Oral Mucositis Complicating Chemotherapy and/or Radiotherapy: Options for Prevention and Treatment

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ABSTRACT Chemotherapy- and radiotherapy-induced oral mucositis represents a therapeutic challenge frequently encountered in cancer patients. This side effect causes significant morbidity and may delay the treatment plan, as well as increase therapeutic expenses.

The pathogenesis of this debilitating side effect can be attributed to the direct mucosal toxicity of cytotoxic agents and ionizing radiation and to indirect mucosal damage caused by a concomitant inflammatory reaction exacerbated in the presence of neutropenia, and the emergence of bacterial, mycotic, and viral infections. The prophylactic and therapeutic armamentarium for the treatment of oral mucositis consists of locally and systemically applied nonpharmacological measures and pharmacotherapeutics. (*CA Cancer J Clin* 2001; 51: 290-315.)

INTRODUCTION

Oral mucositis represents a major non-hematologic complication of cytotoxic chemotherapy and radiotherapy associated with significant morbidity; pain, odynodysphagia, dysgeusia, and subsequent dehydration and malnutrition reduce the quality of life of affected patients. In addition, oral mucositis represents a significant risk factor for systemic infections, particularly in neutropenic patients.[1] Consecutive protraction or termination of antineoplastic therapy may lead to treatment failure and result in increases in therapeutic expenses.[2-6]

The term oral mucositis emerged in the late 1980s to describe the chemotherapy- and radiotherapy-induced inflammation of the oral mucosa, which represents a separate entity distinct from oral lesions with other pathogenic background summarized as stomatitis.[7]

Incidence, Pathogenesis, and Predisposing Factors for Oral Mucositis

The incidence and severity of oral mucositis is influenced by the type of antineoplastic treatment administered and by patient-related factors. Severe courses of oral mucositis are observed during simultaneous radiochemotherapy, which

affects virtually all patients with head and neck cancer who receive this therapeutic modality.[8] However, up to 40% of patients treated with conventional chemotherapy and the more than 70% of patients undergoing conditioning therapy for bone marrow transplantation also experience oral treatment-related complications.[9,10]

The pathogenesis of oral mucositis is not fully understood, yet it is thought to involve direct and indirect mechanisms. Direct mucosal injury by radiation and chemotherapy interfere with the average 5- to 14-day turnover time of the oral epithelium[11] and induce apoptosis. Indirect stomatotoxic effects that result from the release of inflammatory mediators, loss of protective salivary constituents, and therapy-induced neutropenia have been postulated to contribute to the development of oral mucositis and also promote the emergence of bacteria, fungi, and viruses on damaged mucosa.[12] Although a linear relationship among the occurrence of oral mucositis, oral and systemic granulocyte counts, and a coincidence of resolution of mucositis with neutrophil recovery, has been demonstrated,[10,13-15] significant mucositis can occur in the absence of myelotoxicity.[16,17] In addition, the prophylactic or therapeutic elimination of the pathogenic mucosal flora frequently observed in patients developing oral mucositis by various antiseptic and antimicrobial agents can at most alleviate the course of oral mucositis (see *Antimicrobal Agents* p. 302).

Based upon these considerations, newer pathophysiologic concepts have emerged characterizing oral mucositis as having an initial inflammatory/vascular phase, an epithelial phase, a (pseudomembraneous) ulcerative/bacteriological phase and a healing phase.[18] During the inflammatory phase, tissue injury induces release of free radicals, modified proteins and proinflammatory cytokines including interleukin-1β, prostaglandins and tumor necrosis factor-α (TNF-α) by epithelial, endothelial, and connective tissue cells. These inflammatory mediators are thought to cause further damage, either directly or by increasing vascular permeability thus enhancing the accumulation of cytotoxic drugs. In contrast, release of anti-inflammatory cytokines, such as Interleukin-11, may counteract this early inflammatory response.[19]

The epithelial phase occurring 4 to 5 days after cytotoxic treatment is mediated by the proapoptotic and/or cytotoxic effect of chemotherapy and radiotherapy on dividing basal cells. The degree of tissue damage in this phase is directly related to the proliferative rate of the oral epithelium: The higher incidence and the faster recovery from oral mucositis observed in younger patients as compared with elderly patients can be attributed to the higher mitotic rate of their basal cells.[20-23] Experimental data have shown that the course of oral mucositis may be modified by factors such as epidermal growth factor, keratinocyte growth factor, and transforming growth factor-β3,[19] which affect cellular turnover, the inflammatory response of the oral epithelium and immunologic effector cells.

Epithelial breakdown ultimately results in the ulcerative phase of oral mucositis typically occurring one week after the initiation of antineoplastic treatment. Loss of epithelia and fibrinous exudation lead to the formation of pseudomembranes and ulcers. In this phase, microbial colonization of damaged mucosal surfaces by gram-negative organisms and yeast may be exacerbated by concomitant neutropenia. In addition, the release of bacterial metabolites, including endotoxin, results in the respiratory burst of mononuclear cells, which further enhances the release of inflammatory mediators such as interleukin-1, nitric oxide and TNF-α.[18] Genetic polymorphisms in the expression of transcription factors modifying this inflammatory response may, in part, explain the individual differences in the severity of oral mucositis at this stage.[18]

TABLE **1**

Selected mucosatoxic antineoplastic agents (markedly mucosatoxic agents are printed in bold)

Actinomycin D	**Amsacrin**	**Bleomycin**
Carboplatin	Carmustin	**Chlorambucil**
Cisplatin	Cyclophosphamide	**Cytarabine**
Dacarbazine	Dactinomycin	**Daunorubicin**
Docetaxel	**Doxorubicin**	Epirubicin
Estramustine	**Etoposide**	**Floxuridine**
5-Fluorouracil	Fludarabine	Gemcitabine
Hydroxyurea	Idarubicin	Ifosfamide
Irinotecan	Lomustine	Mechlorethamine
Melphalan	Mercaptopurine	Mercaptopurine
Methotrexate	Mithramycin	Mitomycin
Mitotane	**Mitoxantron**	Paclitaxel
Plicamycin	Procarbazin	Streptozotocin
Thioguanin	Thiotepa	Topotecan
Vinblastine	Vincristine	**Vindesine**
Vinorelbine	Interleukin-2	Interferons

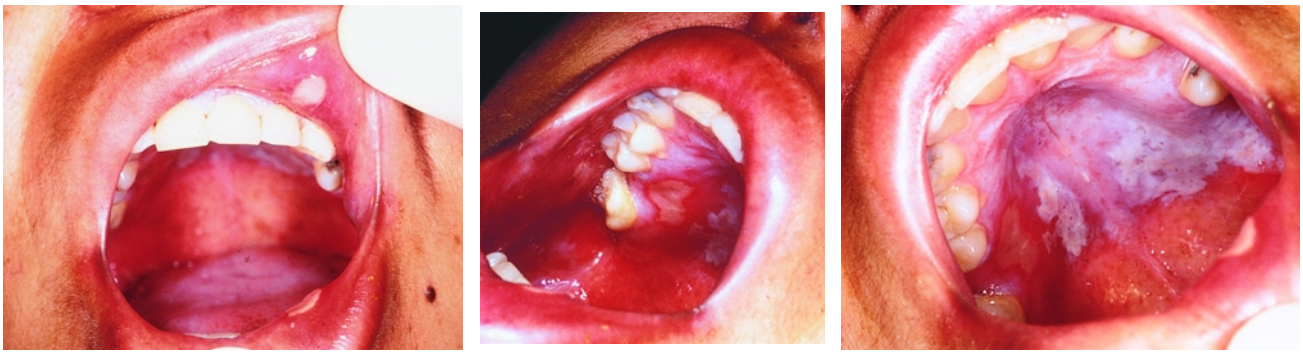
The duration of the healing phase, usually lasting from day 12 to 16, again critically depends upon epithelial proliferation rate, hematopoietic recovery, reestablishment of the local microbial flora, and the absence of factors interfering with wound healing, such as infection and mechanical irritation.[18,24]

