

Systematic review of anti-inflammatory agents for the management of oral mucositis in cancer patients

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Abstract

Purpose The aim of this project was to review the available literature and define clinical practice guidelines for the use of anti-inflammatory agents for the prevention and treatment of oral mucositis in cancer patients.

Materials and methods A systematic review was conducted by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology. The body of evidence for use of each intervention, in each cancer treatment setting, was assigned an evidence level. Based on the evidence level, one of the following three guideline determinations was possible: recommendation, suggestion, and no guideline possible.

Results Forty-one papers were reviewed. There was sufficient evidence to recommend the use of benzydamine mouthwash for the prevention of oral mucositis in head and neck cancer patients receiving moderate-dose radiation therapy (up to 50 Gy), without concomitant chemotherapy. A new suggestion was developed against the use of misoprostol mouthwash for the prevention of oral mucositis in head and neck cancer patients receiving radiation therapy. Positive results were reported for some other anti-inflammatory agents. However, no guidelines were able to be developed for any other agents due to insufficient and/or conflicting evidence.

Conclusions The use of anti-inflammatory agents continues to be a promising strategy for the prevention and treatment of oral mucositis. Additional well-designed studies are

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needed to examine the use of this class of agents for oral mucositis.

Keywords Anti-inflammatory agents · Guidelines · Systematic review · Oral mucositis

Introduction

Considerable evidence has indicated that the inflammatory response to radiation and/or chemotherapy plays an important role in the pathogenesis of oral mucositis [1–3]. Locally produced cytokines can amplify tissue injury. Bacterial colonization of oral mucosal ulcerations can result in the flow of endotoxin (lipopolysaccharides) into the submucosal tissue causing the release of additional cytokines and the increase of tissue toxicity. This understanding of the pathobiology of oral mucositis has led to the evaluation of several agents targeting key components of the radiation- and chemotherapy-induced inflammatory response.

In May 2004, the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) first published evidence-based clinical practice guidelines on the prevention and treatment of oral mucositis [4]. This review examined the literature from January 1966 to May 2002. Due to the exponential increase in mucositis-related research, a need for updating this literature review and guidelines process was critical, so an update was conducted in June of 2005 [5, 6]. Sufficient clinical evidence supported a recommendation for the use of benzydamine mouthwash for the prevention of oral mucositis in patients with head and neck cancer receiving moderate-dose radiation therapy [4–6]. Small numbers of study subjects and varying quality of the studies did not provide enough evidence to support any additional guidelines regarding the use of any other anti-inflammatory agents in the management of oral mucositis [5].

As part of a comprehensive update of the MASCC/ISOO clinical practice guidelines for mucositis, the aim of this project was to systematically review the available literature from January 1966 to December 31st 2010, and define updated clinical practice guidelines for the use of anti-inflammatory agents for the prevention and treatment of oral mucositis in cancer patients.

Methods

The methods are described in detail in Bowen et al. [7] and Elad et al. [8]. Briefly, a literature search was conducted for relevant papers indexed in Medline from 1966 to December 31st, 2010. The intervention keywords used for the literature

search were as follows: Aminosalicyclic acid, Amifostine, Amlexanox, Anti-inflammatory, Anti-TNF, Anti-tumor necrosis factor, Aspirin, Benadryl, Benzydamine, Betamethasone, Celecoxib, Corticosteroid, Dexamethasone, Diphenhydramine, Ethylol, Flurbiprofen, Histamine, Hydrocortisone, Ibuprofen, Indomethacin, Infliximab, Irsogladine, Lactoferrin, Mesalazine, Misoprostol, N-Acetyl cysteine, Non-steroidal anti-inflammatory agents, NSAIDs, Orgotein, Prednisone, Prostaglandin, RK-02-02, Salicylic acid, Steroid, Thalidomide, TNF antibody, TNF inhibitor, and Tumor necrosis factor/TNF. Articles that evaluated anti-inflammatory agents for the prevention and/or treatment of cancer therapy-induced oral mucositis in humans were selected for review. The detailed inclusion and exclusion criteria are presented in Bowen et al. [7]. Each paper was reviewed by two independent reviewers. The large number of papers was divided among 12 calibrated reviewers to keep the workload reasonable. Data was extracted using a standard electronic form. Studies were evaluated based on the list of major and minor flaws published by Hadorn [9]. A Level of Evidence was assigned for each intervention based on the Somerfield criteria [10]. A well-designed study was defined as a study with no major flaws per the Hadorn criteria. Findings from the reviewed studies were integrated into guidelines based on the overall Level of Evidence for each intervention. Guidelines were classified into three types: recommendation, suggestion, and no guideline possible. Guidelines were separated based on (1) the aim of the intervention (prevention or treatment of oral mucositis), (2) the treatment modality [head and neck radiotherapy, head and neck chemoradiotherapy, standard dose chemotherapy, and high-dose chemotherapy prior to hematopoietic stem cell transplant (HSCT)], and (3) the route of administration of the intervention (intravenous, intramuscular, systemic per os, and topical application).

