Review

Cancer Treatment-induced Oral Mucositis

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Abstract. *Oral mucositis is one of the main complications in non-surgical cancer treatments. It represents the major dose-limiting toxicity for some chemotherapeutic agents, for radiotherapy of the head and neck region and for some radio-chemotherapy combined treatments. Many reviews and clinical studies have been published in order to define the best clinical protocol for prophylaxis or treatment of mucositis, but a consensus has not yet been obtained. This paper represents an updated review of prophylaxis and treatment of antineoplastic-therapy-related mucositis using a MEDLINE search up to May 2006, in which more than 260 clinical studies have been found. They have been divided according to antineoplastic therapy (chemotherapy, radiotherapy, chemo-radiotherapy, high-dose chemotherapy). The prophylactic or therapeutic use of the analysed agents, the number of enrolled patients and the study design (randomized or not) were also specified for most studies. Accurate pre-treatment assessment of oral cavity hygiene, frequent review of symptoms during treatment, use of traditional mouthwashes to obtain mechanical cleaning of the oral cavity and administration of some agents like benzydamine, imidazole antibiotics, tryazolic antimycotics, povidone iodine, keratinocyte growth factor and vitamin E seem to reduce the intensity of mucositis. Physical approaches like cryotherapy, low energy Helium-Neon laser or the use of modern radiotherapy techniques with the exclusion of the oral cavity from radiation fields have been shown to be efficacious in preventing mucositis onset. Nevertheless a consensus protocol of prophylaxis and treatment of oral mucositis has not yet been obtained.*

Oral mucositis is one of the main dose-limiting toxicities in cancer patients. This implies that intensification of non-surgical cancer therapies is often limited by the presence of this side-effect. Previously published reviews (1-8) have pointed out that only a few drugs have been demonstrated to be effective in preventing or reducing oral mucositis in patients treated with radio- and/or chemotherapy. Until today a consensus on the prophylaxis and therapy of anticancer-therapy-related mucositis has not yet been obtained. In this review most agents used to prevent or treat oral mucositis have been examined. The aim of this study was to produce an updated review of the literature and to summarize the main studies characteristics in a few tables that could be a rapid resource for consultation in clinical practice.

The references for this review were identified by a comprehensive search of MEDLINE up to May 2006 (with no language restriction). Papers were selected on the basis of their relevance to the topic; "mucositis", "chemotherapy" and "radiotherapy" were the key words used. Preclinical studies, clinical reviews and consensus meetings were not included.

In Table I all the analysed agents are summarized. The studies are grouped according to treatment modality (chemotherapy, radiotherapy, radio-chemotherapy, high-dose chemotherapy), timing of agent administration (prophylaxis or treatment of mucositis) and study design (phase III randomized trial or non-phase III randomized trial). Results are shown in Tables II, III, IV and V. The number of enrolled patients is also specified for most studies.

In the following sections the classification and the main mechanisms of action of the analysed agents are briefly presented.

Oral Care

Oral cavity hygiene should be considered of great importance in preventing oral mucositis. Meticulous pre-treatment assessment with periodontal, dental and radiographic evaluation and, when necessary, restorative dental procedures performed at least three weeks before the beginning of mucosa-toxic therapy, have all been shown to reduce the incidence and duration of mucositis (9-19).

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Table I. *All the analysed agents under review.*