Within the context of chemotherapy, mucosal toxicity depends upon the antineoplastic agent, the therapeutic regimen, duration of treatment and dose intensity, as well as upon concomitant medication and previous mucosatoxic treatments.[25-27] Prolonged or repetitive administration of lower doses of cytotoxic agents have been associated with an increased risk for the development of oral mucositis as compared with bolus infusions, whereas chronomodulation of chemotherapy has been shown to decrease mucosal toxicity without compromising antineoplastic activity.[27-29] The risk of developing oral mucositis increases with the number of chemotherapeutic cycles and previous episodes of chemotherapy-induced mucositis. Drugs affecting DNA synthesis (so-called S-phase specific agents such as 5-fluorouracil, methotrexate and cytarabine) exhibit the most pronounced stomatotoxic effects. (A survey of antineoplastic agents with known mucosal toxicity is given in Table 1.) Concomitant total body irradiation during conditioning therapy for stem cell transplantation further increases the risk of developing oral mucositis.[7]

The degree and duration of mucositis in patients treated with radiotherapy is related to the radiation source, cumulative dose, dose intensity, the volume of irradiated mucosa, smoking and alcohol consumption habits, and other predisposing factors such as xerostomia or infection.[30-32] In standard 200 centi-Gray (cGy) daily fractioned radiotherapy programs, mucosal erythema occurs within the first week of treatment. Patchy or confluent pseudomembranous radiation-induced mucositis peaks during the fourth to fifth week of therapy. Less severe mucositis is noted in programs with daily fractions lower than 200 cGy, however in accelerated radiotherapy programs mucositis peaks within 3 weeks. The effects of radiotherapy upon epithelial cells are further enhanced by connective tissue damage.[33] In immunocompetent hosts, radiotherapy-induced oral lesions usually heal within 3 weeks after cessation of radiotherapy. Mucositis caused by interstitial radioactive implants usually appears in 7 to 10 days and peaks after 2 weeks. These lesions usually heal within several weeks unless large mucosal areas have been damaged.

Other factors influencing an individual's risk of developing oral mucositis include defects of certain metabolic enzymes (e.g., dihydropyrimidine dehydrogenase) and DNA-repair mechanisms, deficiencies of folic acid and vitamin B_{12}, delayed elimination of antineoplastic agents due to impaired renal or hepatic function, and pleural or peritoneal effusions, or the administration of specific antidotes such as leucovorin.[7,10,28,34] Underlying hematologic malignancy[9] and preexisting oral pathology, including xerostomia, also promote

FIGURE **1**



Severe chemotherapy-induced oral mucositis exhibiting erythema. Ulcerations covered by fibrinous pseudomembranes and secondary yeast colonization.

mucositis. The risk caused by xerostomia may be attributed to the decreased production and reduced buffering capacity of saliva, an increase in the viscosity and acidity of saliva, and reduced oral IgA levels favoring the growth of a highly cariogenic and infectious oral flora.[35-39]

Symptoms and Diagnostic Workup

The earliest signs and symptoms of oral mucositis include erythema and edema, a burning sensation, and an increased sensitivity to hot or spicy food. Erythematous areas may develop into elevated white desquamative patches and subsequently into painful ulcers (Figure 1).[7] The latter are not only often secondarily infected, but also impair nutrition and fluid intake, resulting in malnutrition and dehydration which further interfere with mucosal regeneration.

The movable nonkeratinized mucosa of the soft palate, cheeks and lips, the ventral surface of the tongue, and the floor of the mouth are most vulnerable to direct stomatotoxicity, whereas the gingiva, dorsal surface of the tongue, or the hard palate are rarely affected—probably due to their slower rate of cellular turnover. Interestingly, lesions tend to reappear in the same location in each episode of mucositis.[13] Oral lesions usually disappear without scar formation unless mucositis is complicated by serious infection or xerostomia. However, other oral sequelae of cytotoxic therapy such as epithelial hyperplasia and dysplasia, as well as glandular and connective tissue degeneration, may persist.[40] The severity of oral mucositis occurring in the course of antineoplastic therapy is most frequently graded according to National Cancer Institute-CTC or World Health Organization criteria (Table 2), but more detailed scoring schemes may be applied if the prophylaxis or management of oral mucositis represents a primary study endpoint.[41]

TREATMENT

Despite multimodal prophylaxis and therapy, oral mucositis often takes a therapeutically refractory turn necessitating the use of topical and systemic analgesics. Although a variety of new approaches to oral mucositis have been taken, a single efficacious intervention or agent for the prophylaxis or management of radiotherapy- or chemotherapy-induced oral mucositis has not yet been identified. This section attempts to review prophylactic and therapeutic interventions for oral mucositis. However, evaluating these interventions remains difficult because of the polypharmacy of approaches, the heterogeneity

TABLE **2**

Toxicity grading of oral mucositis according to WHO[227] and NCI-CTC[228] criteria

Side effect	Grade 0 (none)	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life threatening)
WHO oral mucositis (stomatitis)	none	oral soreness, erythema	oral erythema, ulcers, can eat solids	oral ulcers, requires liquid diet only	oral alimentation not possible
NCI-CTC chemotherapy-induced stomatitis/pharyngitis (oral/pharyngeal mucositis)	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swallow	painful erythema, edema, or ulcers requiring IV hydration	severe ulceration or requires parenteral or enteral nutritional support or prophylactic intubation
NCI-CTC mucositis due to radiation	none	erythema of the mucosa	patchy pseudomembranous reaction (patches generally ≤1.5 cm in diameter and noncontiguous)	confluent pseudomembranous reaction (contiguous patches generally >1.5 cm in diameter)	necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion
NCI-CTC stomatitis/pharyngitis (oral/pharyngeal mucositis) for BMT studies	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can swallow	painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support	severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia

of patient populations, and the relatively small number of double-blind and placebo-controlled clinical trials. To review the available data, we have categorized preventive and treatment approaches into established, experimental, and inefficacious locally and systemically applied pharmacological and nonpharmacological methods for the prevention and treatment of oral mucositis. (For an overview see Table 3.)

ESTABLISHED METHODS

Locally Applied Nonpharmacological Methods

Oral Hygiene

Poor oral care with concomitant dental and periodontal pathology, such as dental caries, periodontal and pulpal disease, including third molar pathology, leads to a greater risk for oral complications in the course of cytotoxic therapy. Similarly, ill-fitting prostheses, orthodontic appliances, defective restorations, and other sources of mucosal and gingival irritation have been associated with an increased risk of developing oral mucositis during antineoplastic therapy.[23,42-51] Although they are a risk factor for the development of osteoradionecrosis, periapical lesions in endodontically treated teeth do not seem to predispose the development of oral mucositis.[52]

Careful inspection of the oral cavity should be included in the diagnostic workup before initiation of potentially mucosatoxic therapy, and should be repeated in the course of treatment. This practice not only allows for the differentiation of oral mucositis from preexisting changes, such as pemphigoid, lichen planus, leukoplakia, and graft-versus-host diesase, but also permits the identification

and elimination of preexisting potential sources of infection. In addition to an inspection of the oral cavity, the pretherapeutic workup should include peridontal, dental and, if necessary, radiographic evaluation to identify caries, periapical, third molar, and peridontal pathology.[9,53] Additionally, hard and soft, fixed and removable prostheses have to be cautiously examined. If prolonged neutropenic episodes are expected and specific pathogens such as candida or herpes simplex virus are suspected, the procedure can be complemented by histological, cytological, microbiologic, and serologic examinations, and allows for a significant reduction of complications of antineoplastic therapy.[54]

Meticulous pretreatment assessment, restorative dental procedures performed at least three weeks before the initiation of mucosatoxic therapy, and oral care during therapy have all been shown to reduce the incidence and duration of oral mucositis and complicating infections, and therapeutic expenses.[35,36,43,44,55,56] Preexisting xerostomia is associated with an increased bacterial colonization on dental surfaces and prostheses and, thus, a higher incidence of oral mucositis and dental caries in the course of antineoplastic therapy. Furthermore, optimal functioning of oral chemoreceptors requires some moisture. Xerostomia, therefore, reduces taste sensation as well as the neurogenic stimulation of saliva flow initiated by taste. Xerostomia may be ameliorated by treatment of any underlying autoimmune disease, avoidance of other drugs that decrease salivary flow (e.g., tricyclic antidepressants), and by mechanical debridement of the dorsum of the tongue to allow optimal stimulation of chemoreceptors. In addition, stimulation of salivary flow may be achieved by the use of nonirritating, cinnamon-free, mint-free, and sugar-free drops or chewing gum, alkaline saline solutions, or by low dose pilocarpine. Salivary substitutes containing methylcellulose or mucopolysaccharides may be indicated.[37, 57-60]

Although they have not been evaluated in clinical trials, topical fluorides that are applied as (brushing) gels, rinses, and vacuum-formed vinyl splints loaded with fluoride gel are frequently used to prevent caries and mucositis in the course of radiotherapy because they induce fluoride incorporation into tooth enamel and dentin. They also reduce oral bacterial load. Although acidulated fluorides such as stannous fluoride are thought to be most effective, neutral fluorides such as sodium fluoride may be required if there is an irritation of the oral mucosa or a pitting of porcelain prosthetics. In general, a treatment of fluoride prophylaxis followed by calcium phosphate remineralizing rinses is initiated at least one week before radiotherapy and continued indefinitely unless symptoms of oral mucositis require discontinuation of the treatment.

