenous leukemia using PVP-iodine (Isodine) gargle]. Gan To Kagaku Ryoho 19:817–822
38. Worthington HV, Clarkson JE and Eden OB (2007) Interventions for preventing oral mucositis for patients with cancer receiving treatment. Cochrane Database Syst Rev CD000978
39. Worthington HV, Clarkson JE and Eden OB (2006) Interventions for preventing oral mucositis for patients with cancer receiving treatment. Cochrane Database Syst Rev CD000978
40. Rubenstein EB, Peterson DE, Schubert M et al (2004) Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer 100:2026–2046
41. Keefe DM, Schubert MM, Elting LS et al (2007) Updated clinical practice guidelines for the prevention and treatment of mucositis. Cancer 109:820–831
42. McGuire DB, Rubenstein EB and Peterson DE (2004) Evidence-based guidelines for managing mucositis. Semin Oncol Nurs 20:59–66
43. Stokman MA, Spijkervet FK, Boezen HM et al (2006) Preventive intervention possibilities in radiotherapy- and chemotherapy-induced oral mucositis: results of meta-analyses. J Dent Res 85:690–700
44. Sonis ST, Elting LS, Keefe D et al (2004) Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. Cancer 100:1995–2025
45. Joyston-Bechal S (1992) Management of oral complications following radiotherapy. Dent Update 19:232–234, 236–238
46. Blozis GG and Robinson JE (1968) Oral tissue changes caused by radiation therapy and their management. Dent Clin North Am Nov. 643–656
47. Cooper J (1994) Carcinomas of the oral cavity and oropharynx. In: Cox JD (eds) Moss' Radiation Oncology - Rationale, Technique, Results. Mosby, St Louis, pp 169–213
48. Beumer J, 3rd, Curtis T and Harrison RE (1979) Radiation therapy of the oral cavity: sequelae and management, part 1. Head Neck Surg 1:301–312
49. Beumer J, 3rd, Curtis T and Harrison RE (1979) Radiation therapy of the oral cavity: sequelae and management, part 2. Head Neck Surg 1:392–408
50. Rugg T, Saunders MI and Dische S (1990) Smoking and mucosal reactions to radiotherapy. Br J Radiol 63:554–556
51. Vissink A, Jansma J, Spijkervet FK et al (2003) Oral sequelae of head and neck radiotherapy. Crit Rev Oral Biol Med 14:199–212
52. Karthaus M, Rosenthal C and Ganser A (1999) Prophylaxis and treatment of chemo- and radiotherapy-induced oral mucositis - are there new strategies? Bone Marrow Transplant 24:1095–1108
53. Symonds RP, McIlroy P, Khorrami J et al (1996) The reduction of radiation mucositis by selective decontamination antibiotic pastilles: a placebo-controlled double-blind trial. Br J Cancer 74:312–317
54. Kostler WJ, Hejna M, Wenzel C et al (2001) Oral mucositis complicating chemotherapy and/or radiotherapy: options for prevention and treatment. CA Cancer J Clin 51:290–315
55. Mealey BL, Semba SE and Hallmon WW (1994) The head and neck radiotherapy patient: Part 2--Management of oral complications. Compendium 15:442, 444, 446–52 passim; quiz 458
56. Ngeow WC, Chai WL, Rahman RA et al (2006) Managing complications of radiation therapy in head and neck cancer patients: Part V. Management of mucositis. Singapore Dent J 28:16–18

57. Ramli R, Ngeow WC, Rahman RA et al (2006) Managing complications of radiation therapy in head and neck cancer patients: Part IV. Management of osteoradionecrosis. Singapore Dent J 28:11–15
58. Marx RE (1983) A new concept in the treatment of osteoradionecrosis. J Oral Maxillofac Surg 41:351–357
59. Vudiniabola S, Pirone C, Williamson J et al (1999) Hyperbaric oxygen in the prevention of osteoradionecrosis of the jaws. Aust Dent J 44:243–247
60. McGuire DB, Correa ME, Johnson J et al (2006) The role of basic oral care and good clinical practice principles in the management of oral mucositis. Support Care Cancer 14:541–547
61. Shieh SH, Wang ST, Tsai ST et al (1997) Mouth care for nasopharyngeal cancer patients undergoing radiotherapy. Oral Oncol 33:36–41
