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MUCOSAL DISEASES SERIES

Oral mucositis

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Mucositis and xerostomia are the most common oral complications of the non-surgical therapy of cancer. Mucositis, a common sequel of radio- (DXR), chemo- (CXR) and radiochemo-therapy in patients with cancer, or patients requiring haemopoietic stem cell transplants (HSCT), has a direct and significant impact on the quality of life and cost of care, and also affects survival – because of the risk of infection. Apart from dose reduction, preventive and treatment options for mucositis are scarce, although multiple agents have been tested. Evidence suggests that cryotherapy, topical benzydamine and amifostine might provide some benefit in specific situations. The recombinant human keratinocyte growth factor Palifermin (Kepivance®) was recently approved as a mucositis intervention in patients receiving conditioning regimens before HSCT for the treatment of haematological malignancies. A number of mechanistically based interventions are in various stages of development. Unfortunately, many other approaches have not been rigorously tested. This paper reviews the clinical features, prevalence, diagnosis, complications, pathogenesis, prophylaxis and management of mucositis.
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Introduction

Mucositis is a common toxicity associated with both chemotherapy, and head and neck radiation used for the treatment of cancer (Herrstedt, 2000; Mead, 2002; Scully *et al*, 2003, 2004; Trotti *et al*, 2003; Vissink *et al*, 2003; Garfunkel, 2004; Wright *et al*, 2005). It is characterized by ulceration in the oro-oesophageal and gastrointestinal mucosae that results in pain, dysphagia, diarrhoea and dysfunction depending on the tissue affected (Blijlevens *et al*, 2000; Sonis and Fey, 2002).

Oral mucositis results in severe discomfort and impairs patients' ability to eat, swallow and talk. Concomitant therapy-induced myelosuppression places patients at significant risk of bacteraemia and sepsis from oral microorganisms resulting in increased days of fever, antibiotic use and hospitalization (Bergmann, 1988, 1989; Laine *et al*, 1992; Donnelly *et al*, 1995).

Clinical features of mucositis

The early clinical sign of mucositis is erythema presenting about 4–5 days following chemotherapy infusion or at cumulative doses of head and neck radiation of about 10 Gy. Patients also often complain of burning and intolerance of spicey foods at this stage.

Seven to 10 days after chemotherapy or at cumulative radiation doses of 30 Gy, ulcers develop, resulting in marked discomfort, often requiring opioid intervention and in many cases causing patients to alter their diet. In the case of chemotherapy-induced mucositis, lesions are seen mostly on the movable mucosae of the buccal mucosae and lateral and ventral surfaces of the tongue. The hard palate and gingiva appear not susceptible to chemotherapy-induced mucositis. In contrast, radiation-induced mucositis may involve any radiation-exposed area, including the hard palate, albeit rarely (Figure 1).

Chemotherapy-induced mucositis lasts approximately 1 week and generally heals spontaneously by 21 days after infusion. Radiation-induced mucositis stays at a peak for at least 2 weeks following the completion of radiotherapy (typically 60–70 Gy). As a result, it is not uncommon for patients receiving radiotherapy for cancers of the mouth and contiguous areas, to have severe ulcerative oral mucositis persisting for 5–7 weeks. Chronic mucositis following radiation therapy, does occur, but rarely.

The health and economic costs of oral mucositis are significant. Stem cell transplant recipients with oral mucositis have more days of fever, antibiotic use, opioid use and use of total parenteral nutrition than do patients without the condition. Importantly, the length of

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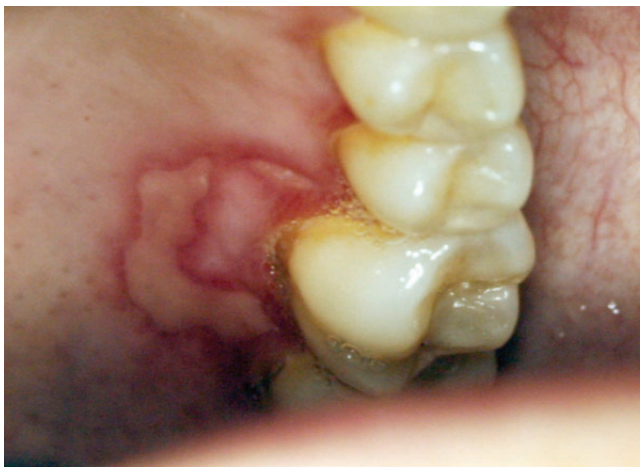

Figure 1 Clinical appearance of mucositis

hospitalization is markedly increased, resulting in hospital charges that dwarf those for patients without mucositis. The economic impact among head and neck cancer patients is equally dramatic, as the condition may require hospitalization of this typically ambulatory population. Elting *et al* (2003) reported that, in their study population of 224 patients, only 7% of individuals without ulceration required hospitalization compared to 27% of patients with ulcerative mucositis. In addition, mucositis, or even the anticipation of mucositis, is a frequent driver of gastrostomy (g-tube or PE G) placement.

Mucositis also has an indirect effect on tumour outcomes as its presence often necessitates an unfavourable modification of anti-cancer therapy such as breaks in radiation treatment or a dose reduction of chemotherapy.

Prevalence of mucositis

Historically, mucositis has been associated with particular high-risk groups such as patients being irradiated for cancers of the head and neck, individuals receiving conditioning regimens for stem cell transplant that include total body irradiation or high dose melphalan and patients receiving specific induction protocols for acute leukaemia. Mucositis has been consistently reported to occur in at least 75% of treated patients in these groups. In contrast, the incidence has been underreported in many other patient groups, especially patients being treated with cycled chemotherapy for solid tumours. This probably reflects the lack of direct patient observation while individuals are between cycles, a reluctance on the part of patients to jeopardize their cancer therapy, a lack of reporting of 'moderate grade toxicities' and a focus by oncologists on tumour kill, rather than toxicities. For example, mucositis has been seen in over 50% of patients being treated with fluorouracil, adriamycin and cytoxan (FAC) for node-positive breast cancer. For patients being treated with the most common chemotherapy regimens for colorectal cancer, the prevalence of mucositis is reportedly approximately 15–20%. However, there are few prospective trials upon which frequency data can be based.

Radiation-induced mucositis occurs in almost all patients who are treated for cancers of the mouth, oropharynx and nasopharynx, and in approximately two-thirds of those treated for cancers of the hypopharynx or larynx. Mucositis risk and severity are determined by the treatment dose, radiation field size and fractionation schedules prescribed for individual patients. Hyperfractionated schedules and combination of radiation with chemotherapy increase the prevalence, severity and duration of mucositis. The effect of intensity-modulated radiation therapy (IMRT) on the incidence and severity of mucositis is still being established, but it seems clear that patients being treated with cancers in or about the mouth may be at equivalent mucositis risk to those being treated with conventional radiation.