During mucosatoxic therapy, patients should be advised to perform frequent and effective mechanical plaque removal using a soft toothbrush and dental floss. To maintain oral moistness and to decrease cariogenic flora, patients should rinse with saline or bicarbonate solutions, use lip lubricants, and employ "sugarfree" products.[35,61] Since mechanical cleansing with a toothbrush may cause microtraumas, which promotes the occurrence of infections, foam brushes and rinsing solutions are most frequently recommended during radiotherapy or myeloablative chemotherapy.[62] In cases of preexisting mucosal irritation or thrombocytopenic hemorrhage, cotton swabs or sponges can be used instead of a toothbrush. In addition, patients should be advised to avoid wearing removable prostheses during mucosatoxic treatment, except while eating. It is also recommended that patients avoid factors that cause irritation, including hot, spicy, and coarse foods, fruits and beverages with a high acid content, and alcohol (including alcohol-containing elixirs). Patients should refrain from smoking.[32]

TABLE **3**

Clinical trials on prevention and treatment of oral mucositis

RT, CT, BMT	Author	Randomized/ Controlled/ Double-blind	P/T	Application/Doses	Results
1. Locally applied nonpharmacological methods					
a) Oral hygiene					
RT	Shieh et al.[55]	yes/yes/no	P	instructions on oral care	significant reduction
	Rugg et al.[32]	no/no/no	P	smoking during RT	higher mucositis incidence in smokers
CT	Greenberg et al.[44]	no/yes/no	P	dental treatment prior to CT	significant reduction of septicemia
CT+RT	Sonis et al.[36]	no/no/no	P	early and aggressive dental intervention	reduced frequency of oral complications
BMT	Peters et al.[52]	no/no/no	P	treatment of asymptomatic periapical radiolucencies	no difference in infectious complications
BMT	Borowski et al.[35]	yes/yes/no	P	intensive vs. regular oral care	significant reduction of mucositis but not septicemia
b) Radiation shields					
RT	Perch et al.[106]	no/no/no	P	midline mucosa sparing blocks	decreased mucositis without affecting tumor control
	Keus et al.[104]	no/yes/no	P	customized beam shaping	lower incidence of mucositis
c) Soft lasers					
BMT	Barasch et al.[109]	yes/yes/no	P	laser on one buccal side, placebo light to the other	significant reduction
	Cowen et al.[110]	yes/yes/no	P	laser vs. no treatment	significant reduction of incidence
CT	Ciais et al.[107]	no/yes/no	P+T	soft laser treatment	lowers incidence and alleviates course of mucositis
d) Cryotherapy					
CT	Mahood et al.[67]	yes/yes/no	P	oral cryotherapy vs. no prophylaxis	significant lower incidence
	Rocke et al.[65]	yes/yes/no	P	30 vs. 60 minutes of cryotherapy during	equivalent
	Cascinu et al.[66]	yes/yes/no	P	oral cryotherapy vs. no prophylaxis	significant lower incidence
	Edelman et al.[68]	no/yes/no	P	ice chips during dose escalation of edatrexate	lower incidence of mucositis
	Gandara et al.[69]	no/yes/no	P	ice chips during edatrexate-based CT	lower incidence of severe mucositis
2. Locally applied pharmacotherapeutics					
e) Mouth-coating agents					
Sucralfate					
CT	Loprinzi et al.[130]	yes/yes/yes	T	sucralfate vs. placebo after cryoprophylaxis	no difference
RT	Scherlacher et al.[120]	yes/yes/no	P	sucralfate vs. standard oral hygiene	significant reduction of incidence and severity of mucositis

RT = Radiotherapy
CT = Chemotherapy
BMT = Bone Marrow Transplantation
P/T = Prevention or Treatment
HD-CT = High-dose Chemotherapy
TBI = Total Body Irradiation

TABLE **3**—Continued

	Allison et al.[121]	yes/yes/no	P+T	sucralfate+fluconazole vs. standard oral care	significant reduced severity and symptomatic relief
	Franzen et al.[122]	yes/yes/yes	P	sucralfate vs. placebo	sig. lower incidence of severe mucositis
	Makkonen et al.[123]	yes/yes/yes	P	sucralfate vs. placebo	only slight protective effect of sucralfate
	Epstein et al.[125]	yes/yes/yes	P+T	sucralfate vs. placebo	nonsignificant reduction of oral discomfort
	Meredith et al.[124]	yes/yes/yes	T	antacid,diphenhydramine, lidocaine ± sucralfate	nonsignificant reduction of severity
	Cengiz et al.[229]	yes/yes/yes	P+T	sucralfate vs. placebo	decreased severity
	Carter et al.[126]	yes/yes/yes	P	sucralfate vs. placebo	no difference
Kaolin-pectin					
RT	Barker et al.[101]	yes/yes/yes	P+T	oral hygiene+sucralfate vs. diphenhydramine+kaolin-pectin	no difference
f) Antiseptic and antibiotic agents					
Hydrogen peroxide					
RT	Feber et al.[211]	yes/yes/no	P	hydrogen peroxide vs. saline	significantly more oral discomfort
Chlorhexidine					
RT	Spijkervet et al.[207]	yes/yes/yes	P+T	chlorhexidine vs. placebo	no difference
	Foote et al.[208]	yes/yes/yes	P	chlorhexidine vs. placebo	slight aggravation
BMT	Ferretti et al.[78]	yes/yes/yes	P	chlorhexidine vs. placebo	significant reduction of incidence and duration, less candidemia
	Weisdorf et al.[205]	yes/yes/yes	P	chlorhexidine vs. placebo	no difference
	Rutkauskas et al.[204]	yes/yes/yes	P	chlorhexidine vs. placebo	significant reduction
HD-CT+RT	Feretti et al.[12]	yes/yes/yes	P+T	chlorhexidine vs. placebo	significant reduction of incidence and severity in the CT group only
CT	McGaw et al.[203]	yes/yes/yes	P	chlorhexidine vs. placebo	significant reduction
	Wahlin et al.[206]	yes/yes/yes	P	chlorhexidine vs. standard oral care	slight aggravation
CT+BMT	Epstein et al.[81]	yes/yes/no	P	nystatin, saline ± chlorhexidine	no difference
PVP-iodine					
CT+RT	Rahn et al.[161]	yes/yes/no	P	nystatin, rutosides, immuno-globuines, panthenol±PVP-iodine	significant reduction
	Adamiez et al.[165]	yes/yes/no	P	nystatin, rutosides, immuno-globulines, panthenol±PVP-iodine	significant reduction
	Hasenau et al.[162]	no/yes/no	P	hydrogen peroxide, PVP iodine, dexpanthenol, nystatin	lower incidence and severity of oral mucositis
Selective decontamination					
RT	Spijkervet et al.[71]	no/yes/no	P	lozenges of polymyxin, tobramycin,amphotericin vs. historical controls	lower incidence of mucositis
	Mattews et al.[98]	yes/yes/no	P	sucralfate+(ciprofloxacin or ampicillin)+ clotrimazole vs. sucralfate	sig. reduction of incidence and severity
	Symonds et al.[90]	yes/yes/yes	P	pastilles containing polymyxin, tobramycin, amphothericin vs. placebo	significant reduction of severe mucositis
	Okuno et al.[89]	yes/yes/yes	P+T	lozenges of polymyxin, tobramy-cin, amphotericin vs. placebo	significant reduction of oral discomfort, no objective difference
BMT	Bondi et al.[88]	yes/yes/no	T	polymyxin, tobramycin, amphothericin, chlorhexidine vs. diphenhydramine, magnesium- and aluminium-hydroxide, lidocaine	antibiotic regimen more effective
g) Antifungal agents					
Nystatin					