62. Borowski B, Benhamou E, Pico JL et al (1994) Prevention of oral mucositis in patients treated with high-dose chemotherapy and bone marrow transplantation: a randomised controlled trial comparing two protocols of dental care. Eur J Cancer B Oral Oncol 30B:93–97
63. Trotti A, Garden A, Warde P et al (2004) A multinational, randomized phase III trial of iseganan HCl oral solution for reducing the severity of oral mucositis in patients receiving radiotherapy for head-and-neck malignancy. Int J Radiat Oncol Biol Phys 58:674–681
64. Perch SJ, Machtay M, Markiewicz DA et al (1995) Decreased acute toxicity by using midline mucosa-sparing blocks during radiation therapy for carcinoma of the oral cavity, oropharynx, and nasopharynx. Radiology 197:863–866
65. Ship JA, Eisbruch A, D'Hondt E et al (1997) Parotid sparing study in head and neck cancer patients receiving bilateral radiation therapy: one-year results. J Dent Res 76:807–813
66. Keus R, Noach P, de Boer R et al (1991) The effect of customized beam shaping on normal tissue complications in radiation therapy of parotid gland tumors. Radiother Oncol 21:211–217
67. Hodgkinson A, Nordin BE, Hambleton J et al (1967) Radiostrontium absorption in man: suppression by calcium and by sodium alginate. Can Med Assoc J 97:1139–1143
68. Oshitani T, Okada K, Kushima T et al (1990) [Clinical evaluation of sodium alginate on oral mucositis associated with radiotherapy]. Nippon Gan Chiryo Gakkai Shi 25:1129–1137
69. Dest VM (2006) Radioprotectants: adding quality of life to survivorship? Semin Oncol Nurs 22:249–256
70. Tannehill SP and Mehta MP (1996) Amifostine and radiation therapy: past, present, and future. Semin Oncol 23:69–77
71. Schuchter LM, Hensley ML, Meropol NJ et al (2002) 2002 update of recommendations for the use of chemotherapy and radiotherapy protectants: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 20:2895–2903
72. Dorr RT (1998) Radioprotectants: pharmacology and clinical applications of amifostine. Semin Radiat Oncol 8:10–13
73. Niibe H, Takahashi I, Mitsuhashi N et al (1985) [An evaluation of the clinical usefulness of amifostine (YM-08310), radioprotective agent. A double-blind placebo-controlled study. 1. Head and neck tumors]. Nippon Gan Chiryo Gakkai Shi 20:984–993
74. Trog D, Bank P, Wendt TG et al (1999) Daily amifostine given concomitantly to chemoradiation in head and neck cancer. A pilot study. Strahlenther Onkol 175:444–449
75. Buntzel J, Kuttner K, Frohlich D et al (1998) Selective cytoprotection with amifostine in concurrent radiochemotherapy for head and neck cancer. Ann Oncol 9:505–509
76. Buntzel J, Schuth J, Kuttner K et al (1998) Radiochemotherapy with amifostine cytoprotection for head and neck cancer. Support Care Cancer 6:155–160
77. Buntzel J, Glatzel M, Kuttner K et al (2002) Amifostine in simultaneous radiochemotherapy of advanced head and neck cancer. Semin Radiat Oncol 12:4–13
78. Antonadou D, Pepelassi M, Synodinou M et al (2002) Prophylactic use of amifostine to prevent radiochemotherapy-induced mucositis and xerostomia in head-and-neck cancer. Int J Radiat Oncol Biol Phys 52:739–747
79. Bourhis J, De Crevoisier R, Abdulkarim B et al (2000) A randomized study of very accelerated radiotherapy with and without amifostine in head and neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys 46:1105–1108
80. Suntharalingam M, Jaboin J, Taylor R et al (2004) The evaluation of amifostine for mucosal protection in patients with advanced loco-regional squamous cell carcinomas of the head and neck (SCCHN) treated with concurrent weekly carboplatin, paclitaxel, and daily radiotherapy (RT). Semin Oncol 31:2–7
81. Buentzel J, Micke O, Adamietz IA et al (2006) Intravenous amifostine during chemoradiotherapy for head-and-neck cancer: a randomized placebo-controlled phase III study. Int J Radiat Oncol Biol Phys 64:684–691