Studied agents	
Basic oral care	
Traditional mouthwashes	Saline solution, hydrogen peroxide, salt and soda, sterile water, chamomile, honey, conventional mouthwashes, methylcellulosa, topical fluoride
Benzydamine	
Antiulcer agents	Sucralfate, prostaglandin, pentoxifylline, azelastine, kaolin-pectin
Physical treatments	Silver nitrate, low-energy Helium-Neon laser, cryotherapy,
Radiotherapy technique	
Growth factors	GM-CSF and G-CSF, interleukins, TGF-β, KGF, EGF
Infections	Antibiotic agents (iseganan, chlorhexidine), antifungal agents, antiviral agents
Glutamine	
Anaesthetics	
Tricyclic antidepressant	
Amifostine	
Vitamins	Vit A, Vit E
Allopurinol	
Povidone-iodine	
Pilocarpine	
Immunoglobulins	
Corticosteroids	
Miscellaneous group:	Coumarin/Troxerutine, proteolytic enzyme, propantheline, orgotein, capsaicin, zinc sulfate, oren-Gedoku-to, syousaikotou, human placental extract, superoxide dismutase (SOD2), sodium alginate, prostaglandin inhibitor, uridine, tetrachlorodacaoxide (TCDO), engineered biopolimer, bioactive milk factor, aloe, Formula C, mesalazine, MF5232 (Mucotrol), Flurbiprofen tooth patch

The daily review of symptoms combined with a well-defined strategy for mouth care and analgesic administration resulted in improved management of radiation-related mucositis compared with sporadic nursing intervention and the absence of an analgesic protocol. Patients with an intensive dental care protocol developed less painful oral complications compared to the limited dental care group of patients (107).

In conclusion, most series showed a reduction in the mucositis incidence and duration when accurate pre-treatment assessment of oral cavity hygiene was performed and when a frequent review of symptoms combined with a well-defined protocol for palliative therapies was given to all treated patients.

Antiulcer Agents

Sucralfate. Sucralfate is a basic aluminium salt of sucrose sulfate (sulphated disaccharide) mainly used as a therapeutic agent in patients with peptic ulcer disease. On ulcerated mucosa, sucralfate produces a paste-like protective coat, promotes the local production of prostaglandin E_2 (PgE_2) and enhances interleukin 1 and interleukin 2 release from fibroblasts. It also has a topical anti-inflammatory effect on oral mucosa. Moreover sucralfate is a well-tolerated agent, nausea and constipation were reported in only 2% of the treated patients. Compared with the well established benefit of sucralfate in pelvic irradiation (127), controversial results have been obtained in head and neck patients.

Prostaglandins. Prostaglandins (Pg) are cytoprotective agents especially for the gastrointestinal tract. Topical application of Pg has been shown to lead to the healing of chronic leg ulcers. On the basis of these results, prostaglandins has also been evaluated in patients with oral mucositis (33, 196-198, 249).

Pentoxifylline. Pentoxifylline is a xanthine derived agent. It down-regulates the expression of tumor necrosis factor alpha (TNF-α), which is thought to be correlated with development of bone marrow transplantation-related complications. As well as for the treatment of chronic atrophic leg ulcers, pentoxifylline have also been studied in oral mucositis (43, 199-204).

Azelastine. Azelastine is a hydrochloride agent with an anti-inflammatory, antioxidant and antihistaminic action. Promising results has been obtained in patients with oral mucositis (250)

Kaolin-pectin. Kaolin is a naturally occurring hydrated aluminium silicate while pectine is a carbohydrate polymer consisting primarily of partially methoxylated polygalactouronic acids. Pectin is soluble in water forming a viscous colloidal solution. Because of these characteristics, Kaolin-pectin complex is thought to have absorbent and protective properties, which may be useful in treating oral mucositis.

Physical Therapies

Silver nitrate. Silver nitrate is a caustic agent, which has been thought to reduce the severity of oral mucositis by stimulating the regeneration of oral mucosa damaged by radiation therapy.

Laser. The application of low-energy Helium-Neon (He-Ne) laser (so called soft laser) on the oral cavity mucosa which affects the inflammatory processes is based on a biochemical effect which increases fibroblast cell division

and collagen production as well as a stimulating mitochondrial cytochrome activities. The molecular effect is thought to be the neutralisation of the free radicals induced by chemotherapy and/or radiotherapy with no modification of oral mucosa vessels perfusion. Soft laser application has also been demonstrated to produce pain relief by the modulation of pain perception by modification of nerve conduction with the release of endorphin and leukephalins.