TABLE **3**—Continued

BMT+CT	Barrett et al.[82]	no/yes/no	P	topical nystatin during granulocytopenia	no impact upon candida infections
	Epstein et al.[81]	no/yes/no	P	chlorhexidine+nystatin+saline vs. historical controls	no reduction in mucositis incidence
CT	Carpentieri et al.[80]	no/yes/no	P	nystatin prophylaxis	lower incidence of mucositis
	Williams et al.[83]	yes/yes/no	P	nystatin vs. natamycin vs. no prophylaxis	no difference
Clotrimazole					
CT	Aviles et al.[86]	no/yes/no	P	topical clotrimazole	lower incidence of oral candidiasis
	Yeo et al.[84]	yes/yes/no	P	topical clotrimazole vs. no prophylaxis	lower incidence of orophayngeal candidiasis
	Yap et al.[85]	yes/yes/yes	T	50 mg vs. 10 mg clotrimazole troches	50 mg troches more effective in manifest oropharyngeal candidiasis
Fluconazole					
CT	Samonis et al.[87]	yes/yes/yes	P	fluconazole p.o. vs. placebo	lower incidence of oropharyngeal candidiasis
Amphotericin B					
CT	Bondi et al.[88]	no/yes/yes	T	amphotericin+tobramycin+ polymyxin vs. diphenhydramine, aluminium- and magnesium-hydroxide+local anesthetic	superior activity
RT	Okuno et al.[89]	yes/yes/no	T	amphotericin+colistin+tobramycin +chlorhexidine vs. placebo	decreased oral discomfort
	Symonds et al.[90]	yes/yes/yes	P	amphotericin+tobramycin+ polymyxin vs. placebo	significant reduction of the incidence of severe mucositis
	Spijkervet et al.[71]	no/yes/no	P	amphotericin+tobramycin+ polymyxin vs. historical chlorhexidine or placebo group	significant reduction of severity of mucositis
h) Anti-inflammatory agents					
Chamomile					
RT	Carl et al.[113]	no/yes/no	P+T	chamomile vs. historical group	low incidence of mucositis
	Fidler et al.[114]	yes/yes/yes	P	chamomile vs. placebo, cryoprophylaxis in all patients	no difference
Betamethasone					
RT	Abdelaal et al.[163]	no/no/no	P	high-dose betamethasone	impressive prevention of mucositis incidence
Benzydamine					
RT	Kim et al.[117]	yes/yes/yes	P+T	benzydamine vs. placebo	significant reduction (less pain)
	Epstein et al.[115]	yes/yes/yes	P+T	benzydamine vs. placebo	significant reduction of incidence and severity
	Samaranayake et al.[118]	yes/no/no	P	benzydamine vs. chlorhexidine	no difference (more discomfort)
CT+RT	Prada et al.[116]	yes/yes/yes	P+T	benzydamine vs. placebo	significant reduction
i) Cytoprotectants					
Allopurinol					
CT	Tsavaris et al.[197]	no/yes/no	P	allopurinol mouthwashes in pats. with mucositis history	lower incidence of mucositis
	Clark et al.[198]	no/yes/no	P	allopurinol mouthwashes in pats. with mucositis history	lower incidence of mucositis
	Loprinzi et al.[200]	yes/yes/yes	P	allopurinol mouthwashes vs. placebo	no difference
Glutamine					
RT	Huang et al.[140]	yes/yes/yes	P	glutamine suspension vs. placebo	sig. reduction of severity and duration
CT	Van Zaanen et al.[143]	yes/yes/yes	P	parenteral glutamine vs. placebo	no difference

TABLE **3**—Continued

CT	Anderson et al.[139]	yes/yes/yes	P	glutamine suspension vs. placebo	reduces severity and incidence of mucositis
CT	Jebb et al.[141]	yes/yes/yes	P	oral glutamine vs. placebo	no difference
BMT	Anderson et al.[142]	yes/yes/yes	P	oral glutamine vs. placebo	significant reduction of mucositis
Prostaglandin E_2					
CT+RT	Porteder et al.[131]	no/yes/no	P	PGE_2 or nothing	significant reduction (less pain)
RT	Matejka et al.[133]	no/yes/no	T	PGE_2 tablets four times a day	reduction of mucositis severity
BMT	Labar et al.[134]	yes/yes/yes	P	PGE_2 vs. placebo	no difference
Vitamin E					
CT	Wadleigh et al.[137]	yes/yes/yes	T	topical vitamin E vs. placebo	accelerated healing in vitamin E group
j) Multiagent mouthrinses					
CT+RT	Hasenau et al.[162]	no/no/no	P+T	hydrogen peroxide, nystatin, PVP-iodine, dexpanthenol	lower incidence of mucositis
RT	Rothwell et al.[164]	yes/yes/yes	P	hydrocortisone, nystatin, tetracyclines, diphenhydramine vs. placebo	significant reduction of incidence
k) Agents influencing mucosal proliferation					
Silver nitrate					
RT	Maciejewski et al.[144]	no/yes/no	P	applied to one side of buccal mucosa	significant reduction compared with contralateral side
	Dorr et al.[145]	no/yes/no	P	applied to one side of buccal mucosa	no difference compared with contralateral side
Tretinoin					
BMT	Cohen et al.[136]	yes/yes/no	P	0.1% topical tretinoin cream vs. controls	significant reduction of mucositis incidence
Transforming growth factor β3					
CT	Wymenga et al.[147]	no/yes/no	P	TGFβ3 mouthwashes	deserve further studies
l) Hematopoetic growth factors					
GM-CSF					
BMT	Bez et al.[151]	no/yes/no	T	GM-CSF mouthrinses	accelerated healing as compared with historical control
	Ovilla-Martinez et al.[152]	no/yes/no	T	GM-CSF mouthwashes	accelerated healing as compared with historical control
CT	Haus et al.[153]	no/yes/no	T	topical GM-CSF	reduction of duration and severity of mucositis
	Ibrahim et al.[17]	no/yes/no	T	GM-CSF mouthwashes	accelerated healing and reduction of severity of oral mucositis
	Cinat et al.[154]	no/yes/no	T	GM-CSF mouthwashes	accelerated healing of oral mucositis
	Lira-Puerto et al.[155]	no/yes/no	T	GM-CSF mouthwashes	accelerated healing of oral mucositis
	Hejna et al.[158]	yes/yes/no	T	GM-CSF mouthwashes vs. PVP-iodine, amphotericin and lidocaine	significant reduction of severity and duration
	Berberoglu et al.[156]	no/yes/no	T	GM-CSF mouthwashes	accelerated healing of mucositis
	Cartee et al.[159]	yes/yes/yes	P	GM-CSF mouthwashes vs. placebo	higher incidence of mucositis in the GM-CSF group
G-CSF					
BMT	Karthaus et al.[160]	yes/yes/no	P	G-CSF mouthwashes vs. placebo	lower incidence of severe mucositis
m) Local anesthetics					
CT	Le Veque et al.[100]	no/yes/no	T	benozcaine+mouth coating agent	significant reduction of oral discomfort
RT	Barker et al.[101]	yes/yes/yes	P+T	oral hygiene+sucralfate vs. diphenhydramine+kaolin-pectin	no difference
CT+RT	Berger et al.[167]	no/yes/no	T	capsaicin in a candy vehicle	significant temporary pain relief