Results

The literature searches identified 908 articles. Of those, 759 articles were excluded after evaluating the title and abstract. Articles that did not report the effects of an intervention on oral mucositis or on related outcomes, animal or in vitro studies, and papers published in a language other than English were excluded. Forty-three review papers were further excluded after detailed evaluation of their title and abstract. The remaining 106 articles were assessed in detail. Of these 40 were related to amifostine and 66 to other anti-inflammatory agents. Due to the large number of articles related to amifostine, the results related to that agent have been published in a separate manuscript [11]. Of the remaining 66 articles related to all other anti-inflammatory agents, 25 articles were excluded after detailed assessment, based on the inclusion/exclusion criteria. Thus, 41 articles

were formally assessed for the present review. These 41 studies investigated the use of 15 anti-inflammatory agents (benzydamine, diphenhydramine, prostaglandin, misoprostol, immunoglobulin, corticosteroids, indomethacin, azelastine, mesalazine, disprin, orgotein, flurbiprofen, histamine, colchicine, and placentex) for the prevention and/or treatment of oral mucositis. Summary data for these publications is presented in Table 1.

Benzydamine mouthwash

Head and neck radiotherapy: prevention

Six studies were reviewed [12–17]. The non-superiority of benzydamine mouthwash when compared with chlorhexidine was reported in one unblinded study, although formal recording of oral mucositis was not conducted [13]. Significantly lower pain ratings by patients who received benzydamine compared to placebo were reported in three randomized, double blind, placebo-controlled studies [12, 14, 15], resulting in fewer patients requiring systemic analgesics. Epstein and colleagues found that up to cumulative doses of 50 Gy, subjects receiving benzydamine to prevent oral mucositis had significantly less erythema and ulceration and were more likely to remain ulcer-free as compared to subjects who received placebo mouthwash [15]. Based largely on the findings of this large well-designed multicenter study, benzydamine was recommended for the prevention of moderate-dose radiation-induced oral mucositis in the 2005 mucositis guidelines update [5]. A beneficial effect of benzydamine mouthwash was also reported in two subsequent studies, which further supported the previous recommendation [16, 17]. In the study conducted by Cheng et al. (2006), oral mucositis was less severe, although the difference was not statistically significant, for the benzydamine group when compared with the chlorhexidine group. [16]. Patients in the benzydamine group required less supplemental analgesics. The total radiation dose varied between 54 and 68 Gy in both groups. In the study conducted by Kazemian et al. (2009), which included 81 patients and was randomized, double blind, and placebo controlled, benzydamine significantly reduced oral mucositis during radiotherapy. The frequency of oral mucositis \geq grade 3 was significantly less in the benzydamine group when compared to the placebo. Benzydamine mouthwash was reported as effective, safe, and well tolerated. The mean total radiation dose was 61.69 Gy for the benzydamine and 64.02 Gy for the placebo group [17]. However, patients with grade 2 or higher mucositis were allowed to use other topical medications including diphenhydramine and nystatin. There was no adjustment for or comparison of the use of such concomitant medications that could potentially affect oral mucositis. These issues prevented the extension of the recommendation

in favor of benzydamine to the population of head and neck cancer patients receiving radiation doses higher than 50 Gy.

Previous guideline: The panel recommends benzydamine for prevention of radiation-induced mucositis in patients with head and neck cancer receiving moderate-dose radiation therapy.

New guideline: The panel recommends benzydamine mouthwash for the prevention of oral mucositis in patients with head and neck cancer receiving moderate-dose radiation therapy (up to 50 Gy), without concomitant chemotherapy.