Cryotherapy. The topical application of ice chips (cryotherapy) on the inflamed mucosa is based on the hypothesis that temporary local vasoconstriction of the oral mucosa vessels could reduce exposure of the replicating epithelium cells to peak levels of some cytostatic agents.

Radiotherapy technique. In spite of technical advances, irradiation of non-target tissue (such as the oral cavity mucosa) remains unavoidable. The use of different sources of energy (like heavy particle) or modern three-dimensional treatment planning (Intensity Modulated Radiation Therapy) permit to better focus the dose around the target area and partially protect normal tissue like oral mucosa.

Growth Factors

Granulocyte-monocyte colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor (G-CSF). Both of these growth factors have been found to enhance keratinocyte and fibroblast growth improving the healing of cuts, leg ulcers and skin grafts. The topical use of both GM-CSF and G-CSF have also given promising results in the treatment of impaired wound healing and chronic venous ulcers suggesting that the mechanism of action of these growth factors could be partially independent of their systemic action (269-276).

Interleukin (IL). One of the methods by which GM-CSF may stimulate cell division in the oral mucosa is by enhancing interleukin 1 (IL-1) transcription and translation. In animal studies, IL-1 has been shown to protect normal cells from radiotherapy- or chemotherapy-related toxicity, while no protective effect was found on tumour cells (277, 278). Also interleukin 11 seems to have a range of activities, which should be potentially relevant to reduce mucositis (169).

Transforming growth factor β (TGF-β). The mechanism of action of TGF-β is to inhibit cell proliferation by inducing a reversible arrest of the cell cycle in the G_1-phase, a well-known radioresistant phase.

Keratinocyte growth factor (KGF). Keratinocyte growth factor is an epithelial cell-specific growth and differentiation factor produced by mesenchymal cells. The up-regulation of KGF after epithelial injury has suggested that it has an important role in tissue repair. In non-treated animals KGF has been shown to enhance epithelial thickening, while in irradiated or chemotherapy-treated mice, it was found to reduce atrophy, to accelerate regrowth and to decrease ulcer formation of oral cavity epithelium (279-284).

Epidermal growth factor (EGF). The hypothesis that the epithelial basal cell rate should be one of the main factors influencing mucosa sensitivity to cancer therapy-related toxic effects has been confirmed by a preclinical study (285). When assessment of changes in salivary EGF in patients receiving radiation therapy was evaluated, a higher level of EGF in saliva, prior to and during radiotherapy, was found to be associated with less severe mucosal damage (286, 287).

Oral Cavity Over-infection

Damage of the oral mucosa during cancer treatments leads to pathologic colonisation by bacteria, fungi and viruses. In addition, the reduction of saliva production, which contains immunoglobulin (IgA) and washes away intraoral debris and bacteria, may modify the normal bacterial flora lying in the upper aero-digestive tract. Compared to bacteria and fungi, viral infection of the oral cavity seems to be a less frequent clinical complication during radiotherapy or chemotherapy.

Iseganan (a synthetic protegrin with broad-spectrum microbicidal activity and a lack of systemic absorption) and clorhexidine (a broad-spectrum antiseptic agent) were grouped with the antibiotic agents.

Glutamine

Glutamine is a neutral amino acid that acts as a substrate for nucleotide synthesis in most dividing cells. Animal studies have suggested that dietary supplementation with glutamine may protect the gut from both radiotherapy and chemotherapy side effects (288-289). Glutamine is also used by cells of the immune system, such as lymphocytes and macrophages. Incidence of bacteraemia was found to be lower in patients in which glutamine was used compared with a control group (290-293).

Anaesthetics

Anaesthetic agents are largely used to reduce mucositis-related pain. Systemic administration is considered the standard approach but topical application should have the potential advantage of local pain control with minimal systemic side effects and better patient compliance. The main problem of topical application remains the alteration of taste, which may exacerbate the hypo-alimentation present during cancer therapies. For this reason, prophylactic administration of local anaesthetics should be discouraged.