TABLE **3**—Continued

	Carnel et al.[99]	yes/yes/yes	T	viscous lidocaine +cocaine vs. dyclonine vs. kaolin-pectin + diphenhydramine+ saline vs. placebo	favored dyclonine
3) Systemically applied pharmacotherapeutics					
n) Agents influencing mucosal proliferation					
Beta carotene					
CT+RT	Mills et al.[190]	yes/yes/no	P	betacarotene or nothing	decreased severity in the treatment group
o) Cytoprotectants					
Amifostine					
RT	Bourhis et al.[181]	yes/yes/no	P	amifostine or nothing	marked reduction of mucositis (tolerance was poor)
	Koukourakis et al.[180]	yes/yes/yes	P	amifostine vs. saline	significant reduction of mucositis
	Schonekas et al.[182]	no/yes/no	P	amifostine vs. controls	significant reduction of mucositis
	Wagner et al.[186]	yes/yes/no	P	amifostine or nothing	significant reduction of mucositis
CT+RT	Buntzel et al.[183]	yes/yes/no	P	amifostine or nothing	sig. reduction of mucositis and xerostomia
	Peters et al.[184]	yes/yes/no	P	amifostine or nothing	no significant difference
	Vacha et al.[185]	yes/yes/no	P	amifostine or nothing	trend towards reduction of mucositis
HD-CT	De Souza et al.[187]	no/yes/no	P	amifostine or nothing	significant reduction of mucositis compared with historical control
TBI	Gabriel et al.[188]	no/yes/no	P	amifostine or nothing	significant reduction of mucositis compared with historical control
CT	Fahlke et al.[189]	no/yes/no	P	amifostine or nothing	significant reduction of mucositis compared with controls
Glutamine					
CT	Jebb et al.[141]	yes/yes/no	P	glutamine or placebo	no difference
Azelastine					
CT+RT	Osaki et al.[191]	yes/yes/no	P	Vitamins C+E, glutathione ± azelastine	significant reduction
Allopurinol					
CT	Ahmann et al.[199]	no/yes/no	P	HD-5-FU + IV allopurinol vs. historical control	no difference
	Weiss et al.[201]	yes/yes/no	P	allopurinol or nothing	no difference
Uridine					
CT	Seiter et al.[202]	no/yes/no	P	uridine rescue after HD-5-FU	no sig. reduction of mucositis incidence
Propantheline					
CT	Ahmed et al.[192]	yes/yes/no	P	propantheline vs. placebo	significant lower incidence and severity of mucositis
p) Immunmodulatory drugs					
Pentoxifylline					
BMT	Bianco et al.[213]	no/no/no	P	IV pentoxifylline (PTX) prophylaxis	less mucositis compared with control group
	Clift et al.[214]	yes/yes/no	P	oral PTX vs. placebo	no difference
	Stockschlader et al.[215]	no/yes/no	P	IV PTX vs. historical controls	significant aggravation
	Attal et al.[216]	yes/yes/yes	P	oral PTX vs. placebo	no difference
	van der Jagt et al.[217]	no/yes/no	P	oral PTX vs. historical controls	no difference
CT	Verdi et al.[219]	yes/yes/yes	P	oral PTX vs. placebo	no difference
Indomethacin					
RT	Pillsbury et al.[135]	yes/yes/yes	P	indomethacin vs. placebo	significant delay of mucositis onset
Immunoglobulines					

TABLE **3**—Continued

CT+RT	Mose et al.[166]	no/yes/no	P	i.m. immunoglobulins	significant reduction in CT+RT patients, no difference in RT
q) Hematopoetic growth factors					
GM-CSF					
CT	Ho et al.[168]	no/yes/no	P	CT+GM-CSF	lower incidence of mucositis
	Archimbaud et al.[171]	no/yes/no	P	CT+GM-CSF vs. historical controls	no difference in mucositis incidence
	Chi et al.[16]	yes/yes/no	P	CT+GM-CSF	significant reduction of incidence and severity and duration of mucositis
BMT	Atkinson et al.[172]	no/yes/no	P	BMT+GM-CSF vs. historical controls	no sig. difference in mucositis incidence
	Nemunaitis et al.[170]	yes/yes/yes	P	myeloablative CT ± GM-CSF	sig. lower incidence of severe mucositis
	Gordon et al.[169]	no/yes/no	P	HD-CT±TBI±GM-CSF	shorter duration of mucositis in TBI+GM-CSF vs. TBI alone
RT	Wagner et al.[176]	no/yes/no	P	RT + GM-CSF vs. historical control	significant lower severity of mucositis
	Makkonen et al.[177]	yes/yes/no	P	sucralfate ± GM-CSF	no difference
	Kannan et al.[230]	no/yes/no	P	RT+GM-CSF	lower incidence of severe mucositis
CT+RT	Rosso et al.[231]	no/yes/no	P	GM-CSF vs. historical control	sig. lower incidence of severe mucositis
G-CSF					
CT	Gabrilove et al.[173]	no/yes/no	P	CT+G-CSF vs. historical controls	significant lower incidence and severity of mucositis
	Crawford et al.[175]	yes/yes/yes	P	G-CSF vs. placebo	significant reduced incidence of mucositis
	Pettengell et al.[4]	yes/yes/no	P	CT±G-CSF	no difference in severe mucositis
	Welte et al.[232]	yes/yes/no	P	CT±G-CSF	lower incidence of mucositis
RT	Mascarin et al.[179]	yes/yes/no	P	RT±G-CSF	less treatment interruptions only
	Schneider et al.[178]	yes/yes/yes	P	RT±G-CSF	sig. reduced incidence of severe mucositis
BMT	Locatelli et al.[233]	no/yes/no	P	BMT±G-CSF	no difference
r) Antiviral agents					
Acyclovir					
CT+RT	Bubley et al.[95]	yes/yes/yes	P	acyclovir vs. placebo	no impact upon incidence and severity of mucositis
BMT	Woo et al.[94]	no/yes/no	P	acyclovir prophylaxis	no impact upon incidence and severity of mucositis
	Epstein et al.[93]	no/yes/no	P	acyclovir prophylaxis	no impact upon incidence and severity of mucositis

Throughout treatment, elimination of apparent infectious foci, mostly through extraction of teeth with infected pulp, has to be emphasized—even in myelosuppressed patients.[63,64] This can be accomplished by antibiotic coverage, meticulous closure, exact hemostasis and, if needed, platelet transfusion. If severe mucosal bleeding occurs, topical application of microfibrillar collagen, thrombin or other hemostatic gels may prove useful.[63,64]

Cryotherapy

The application of popsicles or ice chips is primarily based on the idea that temporary vasoconstriction of the oral mucosa can reduce exposure of replicating oral epithelium to peak levels of cytostatic agents with a relatively short plasma half-life, such as 5-fluorouracil (5-FU). Sucking ice cubes for half an hour during intravenous infusion of 5-FU has uniformly resulted in a significantly lower incidence and

severity of oral mucositis, compared with control groups in three randomized trials.[65-67] A low incidence of chemotherapy-induced oral mucositis was also noted upon prophylactic use of ice chips in patients receiving melphalan and edatrexate-based chemotherapy regimens.[68-70]

LOCALLY APPLIED PHARMACOTHERAPEUTICS

Antimicrobial Agents

The oral mucosa of cancer patients is colonized by a variety of potentially pathogenic microorganisms, especially gram-positive cocci, gram-negative opportunistic bacteria and fungi.[71-73] Disturbed integrity of the oral epithelial barrier, leukopenia, changes in salivary flow, and composition, and a shift of the oral microflora to an abundance of gram-negative organisms—particularly in patients with peridontal disease—favor the emergence of oral infections in the course of antineoplastic therapy.[54,74] Thus, the necessity of antimicrobal agents for the prophylaxis and treatment of oral mucositis has been emphasized by many authors[75] and numerous studies have evaluated the efficacy of a variety of disinfectant, antibacterial, antiviral, and antifungal agents.

Antifungal Agents

Although fungi are not primarily involved in the development of oral mucositis, they account for the most frequent infections of the damaged oral mucosa in immunosuppressed patients.[76-78] Candidiasis is the predominant fungal infection manifesting itself by characteristic white coats or erythematous lesions in the corners of the mouth and on the soft palate and tongue. Aspergillosis and mucormycosis, characterized by painful oral ulcerations which may invade the orofacial skeleton are less frequently observed. Since fungal sepsis can be held responsible for one-third of septic deaths in immunocompromised patients[79] the prophylactic use of various antifungal agents has to be emphasized in patients who are likely to develop prolonged granulocytopenia. Although frequently used, topical prophylaxis with polyene antifungal agents, such as nystatin, was found to be inefficacious in most clinical trials.[80-83] In contrast, randomized trials have provided evidence that prophylactic and therapeutic topical use of imidazole antibiotics such as clotrimazole and fluconazole significantly reduces the incidence and duration of oropharyngeal candidiasis in patients undergoing myeloablative treatment.[84-87]

Multiagent mouth rinses containing amphotericin B have also been applied successfully for both selective decontamination of the oral cavity and treatment of manifest oral candidiasis.[71,88-90] However, evaluation of amphotericin B as a single agent remains difficult. To date, most antifungal agents are available as oral suspensions and troches. Albeit the use of solutions is generally preferred by patients with severe mucositis, some patients may be allergic to parabenes serving as preservatives in oral suspensions.