In patients receiving cancer chemotherapy, the frequency and severity of mucositis is mainly determined by the type(s) and dose of cancer chemotherapeutic agents used. five-fluorouracil (5-FU), cisplatin, etoposide and melphalan are particularly stomatotoxic (Chi *et al*, 1995; Pico *et al*, 1998) and mucositis is common with doxorubicin, vinblastine, taxanes and methotrexate (Symonds, 1998), but uncommon with asparaginase and carmustine (Symonds, 1998). The combining of different chemotherapeutic drugs further intensifies the likelihood of mucositis: from 40% to 70% of patients treated with standard chemotherapy regimens suffer mucositis (Hickey *et al*, 1982; Rodu and Gockerman, 1983; Magrath *et al*, 1984; Schubert *et al*, 1984; Balis *et al*, 1985; Caballero *et al*, 1985; Carl and Higby, 1985; Bishop *et al*, 1986; Dreizen *et al*, 1986; Barrett, 1987; Sonis and Kunz, 1988; Dahllof *et al*, 1989; Weisdorf *et al*, 1989; Roth *et al*, 1991).

Finally, mucositis is seen in 75–99% of patients receiving conditioning regimens for haemopoietic stem cell transplantation (HSCT) particularly in those that combine total body irradiation (TBI) and chemotherapy (Donnelly *et al*, 1992; Blijlevens *et al*, 2000). Mucositis is the most common symptom and distressing complication of HSCT (Bellm *et al*, 2000), and some 30–50% of patients with HSCT complain that mucositis is their most significant toxicity. The only independent risk factor identified for mucositis is the conditioning regimen: high-dose melphalan (HDM) regimens exceed busulphan, busulphan–cyclophosphamide, cyclophosphamide–TBI, cyclophosphamide–carmustine (BCNU) and cyclophosphamide–etoposide–carmustine (Wardley *et al*, 2000). Newer approaches for HSCT including mini-transplants are associated less frequently with mucositis, which is also less severe.

Diagnosis of mucositis

Diagnosis of mucositis is clinical and based on the use of known stomatotoxic therapy, and the appearance, timing and location of oral lesions. Chemotherapy-induced mucositis occurs on the movable mucosae, rarely affecting the dorsum of the tongue, the hard

palate or the gingivae. Radiation-induced mucositis also affects the movable mucosae and may involve the hard palate, albeit rarely. Infections and graft-*vs*-host disease (GVHD) are the most common differential diagnoses.

Viral infections differ clinically from mucositis in that they are typically croppy, localized and involve keratinized mucosa of the hard palate, gingival and dorsal tongue and their onset often coincides with fever. Culture or exfoliative cytology at the time of lesion presentation is prudent.

Graft-*vs*-host disease is limited to patients who have received allogeneic HSCT and develops following haematologic recovery (beyond 21 days after transplant) and typically results in dramatic oral lesions that are often lichenoid in character, sometimes also with xerostomia (Woo *et al*, 1997). Neutropenia, induced by chemotherapy, may be associated with necrotizing gingivitis.

Scoring mucositis

The lack of a universally accepted scale to describe mucositis severity has hampered accurate comparisons of regimen-related toxicity and the efficacy of interventions. A large number of mucositis scoring systems have been devised (summarized by Sonis *et al*, 2004a,b) for the purposes of describing toxicity, guiding nursing patient management and evaluating treatments, but most lack standardization or validation (Parulekar *et al*, 1998).

The two most commonly used scoring tools to describe toxicity are the World Health Organization (WHO) and the National Cancer Institute (NCI) common terminology criteria for adverse events. Scales used as nursing management tools tend to be comprehensively directed at describing overall oral health. Consequently, they contain items related to dental hygiene, dental and gingival health, that may obscure the true level of mucosal damage. Clinical research scales such as the oral mucositis index (OMI) or the oral mucositis assessment scale (OMAS) tend to be sensitive but, because of the their quantitative nature, difficult for routine clinical use (Tables 1 and 2).

Complications of mucositis

Mucositis, especially in the presence of neutropenia, can predispose to bacteraemia, septicaemia and fungaemia (Greenberg *et al*, 1982; Barrett, 1987; Bergmann, 1989; Classen *et al*, 1990; Elting *et al* 1992; Donnelly, 1993; Ruescher *et al*, 1998) which may even be life-threatening. *Streptococcus oralis* and *Streptococcus mitis* are amongst the most common bacterial isolates from blood and *S. mitis* can, especially in those on high dose cytarabine, cause adult respiratory distress syndrome (Elting *et al* 1992; Lucas *et al*, 1997). Mucositis may also be a site of origin of mycoses (Edwards *et al*, 1997), typically infection with *Candida albicans*, but also with other *Candida* species such as *kruseitropicalis*, *parapsilosis*, and *glabrata*, and *Aspergillus* and *Mucor* (Wingard *et al*, 1991; McCarthy and Skillings, 1992; Epstein and Wong, 1994; Feld, 1997).

Oral mucositis may also be a predictor of gastrointestinal toxicity (Rapoport *et al*, 1999) and after HSCT may predict the onset of hepatic veno-occlusive disease (Wingard *et al*, 1991).

Table 1 WHO Mucositis scale (WHO, 1979)

Grade	*Clinical features*
0	–
1	Soreness/erythema
2	Erythema, ulcers but able to eat solids
3	Ulcers but requires liquid diet
4	Oral alimentation not possible

Table 2 Oral Mucositis Assessment Scale (OMAS) (Sonis *et al*, 1999a)

Location	*Ulceration*[a]	*Erythema*[b]
Lip		
Upper	0, 1, 2 or 3	0, 1 or 2
Lower	0, 1, 2 or 3	0, 1 or 2
Buccal mucosa		
Right	0, 1, 2 or 3	0, 1 or 2
Left	0, 1, 2 or 3	0, 1 or 2
Tongue ventrolateral		
Right	0 ,1, 2 or 3	0, 1 or 2
Left	0, 1, 2 or 3	0, 1 or 2
Floor of mouth	0, 1, 2 or 3	0, 1 or 2
Palate		
Soft	0, 1, 2 or 3	0, 1 or 2
Hard	0, 1, 2 or 3	0, 1 or 2

[a]0 = none; 1 = < 1 cm^2; 2 = 1–3 cm^2; 3 = >3 cm^2.
[b]0 = none; 1 = not severe; 2 = severe.

Pathogenesis of mucositis

It is now evident that the pathogenesis of mucositis is far more complex than the historical view that it simply results from the non-specific direct effects of radiation or chemotherapy on rapidly dividing mucosal basal cells. Mucositis appears to involve five biological phases (Sonis, 2004a; Figure 2): (i) initiation, (ii) primary damage response, (iii) signal amplification, (iv) ulceration and (v) healing.