Table II. *The studies on chemotherapy-induced mucositis.*

Agent	Treatment (T) Prophylaxis (P)	Favourable			Not favourable			Study design
		Author	No of pts	(Bib)	Author	No of pts	(Bib)	
Salt and soda	T	Dodd	23	(20)				R
Sterile water	P	Dodd	222	(21)				R
Plant extracts	T	Matsuoka		(22)				R
Chamomile	PT	Mazokipakis	98	(23)				NR
	P	Fidler	164	(24)				R
Benzydamine	T	Sonis		(25)				
		Cheng	34	(26)				NR
Sucralfate	P	Pfeiffer	40	(27)				R
	PT	Allison	40	(28)				NR
	PT				Nottage	81	(29)	R
					Shenep	48	(30)	
	T				Loprinzi	50	(31)	R
					Chiara	40	(32)	
PgE_2	T	Porteder	10	(33)				NR
Pentoxifylline	P				Verdi	10	(34)	R
He-Ne Laser	P	Ciais	67	(35)				NR
		Nes	13	(36)				
		Wong	15	(37				
Cryotherapy	P	Mahood	95	(38)				R(m),R
		Cascinu	84	(39)				
		Nikoletti	67	(40)				
		Karagozoglu	60	(41)				
	P	Gandara	24	(42)				NR
		Edelman	46	(43)				
		Dumontet	22	(44)				
		Baydar M	40	(45)				
		Tartarone		(46)				
GM-CSF	T	Chi	20	(47)				R
		Hejna	31	(48)				
	T	Rossi	31	(49)				NR
		Ibrahim	24	(50)				
	P				Moore	15	(51)	NR
	PT	Mantovani	68	(52)				NR
G-CSF	PT	Katano	14	(53)				NR
	P	Gabrilove	27	(54)				NR
	P	Crawford		(55)				R
TGF	P	Wymenga	11	(56)				NR
	PT				Foncuberta	152	(57)	NR (m)
KGF	P	Meropol	18	(58)				NR
Iseganan	P				Giles	323	(59)	R
Chlorhexidine	T				Dodd	23	(60)	R
	P	Cheng	34	(26)	Dodd	222	(21)	R
					Pitten	47	(62)	
					Wahlin	28	(62)	
	P	Luglie	66	(63)				NR
		Cheng	42	(64)				
		Cheng	40	(65)				
Nystatin	P				Barret	66	(33)	NR
Amphotericin B	T				Lefebvre	123	(67)	R
					Hejna	31	(48)	
Miconazole	P	Brinker	30	(68)				R
	T	Jordan	37	(69)				NR
Clotrimazole	P	Yeo	202	(70)				R
	T	Shechtman	13	(71)				R

Table II. *continued*

Table II. *continued*

Agent	Treatment (T) Prophylaxis (P)	Favourable			Not favourable			Study design
		Author	No of pts	(Bib)	Author	No of pts	(Bib)	
Fluconazole	T	Epstein	19	(72)				NR
	PT	Allison	40	(28)				NR
	T	Finlay	73	(73)				
		Lefebvre	123	(67)				R
Antiviral agents	T	Kubesova	34	(74)				NR
Glutamine	P	Cockerham	21	(75)				NR
		Skubitz	14	(76)				
	P	Anderson	24	(77)	Jebb	28	(79)	R
		Decker-	24	(78)	VanZaanen	20	(80)	
		Baumann			Okuno	134	(81)	
Lidocaine	T	Carnel	18	(82)				NR
		Turhal	31	(83)				
	T				Dodd	23	(20)	R
Benzocaine	T	LeVeque	28	(84)				NR
		Redding CR		(85)				
Dibucaine	T	Yamamura	23	(86)				NR
Doxepin	T	Epstein	41	(87)				NR
Amifostine	P	DeSouza	29	(88)				
		Fahlke	27	(89)	Stokman	24	(90)	NR
Vitamin E	T	Wadleigh	18	(91)				R
		Lopez	19	(92)				
	T	Thornley	37	(93)				NR
Allopurinol	T	Clark	6	(94)				
		Tsavaris	42	(95)	Howell	23	(96)	NR
	T	Porta	44	(97)	Weiss	52	(98)	R
					Loprinzi	77	(99)	
Pilocarpine	P	Awidi	32	(100)				R
Capsaicin	T	Berger	11	(101)				NR
Oren-gedoku-to	P	Yuki	40	(102)				NR
Syousaikotou	P	Matsuoka		(22)				NR
Uridine	P	Seiter	29	(103)				NR
TDCO	T	Malik		(104)				
Formula C	T	Coetxee		(105)				NR