Systemic antifungal prophylaxis, which is frequently used in patients undergoing myeloablative treatment, has been shown to reduce oral complications caused by fungi. Within this context, fluconazole seems to be superior in terms of tolerability as compared with amphotericin B.[91]

Antiviral Agents

Second to fungi, viruses, particularly herpes simplex virus type I (HSV) and varicella zoster virus (VZV), represent the most common pathogens aggravating oral mucositis in the course of antineoplastic therapy.[51] Viral infections of the oral cavity are characterized by ulcerative-necrotizing changes and some-

times labial or extraoral vesicles usually occurring around day 18 after chemotherapy or myeloablative therapy, thus differing from lesions caused by direct stomatotoxicity or fungal and bacterial infections.[92] The reactivation of oral HSV occurs in 50% to 90% of patients—particularly after myeloablative treatment and in patients seropositive for the virus. Oral infection with VZV is characterized by grouped small vesicles that tend to burst, leaving behind painful ulcers. Their distribution is often unilateral usually following a branch of the trigeminal or facial nerve. Infection usually occurs 2 to 3 weeks after discontinuation of chemotherapy.

For seropositive and myelosuppressed patients, topical and systemic acyclovir treatment is effective in the management of oral herpetic infections and for preventing oropharyngeal shedding of herpetic viruses, respectively, but acyclovir prophylaxis does not influence the incidence of chemotherapy-, radiotherapy-, or BMT-related oral mucositis.[51,73,93-95]

Antibacterial Agents

Odontogenic and gingival infections represent the major source of bacteria complicating mucositis.[96] Whereas α-streptococci are not involved primarily in the pathogenesis of oral mucositis,[76-78] aerobic species including pseudomonas *spp*, Staphylococcus epidermidis, anaerobic bacteria such as Bacteroides *spp* and Veillonella *spp* and endotoxin derived from aerobic gram-negative bacilli are thought to play a pivotal role in the bacterial phase. This hypothesis is further corroborated by the observation that elimination of gram-negative bacilli results in a lower incidence of oral mucositis.[71,90,97] Therefore, selective decontamination of the oral cavity for the prophylaxis of oral mucositis has been emphasized by many authors.[71] Antibiotic lozenges containing polymyxin E, tobramycin (and amphotericin B), have successfully eliminated the potentially pathogenic microbial flora and prevented severe forms of oral mucositis when compared with historical controls using placebo or chlorhexidine mouthwashes in patients with head and neck cancer undergoing radiotherapy.[71] Similarly, prophylactic sucralfate-based mouthwashes containing ciprofloxacin or ampicillin (and clotrimazol) also reduced radiation-induced mucositis.[98] However, in other studies, selective decontamination only achieved a moderate reduction of mucositis incidence and severity, suggesting that bacterial infections are not primarily involved in the pathogenesis of oral mucositis, but may alter the course of preexisting oral inflammation.[88-90] Consequently, patients suspected to carry a highly pathogenic flora due to underlying oral pathology may benefit most from the prophylactic use of antibacterial agents.

Local Anesthetics

Although not protecting the integrity or hastening the recovery of the oral mucosa, oral solutions containing local anesthetics such as diphenhydramine, viscous xylocaine, lidocaine, or dyclonine hydrochloride are frequently used to palliate pain caused by oral mucositis. Since these substances also interfere with taste perception, thus possibly contributing to hypoalimentation, the prophylactic use of local anesthetics should be discouraged. The most efficacious local anesthetic remains to be determined. A double-blind randomized trial comparing the efficacy of viscous lidocaine with 1% cocaine to dyclonine, kaolin-pectin plus diphenhydramine and saline, or placebo favored dyclonine but failed to demonstrate a significant difference among the four solutions, mostly due to the low number of enrolled patients.[99] As the duration of pain control by topical anesthetics is usually short, combinations of local anesthetics and mouthcoating agents are frequently applied.[100,101] In patients with severe oral discomfort, however, the systemic use of

analgesics has to be emphasized. Within this context, superior pain relief from oral mucositis and less morphine consumption can be achieved by patient-controlled analgesia, as compared with continuous infusion or staff-controlled analgesia, respectively.[102,103]

EXPERIMENTAL APPROACHES

Locally Applied Nonpharmacological Methods

Radiation Shields

Preliminary data suggest that removal of detachable parts of prostheses and fabrication of protective radiation stents as well as use of midline mucosa-sparing blocks to reduce irradiation of uninvolved mucosa and to avoid secondary electron scatter from large dental restorations and implants, respectively, may reduce oral complications of radiotherapy without affecting local tumor control. However, prospective randomized trials will be needed to confirm these observations.[104-106]

Laser

The application of low-energy helium-neon lasers (soft lasers) has been shown to reduce the incidence and, by hastening oral reepithelialization, favorably influence the outcome of oral mucositis in patients undergoing standard and myeloablative chemotherapy.[107-110] Most interestingly, no notable side effects have been reported for this therapeutic approach. In a small multicenter, placebo-controlled double-blind study, prophylactic treatment with low-energy helium-neon laser before the initiation of radiotherapy for head and neck cancer resulted in a markedly reduced duration and severity of oral mucositis in the treatment group as compared with patients receiving placebo light.[111]

Anti-inflammatory and Mucosa Protectant Agents

Chamomile

The main ingredients of chamomile emulsions are chamazulenes exhibiting anti-inflammatory effects; levomenol having anti-inflammatory, spasmolytic, antipeptic and antibacterial effects; polyines and flavonoids acting additively spasmolytic. Since chamomile is inexpensive and readily available, and because the side effects of chamomile, such as desiccation are generally mild it is frequently used as a mild oral rinse emulsion despite a lack of well-founded data.[112] Only one uncontrolled prevention study reported on encouraging results with chamomile mouthwashes,[113] whereas a placebo-controlled trial in which 164 patients undergoing 5-FU based chemotherapy were enrolled observed no difference between patients receiving chamomile mouthwashes or placebo.[114] Similarly, the efficacy of other frequently used astringent and anti-inflammatory herbal essences including sage, tormentill, and fennel, has not yet been evaluated in clinical trials.

Benzydamine

Benzydamine hydrochloride is a non-steroidal agent frequently used in European countries exhibiting antimicrobal, anti-inflammatory, anesthetic, and analgesic effects. Three randomized trials demonstrated that the topical application of benzydamine resulted in a reduced incidence and significant symptom alleviation of radiotherapy- and chemotherapy-induced oral mucositis as compared with placebo.[115-117] However, studies comparing the efficacy of benzydamine and chlorhexidine in the treatment of radiotherapy-induced mucositis found oral discomfort to be more pronounced in patients rinsing with benzydamine.[118,119]

Sucralfate

Sucralfate is a basic aluminium salt of sucrose sulfate predominantly used as a therapeutic agent in patients with peptic ulcer disease. Upon contact with ulcerated mucosa, sucralfate generates a paste-like protective coat by formation of an ionic bond to proteins. In addition, sucralfate promotes the local production of prostaglandin E_2, which itself is thought to act as a cytoprotectant stimulating epithelial proliferation and migration, mucosal blood flow, and mucus production. The clinical use of sucralfate as a prophylactic or therapeutic agent for oral mucositis has produced controversial results. Two randomized preventive studies and one therapeutic study found a statistically significant reduction of the severity of oral mucositis in patients using topical sucralfate (and fluconazole) during radiotherapy,[120-122] whereas four other randomized studies comparing sucralfate with placebo or the addition of sucralfate to standard treatment with diphenhydramine, viscous lidocaine and antacids, respectively, found at most a nonsignificant decrease in severity and oral discomfort in patients receiving sucralfate.[123-126]

Another prospective double-blind study comparing sucralfate with a mixture of the mouth-coating agent kaolin-pectin and diphenhydramine syrup found no significant differences in the degree of radiotherapy-induced oral mucositis between these two groups,[101] but did find a reduction of oral discomfort in comparison with a historical group through both treatment modalities. Out of three randomized trials evaluating the efficacy of sucralfate in the prevention of chemotherapy-induced oral mucositis, only one found sucralfate to be moderately active, one demonstrated a reduction of mucositis-associated oral discomfort, and the third found no difference as compared with placebo.[127-129] In addition, sucralfate failed to alleviate symptoms in patients experiencing 5-FU induced oral mucositis despite oral cryoprophylaxis.[130] In conclusion, sucralfate seems to have little—if any—benefit when compared with standard oral hygiene and symptomatic treatment of oral mucositis.