The initiation phase occurs quickly after radiation or chemotherapy and is followed by both DNA and non-DNA damage. Direct cellular injury targeting the basal epithelial cells occurs simultaneously with the generation of reactive oxygen species (ROS) such as superoxide. The primary damage response, noted in the cells and tissues of the submucosa, is characterized by the expression of early response genes c-*jun*, c-*fos* and *Erg-1*, the activation of the transcription factors such as nuclear factor kappa beta (NF-κ), and its 26 S proteasome, the *hSNK* gene, and vascular adhesion molecules. This is followed by upregulation of genes that result in the production of a range of destructive proteins and molecules such as the pro-inflammatory cytokines [interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor (TNF) alpha], nitric oxide (NO), ceramide and matrix metalloproteinases (MMPs) that lead to apoptosis and tissue injury (Sonis, 1998, 2002, 2004b;

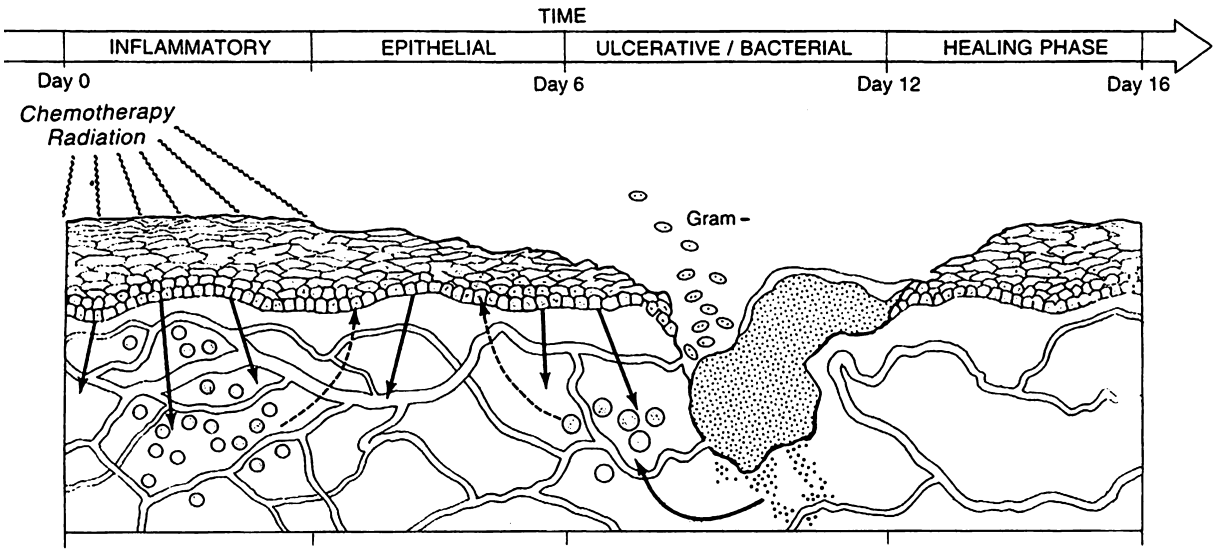

Figure 2 Phases of mucositis. From Sonis (2004a,b)

Table 3 Factors involved in the pathogenesis of mucositis

Free radicals
Reactive oxygen species (ROS)
Apoptosis, via activation of
Nuclear factor NF-κ
AP1 family (c-FOS, c-JUN) and caspase 3
P53 tumour suppressor gene
NRF2 (NF-E2-related factor2)
BAX (pro-apoptotic protein)
Mitogen activated protein kinase: MAPK
Ceramide production from
Sphingomyelinase
Ceramide synthase
Nitric oxide [NO]
Cytokines
Interleukins
IL-1β
IL-6
Tumour necrosis factor α: which also activates NF-κ, MAPK, JNK, AP1 and matrix metalloproteinases [MMP]
Cyclo-oxygenases [COX]
MMP

Table 3). Not only are these substances damaging, but they also provide a positive feedback loop (signal amplification) that drives the destructive process forward, such that the ultimate target tissue, the oral epithelium, eventually breaks down and ulcerates. Infective processes involving the oral microbiota may then come into play, especially when there is also neutropenia (as in chemotherapy and HSCT patients) or other deterioration in host immune defences such as falling levels of salivary IgG, IgA and IgM (Garfunkel *et al*, 1994). Aerobic Gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*), Gram-positive microorganisms (*Streptococcus mitis*, *S. oralis*, *S. sanguis* and staphylococci), capnophylles (Capnocytophaga, *Leptotrichus buccalis*) and anaerobes (particularly Fusobacteria) may be implicated. Myelosuppression increases Gram-negative organisms. Bacterial cell wall products such as lipopolysaccharide (LPS) amplify mechanisms that exaggerate and extend the injury by stimulating infiltrating macrophages to produce additional damaging cytokines.

The healing phase is also biologically dynamic, with signalling from the submucosal extracellular matrix stimulating the migration, differentiation and proliferation of the healing epithelium.

Prophylaxis of mucositis

There are a number of strategies adopted by oncologists to minimize the adverse effects of cancer therapy such as dose reduction, and other preventive treatment options. For example, leucovorin has been used for years to minimize the mucositis resulting from use of 5-FU (Lalla and Peterson, 2005). These are the province of oncologists and are not discussed further here.

There has been a range of interventions developed for prophylaxis of oral mucositis (Table 4) but a more rational approach may be warranted (Table 5). Indeed, there are very few randomized controlled double-blind trials (RCTs) assessing most of the interventions.

A recent Cochrane review (Clarkson, 2003) concluded benefit from use of

- Ice chips (in chemotherapy-induced mucositis)
- Granulocyte-macrophage colony stimulating factor (GM-CSF)

only moderate benefit from

- Antibiotics (topical or pastilles)
- Hydrolytic enzymes

and minimal benefit from

- Amifostine
- Benzydamine, oral care protocols and povidone.

Table 4 Miscellaneous therapeutic approaches that have been tried for prophylaxis and management of mucositis

Methods to reduce exposure of the mucosa to damaging agents
Ice chips
Propantheline
Antimicrobials
Aciclovir
Antibiotics
Amphotericin B
Chlorhexidine
Fluconazole
Protegrin peptides
Anti-inflammatory medications
Biologic response modifiers
Interleukin-1
Interleukin-11
GM-CSF
G-CSF
Keratinocyte growth factors
Thalidomide
TGF-beta 3
Cytoprotective agents
Amifostine
Benzydamine
Glutamine
N-acetyl cysteine
Prostaglandins
Vitamin E
Low-energy lasers
Other agents e.g.
Allopurinol, azelastine, chamomile, chymotrypsin, clopidogrel, coumarin/troxerutine, misoprostol, papain, pentoxifylline, sucralfate, tretinoin, trypsin

Table 5 Rational approaches to management of mucositis

Prevention of free radical DNA damage
Free radical scavengers
Amifostine (Ethyol®) (and see below)
Benzydamine (Difflam, Tantum®) (and see below)
N-acetyl cysteine (NAC)
Manganese superoxide dismutase (detoxifies ROS)
Keratinocyte growth factor 1 (activates NRF2 to induce superoxide dismutase; and see below)
Cytokine reduction
Amifostine
Benzydamine
N-acetylcysteine
COX-2 inhibitors
Apoptosis reduction
Ceramide inhibitors: glutathione, desipramine, fumonisin
COX-2 inhibitors
Keratinocyte growth factors (and see below)
Enhance healing
Keratinocyte growth factors (activate NRF2 to induce superoxide dismutase)
KGF1 = FGF7 (Palifermin®)
Induces
NRF2
IL-13
Downregulates
TNF (and possibly TGF and PDGF)
KGF2, FGF 01 and FGF 20 also in trials
Granulocyte-macrophage colony stimulating factor sargramostine (Leukine®, Prokine®)

The recent approval of recombinant human keratinocyte growth factor (KGF) palifermin (Kepivance®) for the prevention of mucositis induced by conditioning regimens for HSCT for haematological malignancies validates a mechanistically based approach to the problem (Spielberger *et al*, 2003, 2004; Awada *et al*, 2005; Kostler *et al*, 2005; Palmieri and Vigushin, 2005).