Head and neck radiotherapy: treatment

Significant analgesic activity and alleviation of symptoms were observed in a double blind and placebo-controlled study, which tested benzydamine for the treatment of oral mucositis [18, 19]. The authors published results of the same patient cohort on two occasions, the preliminary findings in 1985, and the final results in 1986. Oral pain was the primary endpoint. The findings of this single study, despite the promising results, were not adequate to support establishment of a guideline for the use of benzydamine to treat oral mucositis during head and neck radiotherapy. Therefore, no guideline was possible.

Head and neck chemoradiotherapy: prevention

Three studies were reviewed [20–22]. Oral mucositis prevalence was lower and it appeared significantly later in patients treated with prophylactic benzydamine when compared with placebo in two studies [20, 21]. In the first study investigating benzydamine by Prada and colleagues, methodology reporting was insufficient to determine whether chemotherapy was administered concurrently with radiotherapy [20]. In the second study by Prada and colleagues, in addition to chemoradiotherapy, patients also received chemotherapy or radiotherapy alone [21]. Pain and dysphagia were the primary endpoints in both those studies [20, 21]. The third study, conducted by Putwatana et al. (2009), was a prospective, randomized, single-blinded study, which compared benzydamine mouthwash with papayor drops [22]. Benzydamine was found inferior to papayor herb for preventing and relieving radiation-induced oral mucositis and pain. Fifty percent of patients in the benzydamine group and 56.67 % of those in the papayor group received radiotherapy alone. Due to the insufficient data and the presence of concerns such as lack of double blinding, no guideline was possible regarding the use of benzydamine mouthwash for the prevention of oral mucositis in head and neck chemoradiotherapy.

Table 1 Anti-inflammatory agents evaluated for oral mucositis

Name of agent	Route of administration	Cancer type	Treatment modality	Indication	References	Overall level of evidence	Guideline determination	Comments
Benzylamine	Mouthwash	H&N	RT	P	Epstein 1986 [12], Samanayake 1988 [13], Epstein 1989 [14], Epstein 2001 [15], Cheng 2006 [16], Kazemian 2009 [17]	I	Recommendation The panel recommends benzylamine mouthwash for prevention of oral mucositis in patients with head and neck cancer receiving moderate dose radiation therapy (up to 50 Gy), without concomitant chemotherapy	Evidence for effectiveness of benzylamine during higher dose radiotherapy is still lacking
					Kim 1985 [18], Kim 1986 [19], Prada 1985 [20], Prada 1987 [21], Purwatana 2009 [22]	III	No guideline possible	Same cohort of patients
Diphenhydramine	Mouthwash	H&N	RT	P	Cheng 2003 [23], Cheng 2004a [24], Cheng 2004b [25], Sonis 1985 [26], Schubert 1987 [27], Lever 1987 [28], Rothwell 1990 [29], Carmel 1990 [30], Barker 1991 [31], Turhal 2000 [32], Dodd 2000 [33]	IV	No guideline possible	Same cohort of patients
					Porteder 1988 [34], Labor 1993 [35], Kuhner 1986 [36], Pretmar 1989 [37], Duenas-Gonzalez 1996 [38]	III	No guideline possible	No recent update to the literature
Prostaglandin E2	Lozenges	H&N, hematological malignancies and solid cancers	High-dose chemo (without TBI)	T	Cheng 2003 [23], Cheng 2004a [24], Cheng 2004b [25], Sonis 1985 [26], Schubert 1987 [27], Lever 1987 [28], Rothwell 1990 [29], Carmel 1990 [30], Barker 1991 [31], Turhal 2000 [32], Dodd 2000 [33]	III	No guideline possible	No recent update to the literature
					Porteder 1988 [34], Labor 1993 [35], Kuhner 1986 [36], Pretmar 1989 [37], Duenas-Gonzalez 1996 [38]	IV	No guideline possible	No recent update to the literature
Misoprostol	PO (tablets)	Hematological and solid cancers	High-dose chemo for HSCT	P	Hanson 1997 [39], Veness 2006 [40]	III	Suggestion against misoprostol mouthwash should not be used for prevention of radiation-induced oral mucositis in head and neck cancer patients	Study was prematurely closed due to worsening of mucositis by misoprostol
					Mose 1997 [41], Plevova 1997 [42], Abdelaal 1989 [43], Leborgne 1998 [44], Pillsbury 1986 [45], Osaki 1994 [46], Rymes 1996 [47], Kaushal 2001 [48]	III	No guideline possible	Veness (2006) had a few patients also receiving concurrent chemotherapy
Immunoglobulin	Intravenous	H&N	RT or chemoRT	P	Mose 1997 [41]	III	No guideline possible	
					Plevova 1997 [42]	V	No guideline possible	
Corticosteroids: betamethasone	Oral rinse	Parotid tumors	RT	P	Abdelaal 1989 [43]	V	No guideline possible	
					Leborgne 1998 [44]	III	No guideline possible	
Corticosteroids: prednisone	PO	H&N	RT	P	Pillsbury 1986 [45]	IV	No guideline possible	
					Osaki 1994 [46]	IV	No guideline possible	
Indomethacin	PO	H&N	ChemoRT	P	Rymes 1996 [47]	IV	No guideline possible	
					Kaushal 2001 [48]	III	No guideline possible	
Azelastrine	Topical gel	Hematological malignancies	High-dose chemo, with or without HSCT	T		IV	No guideline possible	
						IV	No guideline possible	
Mesalazine	PO	H&N	RT	T		III	No guideline possible	
						III	No guideline possible	