82. Karacetin D, Yucel B, Leblebicioglu B et al (2004) A randomized trial of amifostine as radioprotector in the radiotherapy of head and neck cancer. J Buon 9:23–26
83. Hogle WP (2007) Cytoprotective agents used in the treatment of patients with cancer. Semin Oncol Nurs 23:213–224
84. Veerasarn V, Phromratanapongse P, Suntornpong N et al (2006) Effect of Amifostine to prevent radiotherapy-induced acute and late toxicity in head and neck cancer patients who had normal or mild impaired salivary gland function. J Med Assoc Thai 89:2056–2067
85. Brizel DM, Wasserman TH, Henke M et al (2000) Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. J Clin Oncol 18:3339–3345
86. Wasserman T, Mackowiak JI, Brizel DM et al (2000) Effect of amifostine on patient assessed clinical benefit in irradiated head and neck cancer. Int J Radiat Oncol Biol Phys 48:1035–1039
87. Hensley ML, Schuchter LM, Lindley C et al (1999) American Society of Clinical Oncology clinical practice guidelines for the use of chemotherapy and radiotherapy protectants. J Clin Oncol 17:3333–3355
88. Rades D, Fehlauer F, Bajrovic A et al (2004) Serious adverse effects of amifostine during radiotherapy in head and neck cancer patients. Radiother Oncol 70:261–264
89. Koukourakis MI, Kyrias G, Kakolyris S et al (2000) Subcutaneous administration of amifostine during fractionated radiotherapy: a randomized phase II study. J Clin Oncol 18:2226–2233
90. Law A, Kennedy T, Pellitteri P et al (2007) Efficacy and safety of subcutaneous amifostine in minimizing radiation-induced toxicities in patients receiving combined-modality treatment for squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 69:1361–1368
91. Ozsahin M, Betz M, Matzinger O et al (2006) Feasibility and efficacy of subcutaneous amifostine therapy in patients with head and neck cancer treated with curative accelerated concomitant-boost radiation therapy. Arch Otolaryngol Head Neck Surg 132:141–145
92. Yuhas JM (1980) Active versus passive absorption kinetics as the basis for selective protection of normal tissues by S-2-(3-aminopropylamino)-ethylphosphorothioic acid. Cancer Res 40:1519–1524
93. Sonis ST (2006) Can oral glutamine prevent mucositis in children undergoing hematopoietic stem-cell transplantation? Nat Clin Pract Oncol 3:244–245

94. Cerchietti LC, Navigante AH, Lutteral MA et al (2006) Double-blinded, placebo-controlled trial on intravenous L-alanyl-L-glutamine in the incidence of oral mucositis following chemoradiotherapy in patients with head-and-neck cancer. Int J Radiat Oncol Biol Phys 65:1330–1337
95. Huang EY, Leung SW, Wang CJ et al (2000) Oral glutamine to alleviate radiation-induced oral mucositis: a pilot randomized trial. Int J Radiat Oncol Biol Phys 46:535–539
96. Anderson PM, Schroeder G and Skubitz KM (1998) Oral glutamine reduces the duration and severity of stomatitis after cytotoxic cancer chemotherapy. Cancer 83:1433–1439
97. Duenas-Gonzalez A, Sobrevilla-Calvo P, Frias-Mendivil M et al (1996) Misoprostol prophylaxis for high-dose chemotherapy-induced mucositis: a randomized double-blind study. Bone Marrow Transplant 17:809–812
98. Hanson WR, Marks JE, Reddy SP et al (1997) Protection from radiation-induced oral mucositis by a mouth rinse containing the prostaglandin E1 analog, misoprostol: a placebo controlled double blind clinical trial. Adv Exp Med Biol 400B:811–818
99. Labar B, Mrsic M, Pavletic Z et al (1993) Prostaglandin E2 for prophylaxis of oral mucositis following BMT. Bone Marrow Transplant 11:379–382
100. Matejka M, Nell A, Kment G et al (1990) Local benefit of prostaglandin E2 in radiochemotherapy-induced oral mucositis. Br J Oral Maxillofac Surg 28:89–91
101. Pretnar J, Glazar D, Mlakar U et al (1989) Prostaglandin E2 in the treatment of oral mucositis due to radiochemotherapy in patients with haematological malignancies. Bone Marrow Transplant 4 [Suppl 3]:106