Radiation mucositis

Shielding the mucosa with mucosa-sparing blocks can reduce the problem of radiation-induced mucositis (Perch *et al*, 1995; Ship *et al*, 1997). The outcomes from studies testing GM-CSF, benzydamine hydrochloride or amifostine are mixed.

Granulocyte-macrophage colony stimulating factor administration concurrently with conventional fractionated radiotherapy was assessed in a consecutive series of patients and was associated with reduced mucositis, suggesting mucosal protection by GM-CSF during radiotherapy (Kannan *et al*, 1997) but this was not shown by others (Tejedor *et al*, 2000). Another trial with granulocyte colony stimulating factor (G-CSF) did not appear to influence mucositis although it reduced the number of treatment breaks (Mascarin *et al*, 1999). Randomized clinical studies are necessary.

Benzydamine HCl can inhibit TNF alpha (Sironi *et al*, 1997), and has been shown in single centre studies and in a multicentre double blind randomized placebo controlled trial in radiation therapy to reduce the intensity and duration of mucosal damage as well as to delay the need to use systemic pain-relievers including opioids (Kim *et al*, 1986; Epstein *et al*, 1989, 2001). Benzydamine was not effective however, in patients receiving accelerated radiotherapy doses of more than 220 cGy day^{-1}. Only a small number of patients in the trial had received combined radiation- and chemotherapy.

Amifostine and its active metabolite, WR-1065, preferentially are cytoprotective of parotid acinar cells exposed to radiation (Koukourakis, 2002). Both agents function as free radical scavengers. The efficacy of amifostine as a mucosal protectant is unclear and nausea, vomiting, hypotension, and allergic reactions are the most common adverse effects (Brizel *et al*, 2000).

Other interventions

Topical prostaglandin E2 has been suggested to be of some benefit in uncontrolled studies (Sinzinger *et al*, 1989). Another method to reduce radiation effects in normal tissue is to stimulate cells to divide before radiotherapy by silver nitrate (Maciejewski *et al*, 1991) although conflicting results have been reported (Dorr *et al*, 1995) and controlled trials are lacking. Growth factors that require further study include IL-1. These methods may be effective for treatment of mucositis when provided in patients treated with hyperfractionated radiation treatment such as CHART (Symonds, 1998).

There is some evidence that low-energy helium-neon laser (LEL) therapy may reduce the severity and duration of oral mucositis associated with radiation therapy (Ciais *et al*, 1992; Bensadoun *et al*, 1999) but considerable more research is needed. Again, RCTs are needed.

Clinical and histopathological demonstrations of a reduction in oral mucositis with sucralfate suggested

that it might be recommended in the prevention of radiation-induced mucositis (Etiz *et al*, 2000), but other researchers have not found reduction in mucositis (Epstein and Wong, 1994). Some have shown the combination of sucralfate with fluconazole to be effective (Allison *et al*, 1995) but double blind studies have not confirmed significant benefit from the use of sucralfate (Epstein and Wong, 1994; Franzen *et al*, 1995) although oropharyngeal pain was decreased (Epstein and Wong, 1994).

Coumarin/Troxerutine (Venalot Depot®) showed a favourable effect in the treatment of radiogenic sialadenitis and mucositis in prospective, randomized placebo-controlled double-blind studies (Grotz *et al*, 1999, 2001).

Radiotherapy is associated with a marked increase in oral Gram-negative microorganisms, including enterobacteria and pseudomonads (Rice and Gill, 1979) and it has been speculated that their presence could contribute to mucositis (Martin, 1993) but might also result in the release endotoxins which could cause adverse systemic effects (Spijkervet *et al*, 1989a). However, a role for antibacterial therapy in the control of radiation-induced mucositis has not been established. The negative results of a clinical trial in which protegrin, a naturally occurring antimicrobial peptide, was tested for its ability to modulate radiation-induced mucositis illustrate the potential complexity of the effects of the local environment on the course and severity of the condition (Chen *et al*, 2000). Meta-analysis suggested that only the narrow-spectrum antibacterial lozenges were effective (Sutherland and Browman, 2001). A placebo-controlled randomized trial of antibiotic pastilles showed a significant reduction in mucositis and weight loss during radiotherapy for head and neck cancer (Symonds *et al*, 1996) but others have not found an improvement in the quality of life (Duncan *et al*, 2005) and an RCT of other antibiotics (polymyxin E, tobramycin and amphotericin B) showed them to be of no significant value (Wijers *et al*, 2001).

Aqueous mouthrinses of chlorhexidine gluconate have, in some single centre studies, been reported to prevent acute oral infections and/or mucositis during cancer therapy (Ferretti *et al*, 1987, 1988; Brown *et al*, 1990; Thurmond *et al*, 1991). They are acceptable to children (Cheng, 2004). However, other studies have shown no effect upon chemotherapy mucositis (Wahlin, 1989; Weisdorf *et al*, 1989; Epstein *et al*, 1992) and no studies have shown significant benefit in radiation mucositis (Samaranayake *et al*, 1988; Spijkervet *et al*, 1989b; Ferretti *et al*, 1990; Foote *et al*, 1994). Proteolytic enzymes such as trypsin, papain and chymotrypsin may be beneficial (Gujral *et al*, 2001) but again, RCTs are required.

Chemotherapy-induced mucositis

Methods have been developed to reduce exposure of the mucosa to chemotherapeutic drugs. The use of ice chips (cryotherapy) producing mucosal cooling, leading to blood vessel constriction, is thought to lead to consequent reduction in exposure of mucosal tissues to the chemotherapy agent. This might be a useful approach for agents with a short half-life. Indeed, ice chips used 5 min before bolus administration of 5-FU and swilled around the mouth for 30 min reduces mucositis by about 50% (Mahood *et al*, 1991; Rocke *et al*, 1993; Cascinu *et al*, 1994; Loprinzi *et al*, 1997). Thirty-eight reports of chemotherapy trials were initially included in a Cochrane review; two were duplicate reports and nine were excluded as there was no useable information (Clarkson *et al*, 2000). Of the 27 useable studies 14 had data for mucositis comprising 945 randomized patients and 15 included data for oral candidosis with 1164 randomized patients but only ice chips prevented mucositis. There is also evidence of some benefit from ice chips in patients treated with methotrexate or melphalan (Dumontet *et al*, 1994; Meloni *et al*, 1996) or edatrexate (Edelman *et al*, 1998). Plain ice is more acceptable than flavoured ice (Nikoletti *et al*, 2005).