Table 1 (continued)

Name of agent	Route of administration	Cancer type	Treatment modality	Indication	References	Overall level of evidence	Guideline determination	Comments
Orogel	Intramuscular	H&N	RT or chemoRT	T	Valencia 2002 [49]	IV	No guideline possible	
Flurbiprofen	Tooth patch	H&N	RT	P	Stokman 2005 [50]	IV	No guideline possible	
Histamine	Topical gel	Hematological & other cancers	High-dose chemo (with or without TBI)	P	Elad 2006 [51]	III	No guideline possible	
Colchicine	Mouthwash	Hematological malignancies	High-dose chemo	T	Garavito 2008 [52]	IV	No guideline possible	
Placenter	Intramuscular	H&N	RT	T	Kaushal 2001 [48]	III	No guideline possible	Placenter compared to disprin, described above

H&N head and neck, P prevention, T treatment, RT radiotherapy, chemo chemotherapy, chemoRT chemoradiotherapy, HSCT hematopoietic stem cell transplant, TBI total body irradiation, PO per os

High-dose chemotherapy: prevention

Three articles reporting results from the same cohort of pediatric patients, who received high-dose or combination chemotherapy for hematological malignancies or solid tumors, were reviewed [23–25]. The original study was a prospective, randomized, non-blinded, two-period crossover study that compared an oral care protocol containing benzydamine to chlorhexidine [23, 24]. In the 34 children evaluated, benzydamine was found inferior to chlorhexidine in the prevention of oral mucositis. The authors commented that the results need to be confirmed in a separate larger trial. The acceptance and tolerance of benzydamine was reported in the third article published in the series [25]. Benzydamine was found acceptable and well tolerated by children over the age of 6 years [25]. The insufficient data did not allow for any guideline for or against the use of benzydamine for the prevention of oral mucositis in patients receiving high-dose chemotherapy.

High-dose chemotherapy: treatment

Three studies were reviewed, two tested benzydamine in adults [26, 27] and one in children [28]. Patients had hematological cancers or solid tumors other than head and neck cancer, and received high-dose chemotherapy. Total body irradiation was included in the conditioning regimen in 17/44 patients in the study conducted by Schubert and colleagues [27]. Benzydamine was consistently more effective than placebo to relieve oral mucositis-associated pain, but the difference was not significant in this multicenter, double-blind, placebo-controlled trial [27]. In a small pilot study of nine patients by Sonis et al. (1985), palliation of pain was reported by seven study subjects [26]. Mucosal irritation and burning, possibly associated with the alcohol base of the mouthwash, was the most frequently reported toxicity. No patient dropped out, however, due to this toxicity [26, 27]. In the pediatric study, three children were unwilling to tolerate the oral pain and irritation associated with benzydamine mouthwash contact and dropped out. Another three of four children who completed the protocol opted to continue therapy with the alternative mouthwash for pain, which included nystatin and lidocaine in sodium chloride [28]. Due to insufficient evidence and inconsistent results, the panel could not support any guideline for or against the use of benzydamine for the treatment of oral mucositis in patients receiving high-dose chemotherapy.