Bib=bibliografic reference, Author=first author, pts=enrolled patients, R=randomized study, NR=non-randomized study, (m)=multicenter study, GM-CSF=granulocyte-monocyte colony stimulating factor, G-CSF=granulocyte colony stimulating factor, TGF=transforming growth factor, KGF=keratinocyte growth factor, TDCO=tetrachlorodacaoxide.

Trycyclic Antidepressants

Based on the concept that mucositis-related pain could have a neuropathic component, some authors have evaluated the efficacy of tricyclic antidepressants during radiotherapy and/or chemotherapy.

Amifostine

Amifostine (WR-2721) is a phosphorylated aminothiol prodrug, which is dephosphorylated by a membrane-bound alkaline phosphatase to its active metabolite, the free thiol WR-1065. The mechanism of action of WR-1065 is scavenging of free radicals created by the action of cytotoxic therapies on tissue. Compared with tumour tissues, normal tissue microenvironments generally have higher concentrations of alkaline phosphatase and are typically less acid. These characteristics favour selective conversion of amifostine to its active metabolite in normal tissues. Amifostine has been demonstrated to have a high level of uptake in salivary gland tissue, so that its use to diminish the incidence of xerostomia is appealing. The impact of amifostine on mucositis is probably due to an indirect effect related to the enhancement of saliva secretion, which has

Table III. *The studies on radiotherapy-induced mucositis.*

Agent	Treatment (T) Prophylaxis (P)	Favourable			Not favourable			Study design
		Author	No of pts	(Bib)	Author	No of pts	(Bib)	
Hydrogen peroxide	P				Feber	40	(106)	R
Saline solution	P	Feber	40	(106)				
	R							
Salt and soda	T	Dodd	30	(60)				R
Chamomile	PT	Carl	98	(108)				NR
Honey	T	Biswal	40	(109)				R
Conventional mouthwashes	T	Rothwell		(110)				NR
Benzydamine	T	Kim Schubert	67	(111)				R
		Samaranayake		(112)				
			25	(113)				
	P	Epstein	172	(114)				R
Sucralfate	P	Scherlacher	24	(115)	Epstein	33	(120)	R
		Franzen	50	(116)	Makkonen	40	(121)	
		Cengiz	28	(117)	Carter	102	(122)	
		Etiz	44	(118)	Lievens	102	(123)	
		Makkonen	40	(119)	Saarilahti	40	(124)	
					Evensen	60	(125)	
	PT	Allison	40	(28)				NR
	T	Merredith	111	(126)	Barker	14	(120)	R
					Dodd	30	(121)	
PgE_2	T	Porteder	10	(33)				NR
Diphenhydramine	T				Barker	14	(128)	R
Misoprostol	P	Hanson	34	(129)				R
Kaolin-Pectin	T				Barker	14	(128)	R
Silver Nitrate	P	Maciejewski	16	(130)	Dorr	13	(131)	NR
He-Ne Laser	P	Bensadoun	30	(132)				R
RT tecnique	P	Perch	125	(133)				NR
GM-CSF	P	Troussard	10	(134)				NR
		Kannan	10	(135)				
	P	Saarilahti	40	(124)	Makkonen	40	(119)	R
	T	Nicolatou	61	(136)				NR
		Nicolatou	17	(137)				
		Rovirosa De	20	(138)				
		La torre		(139)				
	T	Masucci	92	(140)				R
G-CSF	P				Mascarin	26	(141)	NR
	T	Wagner	32	(142)				NR
	P	Schneider	14	(143)				R
Antibiotic agents	P	Symonds	275	(144)	Stokman	65	(146)	R
		Okuno	54	(82)	Wijers	77	(147)	
		Matthews	59	(145)	El-Sayed	137	(148)	
	P	Spijkervert	15	(149)				NR
		El-Sayed	17	(150)				
		Oguchi	52	(151)				
Chlorhexidine	P	Ferretti	30	(152)				R
		Spijkervet	45	(153)				NR
	P				Spijdervet	30	(154)	R
					Foote	52	(155)	
					Samaranayake		(133)	
Iseganan	P				Trotti	545	(156)	R
Nystatin	T	Rotwell		(110)				NR
Amphotericin	P	Spijkervert	15	(149)				NR
Miconazole	T	Oguchi	25	(151)				NR
Clotrimazole	P	Yeo	202	(70)				R
	P	Matthews	59	(145)				NR