Propantheline is another agent that, by altering salivation, might reduce the topical exposure of the oral mucosa to chemotherapeutic drugs excreted in saliva. It may reduce mucositis associated with etoposide (Ahmed *et al*, 1993). or combination chemotherapy (ifosfamide, carboplatin and etoposide) plus autologous HSCT (Oblon *et al*, 1997). Pilocarpine has also been suggested to reduce mucositis (Awidi *et al*, 2001) but a prospective, double-blinded, randomized, placebo-controlled trial in oral mucositis during autologous HSCT showed no benefit (Lockhart *et al*, 2005).

There is evidence that prophylactic use of antifungal agents which are absorbed or partially absorbed from the gastrointestinal tract (e.g. fluconazole) reduce the clinical signs of oral candidosis and systemic infection and the partially absorbed drugs may be more effective (Clarkson *et al*, 2000).

Other agents tested

Chamomile (*Matricaria recutita*) contains a number of anti-inflammatory compounds and a single case report in methotrexate-induced mucositis suggested some success (Mazokopakis *et al*, 2005) but it was proven ineffective in a controlled trial of 5-FU-induced mucositis (Fidler *et al*, 1996).

A daily preventive protocol in leukaemia consisting of: (i) elimination of bacterial plaque; (ii) application of a mouthwash with a non-alcoholic solution of chlorhexidine 0.12% and (iii) topical application of iodopovidone, followed by 'swish and swallow' with nystatin 500 000 units resulted in a significant improvement in oral hygiene and a significant decrease in the incidence of mucositis grade 2 and oral candidosis (Levy-Polack *et al*, 1998). However, others found chlorhexidine may be no more effective than water at reducing mucositis, and suggested that salt and soda mouthwash is cheaper than and as effective as, chlorhexidine or a mouthwash containing lidocaine, Maalox® and Benadryl® (Dodd *et al*, 2000).

Indeed, no clear outcomes have been found with respect to the use of chlorhexidine, clindamycin, fluconazole, Iseganan, povidone iodine or combinations thereof (Donnelly *et al*, 2003). In non-blinded preliminary clinical studies, mouthwashes of GM-CSF and

G-CSF ameliorated mucositis (Ibrahim and al Mulhim, 1997). GM-CSF may reduce the severity and duration of chemotherapy-induced oral mucositis after 5-FU and cisplatin chemotherapy (Chi *et al*, 1995) and others have confirmed this finding, but only in non-blinded open trials (Rosso *et al*, 1997; Crawford *et al*, 1999). GM-CSF given subcutaneously from days 5 to 14 of chemotherapy appears to reduce the severity and duration of mucositis related to 5-FU, cisplatinum, cyclophosphamide, doxorubicin and etoposide, or methotrexate, vinblastine, and adriamycin (Gabrilove *et al*, 1988; Crawford and O'Rourke, 1994; Chi *et al*, 1995; Rosso *et al*, 1997; Karthaus *et al*, 1998). Local application may also have some effect (Sprinzl *et al*, 2001). Transforming growth factor beta (TGF-β3) is another potential therapeutic agent (Spijkervet and Sonis, 1998).

Amifostine may ameliorate mucosal damage after conditioning for peripheral blood progenitor cell autotransplant, However, tolerance due to nausea is of considerable concern (Capelli *et al*, 2000). Further study is needed to confirm the effect and to assess the side-effects associated with potential mucosal protection and to confirm a lack of effect on tumour protection at higher doses.

Topical prostaglandin E2 was suggested to be of some benefit, in uncontrolled studies (Kuhrer *et al*, 1986; Matejka *et al*, 1990) but at least one double blind study has discounted its value (Labar *et al*, 1993).

Topical vitamin E, acting as an antioxidant, has been shown in small placebo controlled double-blind studies to effectively reduce chemotherapy-induced mucositis (Wadleigh *et al*, 1992; Lopez *et al*, 1994).

Allopurinol may theoretically be expected to prevent 5-FU-associated stomatitis via both direct and indirect actions to oral mucosa (Nakamura *et al*, 1996), that include inhibitory actions on xanthine oxidase, superoxide dismutase, orotidylate decarboxylase as well as proteases. However, promising results of a protective effect from an allopurinol mouthwash (Clark and Slevin, 1985; Tsavaris *et al*, 1988) in 5-FU induced mucositis unfortunately have not been confirmed in controlled trials (Loprinzi *et al*, 1990; Porta *et al*, 1994). Results also do not support the use of oral misoprostol for high-dose chemotherapy-induced mucositis prophylaxis (Duenas-Gonzalez *et al*, 1996).

Finally despite promising early reports (Bianco *et al*, 1991), pentoxifylline appears to be of little benefit (Attal *et al*, 1993; Clift *et al*, 1993; Verdi *et al*, 1995) and is ineffective for preventing mucositis in patients receiving cisplatin and 5-FU (Verdi *et al*, 1995).

Chemoradiotherapy-induced mucositis

A phase II trial in cancer patients treated with concurrent carboplatin, paclitaxel and daily radiotherapy, showed that amifostine appears to decrease treatment-related toxicities, including oral mucositis, without impacting efficacy of the chemoradiotherapy (Suntharalingam *et al*, 2004). A phase II trial of propantheline in patients receiving high-dose ICE (ifosfamide, carboplatin and etoposide) chemotherapy plus autologous HSCT, dramatically reduced mucositis (Oblon *et al*, 1997), presumably by reducing salivary drug levels.

Granulocyte-macrophage colony stimulating factor and G-CSF may also ameliorate mucositis in HSCT (Atkinson *et al*, 1991; Gordon *et al*, 1994; Nemunaitis *et al*, 1995) although the benefit has not been impressive when used topically (Wardley and Scarffe, 1996; Karthaus *et al*, 1998). One study found no benefit in HSCT from 300 μg GM-CSF dissolved in a 2% methylcellulose gel applied locally for chemo- and radiotherapy-induced mucositis, compared with a 2% methylcellulose gel alone (van der Lelie *et al*, 2001).

Keratinocyte growth factor (KGF), palifermin (Kepivance®), has a beneficial effect on mucositis in murine models given chemoradiotherapy (Farrell *et al*, 2002) and in human HSCT patients on BCNU, etoposide, cytosine arabinoside and melphalan (Durant, 1999), in patients with haematologic cancers when administered for three consecutive days immediately before the initiation of conditioning therapy (fractionated total-body irradiation plus high-dose chemotherapy) and after autologous HSCT (Spielberger *et al*, 2004) and, in addition it has some effect on GVHD (Krijanovski *et al*, 1999). As compared with placebo, KGF was associated with significant reductions in the prevalence of grade 4 oral mucositis, patient-reported soreness of the mouth and throat, the use of opioid analgesics, and the incidence of use of total parenteral nutrition (Spielberger *et al*, 2004).