Diphenhydramine mouthwash

Head and neck radiotherapy: treatment

Three studies were reviewed [29–31]. Diphenhydramine, combined with hydrocortisone, nystatin, and tetracycline,

reduced oral mucositis in a pilot, double-blind, placebo-controlled study of 12 patients conducted by Rothwell and colleagues [29]. Carnel et al. (1990) compared diphenhydramine, combined with kaolin–pectin, with different oral rinses in a pilot, double-blind study, which included 18 subjects, who received radiotherapy or chemoradiotherapy (number of patients in each treatment modality was not specified) [30]. No conclusions were drawn regarding the effectiveness of diphenhydramine [30]. Finally, no significant difference between groups was found in a prospective, double-blind, non-controlled study by Barker et al. (1991), which tested diphenhydramine, combined with kaolin–pectin, against sucralfate suspension in 12 patients [31]. Pain was the primary endpoint investigated [31]. Insufficient evidence, the concomitant use of confounding agents, and inconsistent results between studies did not allow for any guideline for or against the use of diphenhydramine for the treatment of oral mucositis in patients receiving head and neck radiotherapy.

High-dose chemotherapy: treatment

Two studies were reviewed [32, 33]. Turhal and colleagues conducted a non-controlled study, and found that diphenhydramine, combined with lidocaine and sodium bicarbonate, provided effective symptomatic relief [32]. Nine of the 31 patients evaluated had hematological malignancies and underwent HSCT. Four patients received radiotherapy, not otherwise specified. In the second article reviewed, Dodd et al. (2000) conducted a randomized, double-blinded study, where diphenhydramine combined with lidocaine and aluminum hydroxide (Maalox) was compared with two other mouthwashes, one of which was chlorhexidine 0.12 % and the second was salt and soda in water [33]. The patients received chemotherapy for hematological malignancies and solid tumors. No significant differences in time for the cessation of the signs and symptoms of mucositis were observed among the three groups. Pain relief was the primary endpoint in both studies. Insufficient evidence, the concomitant use of confounding agents, and inconsistent results between the studies did not allow for any guideline for or against the use of diphenhydramine for the treatment of oral mucositis in patients receiving high-dose chemotherapy.

Prostaglandin E2 lozenges

Head and neck chemoradiotherapy, high-dose chemotherapy: prevention

Two papers were reviewed [34, 35]. Firstly, in 10 patients with oral cancers, who received chemoradiotherapy, prostaglandin E2 (PGE2) lozenges reduced pain and oral mucosal

inflammation when compared with controls. No systemic absorption was found [34]. This study was blinded and placebo controlled, but subjects were not randomly assigned to PGE2 or placebo. Statistical analysis of results was not described. In the randomized, double-blind, placebo-controlled study by Labar and colleagues, PGE2 lozenges did not prevent oral mucositis in patients with leukemia, who received high-dose chemotherapy with or without TBI for HSCT [35]. A significantly higher incidence of HSV infections was also found in the prostaglandin group [35]. Due to insufficient evidence, the panel could not support any guideline for or against the use of topical PGE2 to prevent oral mucositis in these cancer settings.

Head and neck chemotherapy or chemoradiotherapy, high-dose chemotherapy: treatment

Two studies were reviewed [36, 37]. In a small, uncontrolled pilot study, topical PGE2 reduced pain and oral inflammation in 4/6 patients with oral mucositis [36]. PGE2 was also reported to prevent oral lesions in two more patients in the same report [36]. Five of the study patients had oral or oropharyngeal cancers. In the second study reviewed, prostaglandin lozenges promoted healing of oral mucositis in 9/11 patients when compared with three control subjects, who used antiseptic lozenges and gargles [37]. All patients had received chemotherapy with or without skull irradiation or high-dose chemotherapy prior to HSCT for the treatment of hematological malignancies. Randomization and blinding were not used, and there was no statistical analysis of the results. As such, insufficient evidence prevented the panel from being able to develop any guideline for or against the use of PGE2 for the treatment of oral mucositis in the above cancer settings.

Misoprostol

High-dose chemotherapy: prevention

In a study by Duenas-Gonzalez et al. (1996), the incidence and severity of oral mucositis was increased in patients with hematological and solid malignancies, who received high-dose chemotherapy prior to HSCT and were treated with misoprostol tablets (nine patients) when compared with the placebo control group (seven patients) [38]. The study was prematurely closed because of the significant difference in the incidence and severity of oral mucositis favoring the placebo patients. No guideline was possible in this population due to the single study reviewed.