Table III. *continued*

Table III. *continued*

Agent	Treatment (T) Prophylaxis (P)	Favourable			Not favourable			Study design
		Author	No of pts	(Bib)	Author	No of pts	(Bib)	
	T	Yap	52	(157)				R
		Schechtman	13	(71)				
Fluconazole	P	Mucke Belazi	50	(158)				NR
			39	(159)				
	T	Epstein	19	(72)				NR
	PT	Allison	40	(28)				NR
	T	Lefebvre	123	(67)				R
Itraconazole	P	Belazi	39	(159)				NR
Clotrimazole	P				El-Sayed	137	(150)	R
Antiviral agents	P				Bubley	57	(160)	R
Glutamine	P	Huang	17	(161)				R
Opioids	T				Shaiova	14	(162)	R
Lidocaine	T	Carnel	18	(163)				NR
Tetracaine	T	Oguchi Alterio	25	(151)				
			50	(164)				NR
Ketamine	T	Slatkin		(165)				
Trycyclic antidepressant	T				Ehrnorooth	43	(166)	R
Doxepin	T	Epstein	41	(87)				NR
Amifostine	P	Antonadou	50	(167)	Brizel	315	(169)	R
		Bourhis	26	(168)				
	P	Wagner		(170)				NR
		Schonekas	20	(171)				
		Koukourakis	140	(172)				
		Kouvaris	220	(173)				
Vitamin E	T	Ferreira	54	(174)				R
Pilocarpine	P	Valdez Warde	9	(175)	Fisher	249	(177)	R
			130	(176)				
Immunoglobulin	P				Mose	42	(178)	NR
					Mose	42	(179)	
Corticosteroids	P	Leborgne	66	(180)				R
	T	Rothwell		(110)				NR
Coumarin/ Troxerutin	P	Grotz	48	(181)				R
Proteolytic enzymes	P	Gujral	100	(182)				R
Orgotein	T	Valencia	41	(183)				NR
Capsaicin	T	Berger	11	(101)				NR
Zinc sulfate	P	Ertekin	30	(184)				R
Human placental extract	T	Kaushal	120	(185)				R
Sodium Alginate	T	Oshitani	(39)	(186)				NR
Pg inhibitors	P	Pillsbury	19	(187)				NR
TCDO	T	Malik	62	(104)				R
	P	Su	58	(188)				NR
Kaolin-Pectin	T	Barker	14	(127)				NR
Formula C	T	Coetxee		105				NR
Aloe vera	P				Su	58	(188)	R
Flurbiprofen tooth patch	P				Stokman	12	(90)	NR

Bib=bibliografic reference, Author=first author, pts=enrolled patients, R=randomized study, NR=non- randomized study, GM-CSF=granulocyte-monocyte colony stimulating factor, G-CSF=granulocyte colony stimulating factor, TGF=transforming growth factor, KGF=keratinocyte growth factor, TDCO=tetrachlorodacaoxide.