Interleukin 11 (IL-11) is a cytokine of potential value, showing efficacy in animal models (Sonis *et al*, 1995; Orazi *et al*, 1996; Potten, 1996). A trial in HSCT using recombinant IL-11, showed a reduction in mucositis in humans (Sonis *et al*, 1999b) but there is the potential for cardiac arrhythmias and oedema.

A preliminary study indicated that the severity of oral mucositis, both objective and subjective, in HSCT patients may be reduced by 0.1% topical tretinoin cream which has anti-inflammatory activity, administered daily from the beginning of the HCST conditioning until marrow engraftment (Cohen *et al*, 1997).

Local antimicrobials containing amphotericin, polymixin and tobramycin may have some activity (Bondi *et al*, 1997) but an RCT discounted any significant benefit (Wijers *et al*, 2001) and, in general, antiseptics (chlorhexidine) appear to have little effect in mucositis (Samaranayake *et al*, 1988). Small single centre trials show that the incidence, severity and duration of radiochemotherapy-induced mucositis can be significantly reduced by oral rinsing with povidone iodine performed in addition to the standard prophylaxis scheme (Rahn *et al*, 1997; Adamietz *et al*, 1998). However, a RCT found no significant differences between the groups in respect of mucositis characteristics, fever of unknown origin and other infections between patients using povidone iodine and normal saline mouthwashes (Vokurka *et al*, 2005).

Topical application of prostaglandin E2 in an uncontrolled patient cohort was found beneficial, but controlled studies have yet to be reported (Matejka *et al*, 1990). Mixed results have been seen with oral glutamine,

which is involved in protein and nucleic acid synthesis: one group showed a decrease in the severity and duration of oropharyngeal mucositis in autologous HSCT patients but not in allogeneic HSCT patients, possibly because of interaction with methotrexate (Anderson *et al*, 1998a,b). While similar results were shown in a trial of intravenous glutamine in HSCT (MacBurney *et al*, 1994), and from an uptake-enhanced glutamine suspension used orally (Peterson 2006), others have found no benefit (Schloerb and Skikne, 1999).

Small studies have shown some beneficial effect of helium-neon (He-Ne) lasers used before autologous HSCT in which chemotherapy consisted of cyclophosphamide, or melphalan and TBI (Barasch *et al*, 1995a,b; Cowen *et al*, 1997; Genot and Klastersky, 2005).

Management of mucositis

Mucositis invariably requires systemic analgesics, adjunctive medications, physical therapy and psychologic therapy in addition to oral care. A recent Cochrane review (Worthington, 2004) concluded that there was

- no evidence that patient controlled analgesia (PCA) is better than continuous infusion method for controlling pain, but less opiate was used per hour, and duration of pain was shorter, for PCA.
- only weak and unreliable evidence that allopurinol mouthwash, vitamin E, immunoglobulin or human placental extract improve or eradicate mucositis.

Treatment guidelines developed by the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology are published (Rubenstein *et al*, 2004), but highlight the need for higher levels of evidence: panelists identified gaps in evidence that made it impossible to recommend or not recommend use of specific agents.

The following management protocol was recommended (Rubenstein *et al*, 2004):

- Patient education
- Patient-controlled analgesia (morphine in HCST)
- Radiotherapy
  - Midline blocks & 3D radiotherapy
  - Benzydamine
- Chemotherapy, cryotherapy for
  - 30 min before 5-FU
  - 20 min before Edatrexate
- Possibly, low level laser therapy

Do not use

- Chlorhexidine
- Aciclovir
- Pentoxifylline.

Minimal care is good oral hygiene plus narcotic analgesics, but a number of other approaches can be helpful (Sonis and Haley, 1996).

Control of pain

Pain from established mucositis can be reduced by systemic analgesics with non-steroidal agents and other non-opiods used first, combined with opioids such as morphine and hydromorphone when pain is severe. In the in-patient setting, PCA provides the most effective pain control with lower total doses of opioid. Topical analgesics may combat pain and dysphagia when used prior to meals. Capsaicin may also provide analgesia (Berger *et al*, 1995).

Avoidance of mucosal irritation

In general, mucositis should be treated conservatively to avoid further tissue irritation and damaging the remaining cells from which the epithelium will regenerate. Plaque control and oral hygiene should be maintained with careful tooth brushing (Borowski *et al*, 1994). The potential benefit of prophylactic rinses with chlorhexidine may be to control plaque levels, gingivitis, reduce caries risk and oropharyngeal candidosis, rather than any direct effect upon oral mucositis. The patient should be advised to take a soft bland diet, avoiding irritants such as tobacco, alcohol or spices. Nutrition should be maintained.

Active treatment of mucositis

Palifermin (Kepivance®) has been approved for the treatment of mucositis induced by conditioning regimens for HSCT for haematological malignancies (Spielberger *et al*, 2004; Awada *et al*, 2005; Kostler *et al*, 2005; Palmieri and Vigushin, 2005). Benzydamine and povidone may have a place.

None of the other many available interventions for the management of mucositis (Table 4), including low energy laser therapy (Nes and Posso, 2005) has been shown to be reliably effective in RCTs.

Conclusions

Despite the multiple approaches to mucositis prevention and management, only cryotherapy, benzydamine and recombinant human KGF might provide some benefit in specific situations. Future advances such as further developments in use of growth factors, or cytokines such as TGF beta 3 (Wymenga *et al*, 1999), or gene therapy using superoxide dismutase to reduce ROS are eagerly awaited (Guo *et al*, 2003).

References

Adamietz IA, Rahn R, Bottcher HD, Schafer V, Reimer K, Fleischer W (1998). Prophylaxis with povidone-iodine against induction of oral mucositis by radiochemotherapy. *Support Care Cancer* **6:** 373–377.

Ahmed T, Engelking C, Szalyga J *et al* (1993). Propantheline prevention of mucositis from etoposide. *Bone Marrow Transplant* **12:** 131–132.

Allison RR, Vongtama V, Vaughan J, Shin KH (1995). Symptomatic acute mucositis can be minimized or prophylaxed by the combination of sucralfate and fluconazole. *Cancer Invest* **13:** 16–22.

Anderson PM, Ramsay NK, Shu XO *et al* (1998a). Effect of low-dose oral glutamine on painful stomatitis during bone marrow transplantation. *Bone Marrow Transplant* **22:** 339–344.

Anderson PM, Schroeder G, Skubitz KM (1998b). Oral glutamine reduces the duration and severity of stomatitis after cytotoxic cancer chemotherapy. *Cancer* **83:** 1433–1439.