102. Sinzinger H, Porteder H, Matejka M et al (1989) Prostaglandins in irradiation-induced mucositis. Lancet 1:556
103. Hanson WR, Marks JE, Reddy SP et al (1995) Protection from Radiation-Induced Oral Mucositis by Misoprostol, a Prostaglandin E(1) Analog: A Placebo-Controlled, Double-Blind Clinical Trial. Am J Ther 2:850–857
104. Veness MJ, Foroudi F, Gebski V et al (2006) Use of topical misoprostol to reduce radiation-induced mucositis: results of a randomized, double-blind, placebo-controlled trial. Australas Radiol 50:468–474
105. Porteder H, Rausch E, Kment G et al (1988) Local prostaglandin E2 in patients with oral malignancies undergoing chemo- and radiotherapy. J Craniomaxillofac Surg 16:371–374
106. Ucuncu H, Ertekin MV, Yoruk O et al (2006) Vitamin E and L-carnitine, separately or in combination, in the prevention of radiation-induced oral mucositis and myelosuppression: a controlled study in a rat model. J Radiat Res (Tokyo) 47:91–102
107. Weiss JF and Landauer MR (2000) Radioprotection by antioxidants. Ann N Y Acad Sci 899:44–60
108. Simone CB, 2nd, Simone NL, Simone V et al (2007) Antioxidants and other nutrients do not interfere with chemotherapy or radiation therapy and can increase kill and increase survival, part 1. Altern Ther Health Med 13:22–28
109. Moss RW (2007) Do antioxidants interfere with radiation therapy for cancer? Integr Cancer Ther 6:281–292
110. Mills EE (1988) The modifying effect of beta-carotene on radiation and chemotherapy induced oral mucositis. Br J Cancer 57:416–417
111. van Acker SA, Koymans LM and Bast A (1993) Molecular pharmacology of vitamin E: structural aspects of antioxidant activity. Free Radic Biol Med 15:311–328
112. Lopez I, Goudou C, Ribrag V et al (1994) [Treatment of mucositis with vitamin E during administration of neutropenic antineoplastic agents]. Ann Med Interne (Paris) 145:405–408
113. Wadleigh RG, Redman RS, Graham ML et al (1992) Vitamin E in the treatment of chemotherapy-induced mucositis. Am J Med 92:481–484
114. El-Housseiny AA, Saleh SM, El-Masry AA et al (2007) The effectiveness of vitamin "E" in the treatment of oral mucositis in children receiving chemotherapy. J Clin Pediatr Dent 31:167–170
115. Sung L, Tomlinson GA, Greenberg ML et al (2007) Serial controlled N-of-1 trials of topical vitamin E as prophylaxis for chemotherapy-induced oral mucositis in paediatric patients. Eur J Cancer 43:1269–1275
116. Ferreira PR, Fleck JF, Diehl A et al (2004) Protective effect of alpha-tocopherol in head and neck cancer radiation-induced mucositis: a double-blind randomized trial. Head Neck 26:313–321
117. Osaki T, Ueta E, Yoneda K et al (1994) Prophylaxis of oral mucositis associated with chemoradiotherapy for oral carcinoma by Azelastine hydrochloride (Azelastine) with other antioxidants. Head Neck 16:331–339
118. Nakamura K, Natsugoe S, Kumanohoso T et al (1996) Prophylactic action of allopurinol against chemotherapy-induced stomatitis--inhibition of superoxide dismutase and proteases. Anticancer Drugs 7:235–239
119. Lalla RV, Schubert MM, Bensadoun RJ et al (2006) Anti-inflammatory agents in the management of alimentary mucositis. Support Care Cancer 14:558–565
120. Clark PI and Slevin ML (1985) Allopurinol mouthwashes and 5-fluorouracil induced oral toxicity. Eur J Surg Oncol 11:267–268
121. Dozono H, Nakamura K, Motoya T et al (1989) [Prevention of stomatitis induced by anti-cancer drugs]. Gan To Kagaku Ryoho 16:3449–3451
122. Elzawawy A (1991) Treatment of 5-fluorouracil-induced stomatitis by allopurinol mouthwashes. Oncology 48:282–284
123. Fujimura T, Shima Y, Sawasaki K et al (1991) [Prophylactic effect of allopurinol mouthwash against stomatitis induced by the chemotherapy (PMUE regimen) for gastrointestinal malignancies]. Gan To Kagaku Ryoho 18:2463–2466