Head and neck radiotherapy: prevention

Misoprostol oral rinse was studied in a randomized double-blind placebo controlled study in head and neck cancer

patients, receiving post-operative radiotherapy at one of two study sites. Data from one study site showed a decrease in the mean mucositis scores in the misoprostol group at the fourth and fifth week of RT, with no significant decrease seen at the sixth and seventh weeks. No benefit of misoprostol was seen at the second site or when data from both sites were analyzed together [39]. In another study of 83 subjects, misoprostol, used as an oral rinse before swallowing, did not reduce the incidence of oral mucositis in head and neck cancer patients, who received radiotherapy or chemoradiotherapy [40]. There was also no difference in oropharyngeal/oral soreness and general well-being, as reported by study subjects. Both studies were randomized, double blind, and placebo-controlled. The overall negative results from both studies supported a new suggestion against the use of misoprostol for the prevention of radiation-induced oral mucositis in head and neck cancer patients.

Previous guideline None

New guideline The panel suggests that misoprostol mouthwash should not be used for the prevention of radiation-induced oral mucositis in head and neck cancer patients.

Immunoglobulin

Head and neck radiotherapy or chemoradiotherapy/ intramuscular administration: prevention

Weekly intramuscular administration of immunoglobulin in head and neck cancer patients, who received radiotherapy or chemoradiotherapy reduced, though not significantly, oral mucositis severity when compared with controls [41]. The study was not randomized nor double blinded. No guideline was possible due to insufficient evidence.

High-dose chemotherapy/i.v. administration: prevention

A single, intravenous administration of immunoglobulin reduced oral mucositis in two children with leukemia, who received high-dose chemotherapy [42]. Those two children had developed grade 3 oral mucositis following previous chemotherapy without immunoglobulin. No guideline was possible due to insufficient evidence.

Corticosteroids

Head and neck radiotherapy: prevention

6a Betamethasone rinse, without swallowing, prevented oral mucositis in a total of five study patients (100 %) with parotid tumors, who were irradiated [43].

Methodology was not adequately described and controls were not used.

6b Prednisone tablets given orally, 40 mg/day, administered for 8 days following the initiation of radiotherapy in 32 head and neck cancer patients, did not reduce the intensity or duration of oral mucositis in a randomized, double-blind, placebo-controlled study [44]. These two studies provided insufficient evidence to support any guideline for or against the use of corticosteroids for prevention of oral mucositis due to cancer therapy.

Indomethacin PO (tablets given orally)

Head and neck radiotherapy: prevention

Daily per os indomethacin significantly delayed the onset of grade 3 oral mucositis in 10 head and neck cancer patients, who received radiotherapy when compared to eight controls [45]. The study was prospective, randomized, double blind, and placebo controlled. The grades of oral mucositis were not adequately described and the number of study patients was small. As such, there was insufficient evidence to support any guideline for the use of indomethacin for the prevention of oral mucositis due to cancer therapy.

Azelastine PO (tablets given orally)

Head and neck chemoradiotherapy: prevention

Azelastine hydrochloride is thought to have an anti-inflammatory action, based on its leukocyte suppression effect. Daily per os azelastine significantly reduced the severity of oral mucositis in 37 patients with oral cancer, treated with chemoradiotherapy, when compared with 26 controls [46]. The study was prospective, randomized, and controlled but not blinded. The beneficial effect of azelastine was attributed to the anti-oxidant action of the agent. The authors suggested further studies. This single study provided insufficient evidence to support any guideline for the use of azelastine for the prevention of oral mucositis due to cancer therapy.

Mesalazine topical gel

High-dose chemotherapy: treatment

Some symptomatic relief following daily topical mesalazine (5-aminosalicylic acid) gel was reported, using a questionnaire, by 10 of 12 patients with hematological malignancies, treated with high-dose chemotherapy with or without HSCT [47]. The study was open-label, non-randomized, and oral

mucositis was not formally graded. This study provided insufficient evidence to support any guideline for the use of mesalazine for the treatment of oral mucositis due to cancer therapy.