Atkinson K, Biggs JC, Downs K *et al* (1991). GM-CSF after allogeneic bone marrow transplantation: accelerated recovery of neutrophils, monocytes and lymphocytes. *Aust N Z J Med* **21:** 686–692.

Attal M, Huguet F, Rubie H *et al* (1993). Prevention of regimen-related toxicities after bone marrow transplantation by pentoxifylline: a prospective, randomized trial. *Blood* **82:** 732–736.

Awada A, Genot MT, Klastersky J (2005). Palifermin and chemotherapy-induced oral mucositis. *N Engl J Med* **352:** 1264–1265 (author reply).

Awidi A, Homsi U, Kakail RI *et al* (2001). Double-blind, placebo-controlled cross-over study of oral pilocarpine for the prevention of chemotherapy-induced oral mucositis in adult patients with cancer. *Eur J Cancer* **37:** 2010–2014.

Balis FM, Savitch JL, Bleyer WA, Reaman GH, Poplack DG (1985). Remission induction of meningeal leukemia with high-dose intravenous methotrexate. *J Clin Oncol* **3:** 485–489.

Barasch A, Peterson DE, Tanzer JM *et al* (1995a). Helium-neon laser effects on conditioning-induced oral mucositis in bone marrow transplantation patients. *Cancer* **76:** 2550–2556.

Barasch A, Peterson DE, Tanzer JM *et al* (1995b). Helium-neon laser effects on conditioning-induced oral mucositis in bone marrow transplantation patients. *Cancer* **76:** 2550–2556.

Barrett AP (1987). A long-term prospective clinical study of oral complications during conventional chemotherapy for acute leukemia. *Oral Surg Oral Med Oral Pathol* **63:** 313–316.

Bellm LA, Epstein JB, Rose-Ped A, Martin P, Fuchs HJ (2000). Patient reports of complications of bone marrow transplantation. *Support Care Cancer* **8:** 33–39.

Bensadoun RJ, Franquin JC, Ciais G *et al* (1999). Low-energy He/Ne laser in the prevention of radiation-induced mucositis. A multicenter phase III randomized study in patients with head and neck cancer. *Support Care Cancer* **7:** 244–252.

Berger A, Henderson M, Nadoolman W *et al* (1995). Oral capsaicin provides temporary relief for oral mucositis pain secondary to chemotherapy/radiation therapy. *J Pain Symptom Manage* **10:** 243–248.

Bergmann OJ (1988). Oral infections and septicemia in immunocompromised patients with hematologic malignancies. *J Clin Microbiol* **26:** 2105–2109.

Bergmann OJ (1989). Oral infections and fever in immunocompromised patients with haematologic malignancies. *Eur J Clin Microbiol Infect Dis* **8:** 207–213.

Bianco JA, Appelbaum FR, Nemunaitis J *et al* (1991). Phase I-II trial of pentoxifylline for the prevention of transplant-related toxicities following bone marrow transplantation. *Blood* **78:** 1205–1211.

Bishop JF, Joshua DE, Lowenthal RM *et al* (1986). A phase I-II study of cytosine arabinoside, daunorubicin, and VP16–213 in adult patients with acute non-lymphocytic leukemia. *Aust N Z J Med* **16:** 48–51.

Blijlevens NM, Donnelly JP, De Pauw BE (2000). Mucosal barrier injury: biology, pathology, clinical counterparts and consequences of intensive treatment for haematological malignancy: an overview. *Bone Marrow Transplant* **25:** 1269–1278.

Bondi E, Baroni C, Prete A *et al* (1997). Local antimicrobial therapy of oral mucositis in paediatric patients undergoing bone marrow transplantation. *Oral Oncol* **33:** 322–326.

Borowski B, Benhamou E, Pico JL, Laplanche A, Margainaud JP, Hayat M (1994). Prevention of oral mucositis in patients treated with high-dose chemotherapy and bone marrow transplantation: a randomised controlled trial comparing two protocols of dental care. *Eur J Cancer B Oral Oncol* **30B:** 93–97.

Brizel DM, Wasserman TH, Henke M *et al* (2000). Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. *J Clin Oncol* **18:** 3339–3345.

Brown AT, Shupe JA, Sims RE *et al* (1990). In vitro effect of chlorhexidine and amikacin on oral Gram-negative bacilli from bone marrow transplant recipients. *Oral Surg Oral Med Oral Pathol* **70:** 715–719.

Caballero GA, Ausman RK, Quebbeman EJ (1985). Long-term, ambulatory, continuous IV infusion of 5-FU for the treatment of advanced adenocarcinomas. *Cancer Treat Rep* **69:** 13–15.

Capelli D, Santini G, De Souza C *et al* (2000). Amifostine can reduce mucosal damage after high-dose melphalan conditioning for peripheral blood progenitor cell auto-transplant: a retrospective study. *Br J Haematol* **110:** 300–307.

Carl W, Higby DJ (1985). Oral manifestations of bone marrow transplantation. *Am J Clin Oncol* **8:** 81–87.

Cascinu S, Fedeli A, Fedeli SL, Catalano G (1994). Oral cooling (cryotherapy), an effective treatment for the prevention of 5-fluorouracil-induced stomatitis. *Eur J Cancer B Oral Oncol* **30B:** 234–236.

Chen J, Falla TJ, Liu H *et al* (2000). Development of protegrins for the treatment and prevention of oral mucositis: structure-activity relationships of synthetic protegrin analogues. *Biopolymers* **55:** 88–98.

Cheng KK (2004). Children's acceptance and tolerance of chlorhexidine and benzydamine oral rinses in the treatment of chemotherapy-induced oropharyngeal mucositis. *Eur J Oncol Nurs* **8:** 341–349.

Chi KH, Chen CH, Chan WK *et al* (1995). Effect of granulocyte-macrophage colony-stimulating factor on oral mucositis in head and neck cancer patients after cisplatin, fluorouracil, and leucovorin chemotherapy. *J Clin Oncol* **13:** 2620–2628.

Ciais G, Namer M, Schneider M *et al* (1992). Laser therapy in the prevention and treatment of mucositis caused by anticancer chemotherapy. *Bull Cancer* **79:** 183–191.

Clark PI, Slevin ML (1985). Allopurinol mouthwashes and 5-fluorouracil induced oral toxicity. *Eur J Surg Oncol* **11:** 267–268.

Clarkson A (2003). *Cochrane Database Syst Rev* CD000978.

Clarkson JE, Worthington HV, Eden OB (2000). Prevention of oral mucositis or oral candidiasis for patients with cancer receiving chemotherapy (excluding head and neck cancer). *Cochrane Database Syst Rev* CD000978.

Classen DC, Burke JP, Ford CD *et al* (1990). *Streptococcus mitis* sepsis in bone marrow transplant patients receiving oral antimicrobial prophylaxis. *Am J Med* **89:** 441–446.

Clift RA, Bianco JA, Appelbaum FR *et al* (1993). A randomized controlled trial of pentoxifylline for the prevention of regimen-related toxicities in patients undergoing allogeneic marrow transplantation. *Blood* **82:** 2025–2030.