Table IV. *The studies on high-dose chemotherapy and bone marrow transplant-stem cell transplant- induced mucositis.*

Agent	Treatment (T) Prophylaxis (P)	Favourable			Not favourable			Study design
		Author	No of pts	(Bib)	Author	No of pts	(Bib)	
Saline solution	P	Epstein	86	(189)				R
		Varcalcel	41	(190)				
		Vokurka	132	(191)				
Conventional mouthwashes	T	Dazzi	90	(192)				R
Methylcellulosa	PT	Van der Lelie	36	(193)				R
Topical fluoride	P	Papas	95	(194)				R(m)
Sucralfate	P				Castagna	105	(195	R
PgE_2	T	Pretnar		(196)				NR
	P				Labar	60	(197)	R
					Duenas-G.	15	(198)	
Misoprostol	P				Duenas G.	15	(198)	R
Pentoxifylline	P				Ferra	37	(199)	NR
					Van der Jagt	49	(200)	
					Lopez	49	(201)	
					Stockschlader	92	(202)	
					Attal Clift	140	(203)	R
							(204)	
He-Ne Laser	P	Barash	20	(205)				R
		Cowen	30	(206)				
GM-CSF	T	Gordon Ho	13	(207)				NR
		Bez	37	(208)				
			39	(209)				
	P	Cartee	45	(210)	Dazzi	90	(211)	R
	T	Nemunaitis	109	(212)	Valcarcel	41	(213)	R
	PT				Van der Leile	36	(214)	R
G-CSF	T	Karthaus	8	(215)				R
IL11	P				Antin	13	(216)	R
KGF	P	Spielberger	212	(217)				R
		Siddiqui		(218)				
	P	Freytes	42	(219)				NR
Antibiotic agents	P				Ferra	37	(199)	NR
Chlorhexidine	P	Mc Gaw	16	(220)	Epstein	86	(224)	R
		Ferretti	51	(221)	Weisdorf	100	(225)	
		Ferretti	40	(222)	Raether	47	(226)	
		Rutkauskas		(223)				
Nystatine	P				Epstein	86	(224)	R
Fluconazole	T	Epstein	19	72				NR
	P	Gava	80	(227)				R
		Koc	80	(228)				
Antiviral agents	P	Epstein	83	(229)				NR
		Eisen	60	(230)				
Glutamine	P	Anderson	193	(231)	Schloerb	89	(234)	R
		Aquino	120	(232)	Pytlik	40	(235)	
		Piccirillo	48	(233)	Coghlin	58	(236)	
Systemic opioids	T	Coda	119	(237)				R
Fentanyl	T	Denarosi	62	(238)	Strupp	74	(239)	NR
Pilocarpine	P				Lockhart	36	(240)	R
Vitamin A	P	Cohen	11	(241)		R		
Corticosteroid	P				Ferra	37	(199)	NR
Propantheline	P	Ahmed	20	(242)				R
	P	Oblon	31	(243)				NR
Povidone iodine	PT				Vokurka	132	(191)	R
PV701 milk-derived GF extract	P	Prince	98	(244)				NR
Mesalazine	T	Rymes	21	(245)				NR

Bib=bibliografic reference, Author=first author, pts=enrolled patients, R=randomized study, NR=non- randomized study, m=multicenter study, GM-CSF=granulocyte-monocyte colony stimulating factor, G-CSF=granulocyte colony stimulating factor, TGF=transforming growth factor, KGF=keratinocyte growth factor, TDCO=tetrachlorodacaoxide.