Prostaglandin E_2

Studies evaluating the prophylactic use of the prostaglandin E_2 (PGE_2) derivate misoprostol have produced controversial results. Two small studies comparing its topical use with placebo in patients undergoing simultaneous chemoradiation and the therapeutic potency of PGE_2 in chemotherapy-induced oral mucositis, respectively, found the substance to be effective in reducing oral discomfort as well as the duration of reepithelialization.[131,132] Another prophylactic pilot study enrolling patients undergoing radiotherapy found an impressive reduction of severe cases of radiotherapy-induced mucositis.[133] In contrast, a randomized study that used lower doses of PGE_2 as compared with the previously mentioned trials did not note any benefit in patients who were undergoing bone marrow transplantation, but observed a higher incidence of herpes virus reactivation and severe mucositis in patients using PGE_2.[134] These findings are mirrored by a randomized placebo-controlled trial demonstrating that prophylactic systemic administration of indomethacin, a cyclooxygenase inhibitor, significantly reduced the severity and delayed the onset of radiotherapy-induced oral mucositis.[135]

Retinoids

Vitamin A and its derivates exert significant inhibitory effects upon inflammation and epithelial proliferation and have been used for the chemoprevention of squamous cell carcinomas. Based upon the consideration that temporary cell cycle arrest of oral epithelium may enhance mucosal resistance to cycle-

specific cytotoxic treatment, the prophylactic use of topical tretinoin has been found to reduce oral complications during bone marrow transplantation.[136]

Vitamin E

The rationale for the topical use of tocopherol is based upon its antioxidant and membrane stabilizing potency, thus, potentially interfering with the inflammatory damage caused by reactive oxygen species and free radicals created in the course of chemotherapy or radiotherapy. In a randomized clinical trial including patients who had experienced chemotherapy-induced oral mucositis the topical application of vitamin E was found to have a significantly superior activity as compared with placebo.[137] Since tocopherol is inexpensive, readily available, and well tolerated, confirmatory and prophylactic trials will be of great interest.

Glutamine

Glutamine is a nonessential amino acid and well-known protector of the bowel, from radiation-induced mucosal injury.[138] In two small, randomized studies prophylactic glutamine mouthwashes significantly reduced the incidence, severity, and duration of oral mucositis in patients undergoing radiotherapy or chemotherapy, respectively.[139,140] Oral and parenteral glutamine supplementation, however, produced inconsistent results concerning the prevention of (myeloablative) chemotherapy-induced oral mucositis.[141-143] Further studies on this approach are needed.

Silver Nitrate

Silver nitrate is a caustic agent that has been thought to reduce the severity of oral mucositis by stimulating the regeneration of the oral mucosa damaged by radiotherapy. But the favorable results of Maciejewski et al.[144] could not be confirmed in a subsequent trial.[145] Data on the therapeutic use of silver nitrate are lacking so far.

Sodium Alginate

Only one randomized study has evaluated the prophylactic topical use of sodium alginate and found a reduction of the discomfort and severity of radiotherapy-induced oral mucositis.[146]

Cytokines

Transforming Growth Factor-β3

Transforming growth factor beta 3 (TGF-β3) inhibits oral basal cell proliferation, decreasing the incidence and alleviating the course of oral mucositis in an animal model when used prophylacticly.[19] Based upon these considerations, a pilot study evaluated the prophylactic topical application TGF-β3 in breast cancer patients undergoing chemotherapy and demonstrated a good tolerability and a low incidence of oral mucositis.[147] Since the patient cohort observed was very small, the authors said they would perform further studies.

G-CSF and GM-CSF

The local accumulation of activated neutrophils subsequent to systemic administration of granulocyte colony-stimulating factor (G-CSF, filgrastim) and granulocyte-macrophage colony-stimulating factor (GM-CSF, molgramostim) has been shown to enhance defense mechanisms of the oral mucosa.[15] In addition, topical use of G-CSF and GM-CSF has promising effects in the treatment of impaired wound healing and chronic venous ulcers,[148] suggesting that the mechanisms of action of these cytokines are, in part, independent of their effect upon systemic neutrophil recovery. Thus, both the systemic

and local use of G-CSF and GM-CSF, respectively, have been evaluated for the prevention and treatment of chemotherapy-induced oral mucositis (reviewed in [149]).

GM-CSF mouthwashes have been shown to cause marked alleviation of existing oral mucositis in several studies without detectable systemic accumulation of GM-CSF or effects upon systemic neutrophil counts.[17,150-157] In our hands, GM-CSF mouthwashes significantly abbreviated oral mucositis caused by 5-FU chemotherapy when compared with mouthwashes with povidone-iodine, amphotericin B and viscous lidocaine.[158] However, a double-blind, randomized placebo-controlled clinical trial failed to demonstrate a reduction in the incidence of mucositis upon prophylactic use of GM-CSF.[159] To date, only one prospective, placebo-controlled clinical trial has evaluated the topical use of G-CSF as mucositis prophylaxis in patients undergoing bone marrow transplantation and found a significant reduction of severe cases of oral mucositis and days of hospitalization.[160]

Antiseptic Agents

Povidone-iodine

The wide antiseptic effects including antiviral, antibacterial, and antifungal efficacy and good tolerability have resulted in the frequent use of povidone-iodine (PVP-iodine) as a preventive and therapeutic drug in radiotherapy- and chemotherapy-induced oral mucositis. A prospective randomized trial using prophylactic PVP-iodine mouthwashes in addition to standard treatment with topical nystatin, rutosides, panthenol and systemic immunoglobulins demonstrated a reduction in the incidence, severity, and duration of oral mucositis in 40 patients with head and neck cancer.[161] Similar data were obtained by the prophylactic use of another PVP-iodine containing multiagent mouth rinse.[162] However, data from single-agent prophylactic and therapeutic trials are lacking so far and PVP-iodine may not yet be recommended as a standard preventive or therapeutic regimen.

Multiagent Mouth Rinses: Role of Corticosteroids, Mouth-Coating Agents, and Dexpanthenol

Various topical mouth rinses containing corticosteroids, disinfectants, antimicrobial substances, sucralfate, baking soda, or local anesthetics are used in the prophylaxis and therapy of chemotherapy or radiotherapy-induced oral mucositis. While many "mucositis cocktails" containing corticosteroids have shown promising results in pilot studies,[163,164] data on larger, single-agent trials evaluating the prophylactic and therapeutic use of topical and systemic steroids are lacking. Similarly, dexpanthenol,[161,162,165,166] a granulation-promoting agent; caustic compounds such as aluminium hydroxide, and milk of magnesia;[88] and mouth-coating agents including kaolin-pectin are part of many multiagent mouthrinses, although their efficacy has not yet been demonstrated in single-agent trials.

Capsaicin

A pilot trial using capsaicin, a potent inhibitor of neuropathic pain in a candy vehicle has demonstrated a marked reduction of oral pain in patients experiencing oral mucositis in the course of chemotherapy or radiotherapy.[167]

SYSTEMICALLY APPLIED PHARMACOTHERAPEUTICS

G-CSF and GM-CSF

The systemic administration of GM-CSF was found to significantly reduce the incidence and severity of oral mucositis in patients undergoing conventional chemotherapy.[16,168] GM-CSF was also found to shorten the duration of mucositis in some myeloablative

regimens[169,170] without influencing the incidence of oral mucositis subsequent to myeloablative chemotherapy.[171,172] These results are possibly due to a lack of mucosal accumulation of GM-CSF subsequent to subcutaneous administration.[150]

Several clinical trials have addressed the issue of whether systemic administration of G-CSF also exerts protective effects upon mucosal integrity, most of which clearly demonstrated a reduction of the incidence and severity of oral mucositis subsequent to standard or myeloablative chemotherapy.[4,15,173-175] The effects observed with these cytokines in the prophylaxis and treatment of chemotherapy-induced oral mucositis have raised the issue of whether they might be beneficial for patients treated with radiotherapy, too. Whereas a pilot trial evaluating the prophylactic subcutaneous application of GM-CSF during radiotherapy has been shown to reduce oral toxicity as compared with a historic control,[176] a randomized preventive study failed to demonstrate a reduction of oral mucositis by the additional subcutaneous administration of GM-CSF as compared with the control group treated by sucralfate mouthwashes alone.[177] Similarly, the prophylactic use of G-CSF during radiotherapy reduced treatment interruptions and the occurrence of severe mucositis[178,179] without significantly altering the incidence or severity of oral mucositis.