Disprin PO (tablets dissolved in water)

Head and neck radiotherapy: treatment

Guideline No guideline possible. Disprin (aspirin) tablets, dissolved in water and combined with betamethasone drops, were tested in the treatment of radiation-induced oral mucositis. The agent did not show a beneficial effect on oral mucositis when compared with placentrex extracts [48]. The study was prospective and randomized. The blinded method was not used, statistical analysis was not shown, and oral mucositis was not adequately recorded. This single study provided insufficient evidence to support any guideline for the use of Disprin/aspirin for the treatment of oral mucositis due to cancer therapy.

Orgotein intramuscular injection

Head and neck radiotherapy or chemoradiotherapy: treatment

Orgotein (superoxide dismutase) catalyzes the dismutation of damaging superoxide radicals, acting as an antioxidant. In a retrospective study, orgotein administered three times per week appeared to reduce the severity of oral mucositis in 40 head and neck cancer patients treated with radiotherapy or chemoradiotherapy [49]. A 92.5 % overall response was reported. No controls were used. The authors suggested additional, controlled studies to define the exact role of orgotein in the treatment of oral mucositis. To date, there is insufficient evidence from this single study to support any guideline for the use of orgotein for the treatment of oral mucositis due to cancer therapy.

Flurbiprofen tooth patch

Head and neck radiotherapy: prevention

Flurbiprofen, administered as a tooth patch that released drug locally in the oral cavity, did not reduce the severity and duration of oral mucositis in 12 head and neck cancer patients treated with RT, when compared with historical controls [50]. However, the onset of pseudomembranous/ulcerative mucositis occurred significantly later in the flurbiprofen group. This single study provided insufficient evidence to support any guideline regarding the use of

flurbiprofen for the prevention of oral mucositis due to cancer therapy.

Histamine topical gel

High-dose chemotherapy: prevention

Histamine dihydrochloride did not prevent oral mucositis in patients with hematological and other cancers, who received chemotherapy and HSCT, with or without total body irradiation (TBI) [51]. Histamine gel was safe without severe adverse events. A total of 45 patients were enrolled in the study which was prospective, longitudinal, placebo controlled, and double blind. Further studies were suggested to compare various dosages of the agent in HSCT patients in order to establish an optimal clinical effect with minimum side effects. Insufficient evidence provided by this single study did not allow for the generation of any guideline regarding the use of histamine for the prevention of oral mucositis due to cancer therapy.

Colchicine mouthwash

High-dose chemotherapy: treatment

Colchicine is an anti-gout agent that has anti-inflammatory activity. Colchicine significantly reduced the severity and duration of oral mucositis in 40 patients with hematological malignancies treated with high-dose chemotherapy, when compared with 42 historical controls who used saline mouthwash [52]. Colchicine was well tolerated. This single study provided insufficient evidence to support any guideline for the use of colchicine for the treatment of oral mucositis due to cancer therapy.

Placentrex intramuscular injection

Head and neck radiotherapy: treatment

Placentrex (human placental extract) has been suggested to have anti-inflammatory, analgesic, and immunostimulant properties. It was administered intramuscularly to 60 head and neck cancer patients with radiotherapy-induced oral mucositis, and resulted in decreased oral pain when compared with 60 controls, who had received disprin gargles and betamethasone [48]. The study was prospective and randomized. However, the blinded method was not used, statistical analysis was not shown, and oral mucositis was not adequately recorded. Insufficient evidence was provided by this single study to support any guideline for the use of placentrex for the treatment of oral mucositis due to cancer therapy.

Discussion

Several studies have demonstrated that the administration of chemotherapy or radiation therapy results in a pronounced inflammatory response in the oral mucosa. For example, in a hamster cheek pouch model of radiation mucositis, it has been demonstrated that peak clinical mucosal injury is accompanied by a significant increase in inflammatory cell infiltrate as compared to baseline. Further, mRNA levels of TNF- α and IL-1 β in the oral mucosal tissue correlated with severity of mucosal injury [53]. In a human study, levels of cyclooxygenase-2 (COX-2) and nuclear factor kappa-B (NFkB) in the oral mucosa were significantly increased following cytotoxic chemotherapy [54]. These and other studies have provided a rationale for testing anti-inflammatory agents for the prevention or treatment of oral mucositis.