Table V. *The studies on chemo-radiotherapy- induced mucositis.*

Agent	Treatment (T) Prophylaxis (P)	Favourable			Not favourable			Study design
		Author	No of pts	(Bib)	Author	No of pts	(Bib)	
Conventional mouthwashes	T	Sprinzl	35	(246)				R
Benzydamine	T	Prada Prada	20	(247)				NR
			40	(248)				
PgE_2	T	Matejka	15	(249)				NR
Azelastine	P	Osaki	63	(250)				NR
GM-CSF	P	Rosso	29	(251)				NR
	PT	Mantovani	68	(252)				NR
	PT				Sprinzl	35	(253)	R
G-CSF	P	Tejdor	20	(254)	Abibitol	70	(255)	NR
Nystatin	P-T	Hasenau		(256)				NR
Clotrimazole	P	Yeo	70	(202)				R
	T	Yap	52	(157)				R
		Shechtman	13	(71)				
Fluconazole	P	Samonis		(257)				R
		Bodey	112	(258)				
Opioids	T	Cerchietti	26	(259)				R
		Cerchietti	32	(260)				
Amifostine	P	Bruntzel	39	(261)	Peters	14	(264)	R
		Vacha	42	(262)	Buentzel	132	(265)	
		Vacha	53	(263)				
	P	Suntharalingam	19	(266)				NR
Povidone iodine	P	Adamietz	40	(277)				R
	PT	Hasenau		(256)				NR
MF 5232 (Mucotrol)	T	Naidu	30	(268)				R

Bib=bibliografic reference, Author=first author, pts=enrolled patients, R=randomized study, NR=non-randomized study, GM-CSF=granulocyte-monocyte colony stimulating factor, G-CSF=granulocyte colony stimulating factor.

been demonstrated to reduce the intensity of mucositis (294-296). Topical application of amifostine on oral mucosae did not seem to provide clinical benefit in patients treated with epirubicin (297).

Vitamins

Vitamin A. Vitamin A has a significant inhibitory effect on the inflammation process and epithelial proliferation. A reduction in vitamin A level was found to be a common condition in subjects with severe mucositis, and was associated with an increased risk of Herpes zoster infection (298).

Vitamin E. Vitamin E (α-tocopherol) is an antioxidant agent which may limit tissue damage from free oxygen radicals and, thus, may reduce the severity of mucositis during cancer treatments.

Allopurinol

The mechanism of action of allopurinol is related to the inhibition of xanthin oxidase and protease action. For this reason it has mainly been studied in relation to chemotherapy-related toxicity.

Povidone Iodine

In *in vitro* studies, povidone-iodine has been demonstrated to have good microbicide effect against bacteria, fungi, protozoa and some viruses but in *in vivo* trials, only antibacterial efficacy has been confirmed. In contrast to other antiseptic agents, povidone-iodine does not lead to any irritation or damage to the oral mucosa

Pilocarpine

Pilocarpine is thought to reduce mucositis by the stimulation of saliva production during cancer therapies.

Immunoglobulin

Based on the observation that radiation therapy reduces salivary and systemic immunoglobulins (Ig) it has been hypothesised that prophylactic administration of Ig could reduce oral mucositis.

Corticosteroids

Corticosteroid agents have an anti-inflammatory action that could be used in treating oral mucositis.

Miscellaneous Group

All the agents for which only one or two clinical studies were found in the MEDLINE search and which were not classified in the previous studied categories have been included in this group.

Conclusion

The prophylaxis and treatment of oral mucositis during cancer therapies remains an unsolved problem. Accurate pre-treatment assessment of oral cavity hygiene, and mechanical cleaning using traditional mouthwashes seem to be effective in preventing the onset of oral mucositis. Some therapeutic agents, such as benzydamine, imidazole antibiotics, tryazolic antimycotic and povidone iodine, have shown some clinical evidence of their efficacy in reducing oral mucositis. Additionaly, some physical therapies, such as cryotherapy, low energy Helium-Neon laser or exclusion of the oral cavity from radiation fields have been shown to reduce oral mucositis. A consensus protocol regarding prophylaxis and treatment is needed.

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