Amifostine

Amifostine is an antioxidant cytoprotective agent selectively taken up by nonmaligant cells without detectable protection of tumor cells. A series of clinical trials have reported on mucosaprotective effects of subcutaneous dosages up to 500 mg and on intravenous use at doses up to 740 mg/m^2.[180-189] Side effects, mostly nausea and hypotension, seem to be more pronounced at higher doses and upon intravenous use, whereas, the optimal mucosaprotectant dose and route of administration remains to be defined. Studies evaluating the prophylactic use of amifostine during radiotherapy have uniformly reported a reduction of the incidence and severity of oral mucositis, but produced inconsistent results concerning the tolerability of the substance—regardless of its dosage and route of administration.[180-182] Similarly, three out of four studies have demonstrated mucosaprotective effects of amifostine during simultaneous radiochemotherapy.[183-186] Data on the use of amifostine in the prevention of chemotherapy-induced oral mucositis are scant, because the evaluation of mucositis does not constitute a primary endpoint of most studies. The substance has been shown to reduce the occurrence and severity of oral mucositis during peripheral blood stem cell mobilization with high-dose cyclophosphamide and total body irradiation.[187,188] Comparable results were obtained in a phase II study evaluating the mucosaprotective effect of amifostine in patients receiving high-dose 5-FU for metastatic colorectal carcinoma.[189]

Beta Carotene

Based upon the observation that beta carotene can produce regression of oral leukoplakia by inducing cellular differentiation, the effects of beta carotene have been evaluated in a small randomized study in patients undergoing simultaneous chemoradiation. In this trial a significantly decreased incidence of severe oral mucositis has been noted.[190]

Azelastine

Azelastine hydrochloride is an anti-inflammatory antioxidant and antihistamine. Osaki et al.[191] reported a significant reduction of the incidence and severity of oral mucositis during chemoradiation in patients treated

prophylactically with azelastine, vitamins C+E, and glutathione as compared with a control group that did not receive azelastine.

Propantheline

A pilot trial of orally administered propantheline has demonstrated a significant reduction of oral mucositis caused by etoposide. Propantheline is an anticholinergic agent that reduces salivary flow and, therefore, salivary excretion of etoposide.[192] Confirmatory trials are lacking.

Immunoglobulins

Based upon the observed decrease of salivary and systemic immunoglobulin levels subsequently to antineoplastic treatment[193] and the immunomodulating anti-inflammatory propensities,[194] intravenous or intramuscular immunoglobulins are frequently used in multimodal prophylactic and therapeutic regimens for radiotherapy-induced mucositis.[161,166] Consequently, a validation of their impact upon the occurrence and course of oral mucositis is difficult. In the near future, the topical application of protease-resistant immunoglobulins will be of great interest.[195]

INEFFICACIOUS APPROACHES

Locally Applied Pharmacotherapeutics

Allopurinol and Uridine

The rationale for the topical use of allopurinol for the prevention of 5-FU-induced oral mucositis was based upon its inhibition of orotidylate decarboxylase, an enzyme responsible for the intracellular formation of cytotoxic 5-FU metabolites.[196] Whereas initial studies of topically administered allopurinol reported a reduction of mucosal toxicity in patients receiving 5-FU-based chemotherapy,[197,198] consecutive trials failed to confirm these findings.[199-201] In contrast, one double-blind, randomized, clinical trial found a higher incidence of oral mucositis in patients treated prophylactically with allopurinol.[200]

Similarly, systemic administration of uridine, another substance postulated to protect tissues from the toxic effects of 5-FU, failed to demonstrate a reduction of chemotherapy-induced oral mucositis.[202]

Chlorhexidine

Chlorhexidine gluconate, a bisguanidine exhibiting broad-spectrum antibacterial and antimycotic activity and sustained binding to oral surfaces has been investigated intensely concerning its prophylactic and therapeutic efficacy in oral mucositis. Although much emphasis has been put on the effects of chlorhexidine for the prevention and treatment of chemotherapy- and radiotherapy-induced oral mucositis,[12,78,203,204] randomized trials failed to confirm the postulated effects of chlorhexidine.[81,205-208] Furthermore, the emergence of infections caused by gram-negative bacilli despite chorhexidine mouthwashes, mouthwash-induced discomfort, and interference with the antifungal effect of nystatin have been reported.[205,206,208-210] According to the evidence derived from randomized clinical trials, chlorhexidine cannot be recommended for the prophylaxis or treatment of oral mucositis occurring in the course of antineoplastic treatment.

Hydrogen Peroxide

In a prospective trial involving patients undergoing radical radiotherapy, treatment with hydrogen peroxide (3.5%) rinses was associated with an increased risk for mucositis as compared with mouthwashes with regular saline.[211]

Hydrogen peroxide applied as 1% rinsing solution has failed to demonstrate activity as a prophylactic mucosal disinfectant or therapeutic drug in patients with mucositis.[212] Subsequent to rinsing with hydrogen peroxide, patients reported that symptoms of oral mucositis seemed to intensify, leading to withdrawal of the drug due to glossodynia. In addition, the rationale for the therapeutic application of hydrogen peroxide has been challenged due to the substance's antifibroblastic effect resulting in impaired wound healing. Consequently, the use of hydrogen peroxide for the prevention or treatment of oral mucositis has to be discouraged.

Systemically Applied Pharmacotherapeutics

Pentoxifylline

Systemic use of pentoxifylline, which can down regulate endotoxin-induced production of TNF-α, has been evaluated intensely based upon a relatively small study that reported efficacy in preventing oral mucositis in patients undergoing myeloablative therapy.[213] However, none of the consecutive randomized, placebo-controlled trials found pentoxifylline to be effective.[214-220]

CONCLUSIONS

Since treatment options for chemotherapy- and radiotherapy-induced oral mucositis are limited, prophylaxis of this debilitating complication has to be emphasized. Pre-therapeutic assessment and treatment of underlying oral pathology are essential to minimize acute and chronic oral and systemic sequelae of antineoplastic therapy. The therapeutic approach to manifest oral mucositis has a supportive and palliative character. It is aimed at alleviating symptoms and avoiding secondary complications, such as dehydration, cachexia, and infection. It is also aimed at improving the patient's quality of life and enabling the patient to adhere to the treatment plan. Despite their widespread clinical use, many drugs and other modalities have not been evaluated in controlled clinical trials. Con-sequently, no therapeutic modality has become a standard approach for patients who suffer from oral mucositis.

Aside from nonpharmacological interventions, including cryotherapy, radiation shields, soft laser treatment, and oral hygiene, a multitude of drugs have been evaluated successfully as prophylactic and therapeutic agents for oral mucositis. The latter not only include local anesthetics and antimicrobal substances, but more recently cytoprotectant substances, such as amifostine and a series of cytokines, which may soon become standard therapy. In contrast, sucralfate, misoprostol, hydrogen peroxide, chlorhexidine, pentoxifylline, uridine, and allopurinol have not proven particularly efficacious in the prevention or treatment of chemotherapy-induced oral mucositis.

Promising, but not yet sufficiently evaluated approaches include antiseptic substances, such as povidone iodine and benzydamine, vitamin E, tretinoin, beta carotene and cytokines such as TGF-β3. Novel agents such as Interleukin-11, dehydroascorbic acid, keratinocyte growth factor, and epidermal growth factor, which hasten growth, cellular differentiation, and cell migration of the oral epithelium[192,221-225] are being evaluated. However, aside from all of these mechanistic and pharmacological interventions, medical personnel must not ignore the positive effect of attentive medical care. In a randomized trial, Janjan et al.[226] demonstrated that daily intensive personal contact by the nursing staff, as well as prompt adaptation of the required analgesic regimen during chemotherapy or radiotherapy, significantly reduced the oral discomfort associated with mucositis, which decreased the need for pain medication. CA

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