Benzylamine hydrochloride is a non-steroidal anti-inflammatory drug (NSAID), which has been shown to inhibit inflammatory cytokine production, such as TNF- α and IL-1 β [55, 56]. In vivo treatment with benzylamine protected mice against lipopolysaccharide (LPS)-induced lethality. Protection against LPS toxicity was associated with a marked reduction of serum levels of TNF- α and IL-1 β . The previous version of our guidelines included a recommendation for the use of benzylamine mouthwash to prevent oral mucositis in head and neck cancer patients, who receive moderate-dose radiotherapy [4–6, 12, 14–17]. This was based on evidence from studies showing a benefit in radiation doses up to 50 Gy, in patients who did not receive concomitant chemotherapy. For this update, we reviewed two additional studies in this patient population. However, these studies did not allow the extension of this recommendation to patients receiving over 50 Gy radiation. Similarly, in other cancer treatment settings, including head and neck cancer patients receiving concomitant chemoradiation, the evidence did not support the development of any guidelines. Some studies reported intolerance to the topical benzylamine, with the alcohol base considered a major cause of noncompliance in children [28]. Well-designed studies with new formulations of benzylamine would clarify the potential promising effect of this agent in various cancer populations.

In general, NSAIDs are known to have anti-inflammatory properties, including suppression of the cyclooxygenase pathway and inhibition of production of pro-inflammatory prostaglandins. A number of NSAIDs have been evaluated for oral mucositis, including systemic indomethacin and aspirin. We also reviewed studies on the use of topical mesalazine and flurbiprofen. However, these single studies of different NSAIDs had inconsistent results and no clear conclusion could be drawn. Corticosteroids are more potent anti-inflammatory agents than NSAIDs. One

uncontrolled case series of topical steroids suggested a beneficial effect in radiation-induced oral mucositis. But a randomized, double-blind, placebo-controlled study of systemic prednisone demonstrated no benefit in a similar population [44].

Misoprostol is a synthetic analog of prostaglandin E1 (PGE1), which has anti-inflammatory properties. Misoprostol also protects the mucosa and has been approved for reducing the risk of gastric ulcers induced by NSAID use. However, the studies we reviewed supported the development of a new suggestion against the use of misoprostol mouthwash to prevent radiation-induced oral mucositis in head and neck cancer patients [38–40]. We reviewed a single study of misoprostol in chemotherapy-induced mucositis, which was prematurely closed due to more severe mucositis in the misoprostol group. No guideline was possible in chemotherapy patients based on this one study. However, a recent study by Lalla et al., published after the cut-off date for this review, also indicates a lack of efficacy of this agent for chemotherapy-induced oral mucositis [57]. Unlike PGE1, prostaglandin E2 is considered to be pro-inflammatory, but is also cytoprotective and promotes healing of gastric ulcerations. Interestingly, three of four studies of topical PGE2 reported a positive effect. However, these were uncontrolled preliminary studies. The only randomized double-blind placebo-controlled study of topical PGE2 found no difference in the incidence or duration of severe oral mucositis and a higher incidence of HSV infection in the PGE2 group [35].

Diphenhydramine HCL is an antihistamine which also has topical and local anesthetic properties. It is a common component of various combination rinses that are called “Magic” or “Miracle” mouthwashes. Although a number of studies examined the use of diphenhydramine for mucositis, it was always used in combination with other agents that made it difficult to definitively ascribe any benefit or lack thereof to diphenhydramine. Further, the results of these studies were mixed. Mild pain relief can be expected with topical diphenhydramine use, but the evidence does not support a direct effect of this antihistaminic on the prevention or treatment of mucositis lesions. Related to this, the use of topical histamine was also found to have no effect on oral mucositis in patients receiving high-dose chemotherapy for HSCT [51].

Despite the lack of clear evidence supporting the use of any anti-inflammatory agent other than benzylamine, the use of anti-inflammatory agents continues to be a promising strategy for the prevention and treatment of oral mucositis. Preliminary studies of a few anti-inflammatory agents have suggested potential benefit. However, definitive conclusions were hampered by flawed study designs, non-homogeneous patient populations and treatment modalities, small numbers of study subjects, varied modes of administration of study

drug, administration in combination with other potentially active agents, intolerance of the vehicle/base leading to noncompliance, and other factors. Additional well-designed studies are needed to examine the use of anti-inflammatory agents for oral mucositis in various cancer treatment settings.

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