124. Kitagawa J, Nasu M, Okumura H et al (2008) Allopurinol gel mitigates radiation-induced mucositis and dermatitis. J Radiat Res (Tokyo) 49:49–54
125. Montecucco C, Caporali R, Rossi S et al (1994) Allopurinol mouthwashes in methotrexate-induced stomatitis. Arthritis Rheum 37:777–778
126. Porta C, Moroni M and Nastasi G (1994) Allopurinol mouthwashes in the treatment of 5-fluorouracil-induced stomatitis. Am J Clin Oncol 17:246–247
127. Tsavaris N, Caragiauris P and Kosmidis P (1988) Reduction of oral toxicity of 5-fluorouracil by allopurinol mouthwashes. Eur J Surg Oncol 14:405–406
128. Tsavaris NB, Komitsopoulou P, Tzannou I et al (1991) Decreased oral toxicity with the local use of allopurinol in patients who received high dose 5-fluorouracil. Sel Cancer Ther 7:113–117
129. Yokomizo H, Yoshimatsu K, Hashimoto M et al (2004) Prophylactic efficacy of allopurinol ice ball for leucovorin/5-fluorouracil therapy-induced stomatitis. Anticancer Res 24:1131–1134
130. Abbasi Nazari M, Sadrolhefazi B, Nikoofar A et al (2007) Allopurinol mouthwash for prevention or alleviation radiotherapy induced oral mucositis: a randomized, placebo-controlled trial. DARU 15:27–230
131. Loprinzi CL, Cianflone SG, Dose AM et al (1990) A controlled evaluation of an allopurinol mouthwash as prophylaxis against 5-fluorouracil-induced stomatitis. Cancer 65:1879–1882
132. Truong-Tran AQ, Carter J, Ruffin R et al (2001) New insights into the role of zinc in the respiratory epithelium. Immunol Cell Biol 79:170–177
133. Bagchi D, Bagchi M and Stohs SJ (1997) Comparative in vitro oxygen radical scavenging ability of zinc methionine and selected zinc salts and antioxidants. Gen Pharmacol 28:85–91

134. Bagchi D, Garg A, Krohn RL et al (1998) Protective effects of grape seed proanthocyanidins and selected antioxidants against TPA-induced hepatic and brain lipid peroxidation and DNA fragmentation, and peritoneal macrophage activation in mice. Gen Pharmacol 30:771–776
135. Rostan EF, DeBuys HV, Madey DL et al (2002) Evidence supporting zinc as an important antioxidant for skin. Int J Dermatol 41:606–611
136. Ertekin MV, Koc M, Karslioglu I et al (2004) The effects of oral zinc sulphate during radiotherapy on anti-oxidant enzyme activities in patients with head and neck cancer: a prospective, randomised, placebo-controlled study. Int J Clin Pract 58:662–668
137. Lin LC, Que J, Lin LK et al (2006) Zinc supplementation to improve mucositis and dermatitis in patients after radiotherapy for head-and-neck cancers: a double-blind, randomized study. Int J Radiat Oncol Biol Phys 65:745–750
138. Nagy K, Urban E, Fazekas O et al (2007) Controlled study of lactoperoxidase gel on oral flora and saliva in irradiated patients with oral cancer. J Craniofac Surg 18:1157–1164
139. Nieuw Amerongen AV and Veerman EC (2003) Current therapies for xerostomia and salivary gland hypofunction associated with cancer therapies. Support Care Cancer 11:226–231
140. Symonds RP (1998) Treatment-induced mucositis: an old problem with new remedies. Br J Cancer 77:1689–1695
141. Daeffler R (1981) Oral hygiene measures for patients with cancer. III. Cancer Nurs 4:29–35
142. Segelman AE and Doku HC (1977) Treatment of the oral complications of leukemia. J Oral Surg 35:469–477
143. Maurer J (1977) Providing optimal oral health. Nurs Clin North Am 12:671–685
144. Carl W (1980) Dental management of head and neck cancer patients. J Surg Oncol 15:265–281
145. Dodd MJ, Dibble SL, Miaskowski C et al (2000) Randomized clinical trial of the effectiveness of 3 commonly used mouthwashes to treat chemotherapy-induced mucositis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 90:39–47
146. Epstein J, Ransier A, Lunn R et al (1994) Enhancing the effect of oral hygiene with the use of a foam brush with chlorhexidine. Oral Surg Oral Med Oral Pathol 77:242–247