Cohen G, Elad S, Or R, Galili D, Garfunkel AA (1997). The use of tretinoin as oral mucositis prophylaxis in bone marrow transplantation patients: a preliminary study. *Oral Dis* **3:** 243–246.

Cowen D, Tardieu C, Schubert MM *et al* (1997). Low energy helium-neon laser in the prevention of oral mucositis in patients undergoing bone marrow transplant: results of a double blind randomized trial. *Int J Radiat Oncol Biol Phys* **38:** 697–703.

Crawford J, O'Rourke MA (1994). Vinorelbine (Navelbine)/carboplatin combination therapy: dose intensification with granulocyte colony-stimulating factor. *Semin Oncol* **21** (5 Suppl. 10)**:** 73–78.

Crawford J, Tomita DK, Mazanet R *et al* (1999). Reduction of oral mucositis by filgrastim 9r-met HUG-CFF) in patients receiving chemotherapy. *Cytokines Cell Mol Ther* **5:** 187–193.

Dahllof G, Heimdahl A, Modeer T, Twetman S, Bolme P, Ringden O (1989). Oral mucous membrane lesions in children treated with bone marrow transplantation. *Scand J Dent Res* **97:** 268–277.

Dodd MJ, Dibble SL, Miaskowski C *et al* (2000). Randomized clinical trial of the effectiveness of 3 commonly used mouthwashes to treat chemotherapy-induced mucositis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **90:** 39–47.

Donnelly JP (1993). Selective decontamination of the digestive tract and its role in antimicrobial prophylaxis. *J Antimicrob Chemother* **31:** 813–829.

Donnelly JP, Muus P, Schattenberg A, De Witte T, Horrevorts A, DePauw BE (1992). A scheme for daily monitoring of oral mucositis in allogeneic BMT recipients. *Bone Marrow Transplant* **9:** 409–413.

Donnelly JP, Dompeling EC, Meis JF, De Pauw BE (1995). Bacteremia due to oral viridans streptococci in neutropenic patients with cancer: cytostatics are a more important risk factor than antibacterial prophylaxis. *Clin Infect Dis* **20:** 469–470.

Donnelly JP, Bellm LA, Epstein JB *et al* (2003). Antimicrobial therapy to prevent or treat oral mucositis. *Lancet infect Dis* **3:** 405–412.

Dorr W, Jacubek A, Kummermehr J, Herrmann T, Dolling-Jochem I, Eckelt U (1995). Effects of stimulated repopulation on oral mucositis during conventional radiotherapy. *Radiother Oncol* **37:** 100–107.

Dreizen S, McCredie KB, Bodey GP, Keating MJ (1986). Quantitative analysis of the oral complications of antileukemia chemotherapy. *Oral Surg Oral Med Oral Pathol* **62:** 650–653.

Duenas-Gonzalez A, Sobrevilla-Calvo P, Frias-Mendivil M *et al* (1996). Misoprostol prophylaxis for high-dose chemotherapy-induced mucositis: a randomized double-blind study. *Bone Marrow Transplant* **17:** 809–812.

Dumontet C, Sonnet A, Bastion Y, Salles G, Espinouse D, Coiffier B (1994). Prevention of high dose L-PAM-induced mucositis by cryotherapy. *Bone Marrow Transplant* **14:** 492–494.

Duncan GG, Epstein JB, Tu D *et al* (2005). Quality of life, mucositis, and xerostomia from radiotherapy for head and neck cancers: a report from the NCIC CTG HN2 randomized trial of an antimicrobial lozenge to prevent mucositis. *Head Neck* **27:** 421–428.

Durant JR (1999). High-dose chemotherapy for breast cancer in USA. *Lancet* **354:** 252–253.

Edelman MJ, Gandara Dr, Perez EA *et al* (1998). Phase 1 trial of edatrexate plus carboplatin in advanced solid tumors: amelioration of dose-limiting mucositis by ice chip cryotherapy. *Invest New Drugs* **16:** 69–75.

Edwards JE, Jr, Bodey GP, Bowden RA *et al* (1997). International conference for the development of a consensus on the management and prevention of severe candidal infections. *Clin Infect Dis* **25:** 43–59.

Elting LS, Bodey GP, Keefe BH (1992). Septicemia and the shock syndrome due to Viridans streptococci: a case control study of predisposing factor. *Clin Infect Dis* **14:** 1201–1207.

Elting LS, Cooksley C, Chambers M, Cantor SB, Manzullo E, Rubenste EB (2003). The burdens of cancer therapy. Clinical and economic outcomes of chemotherapy-induced mucositis. *Cancer* **14:** 1201–1207.

Epstein JB, Wong FL (1994). The efficacy of sucralfate suspension in the prevention of oral mucositis due to radiation therapy. *Int J Radiat Oncol Biol Phys* **28:** 693–698.

Epstein JB, Silverman S, Paggiarino DA *et al* (2001). Benzydamine HCI for prophylaxis of radiation-induced oral mucositis: results from a multicenter, randomized, double-blind, placebo-controlled trial. *Cancer* **92:** 875–885.

Epstein JB, Stevenson-Moore P, Jackson S, Mohamed JH, Spinelli JJ (1989). Prevention of oral mucositis in radiation therapy: a controlled study with benzydamine hydrochloride rinse. *Int J Radiat Oncol Biol Phys* **16:** 1571–1575.

Epstein JB, Vickars L, Spinelli J, Reece D (1992). Efficacy of chlorhexidine and nystatin rinses in prevention of oral complications in leukemia and bone marrow transplantation. *Oral Surg Oral Med Oral Pathol* **73:** 682–689.

Etiz D, Erkal HS, Serin M *et al* (2000). Clinical and histopathological evaluation of sucralfate in prevention of oral mucositis induced by radiation therapy in patients with head and neck malignancies. *Oral Oncol* **36:** 116–120.

Farrell CL, Rex KL, Chen JN (2002). The effects of keratinocyte growth factor in preclinical models of mucositis. *Cell Prolif* **35** (Suppl. 1)**:** S78–S85.

Feld R (1997). The role of surveillance cultures in patients likely to develop chemotherapy-induced mucositis. *Support Care Cancer* **5:** 371–375.

Ferretti GA, Ash RC, Brown AT, Largent BM, Kaplan A, Lillich TT (1987). Chlorhexidine for prophylaxis against oral infections and associated complications in patients receiving bone marrow transplants. *J Am Dent Assoc* **114:** 461–467.

Ferretti GA, Ash RC, Brown AT, Parr MD, Romond EH, Lillich TT (1988). Control of oral mucositis and candidiasis in marrow transplantation: a prospective, double-blind trial of chlorhexidine digluconate oral rinse. *Bone Marrow Transplant* **3:** 483–493.

Ferretti GA, Raybould TP, Brown AT *et al* (1990). Chlorhexidine prophylaxis for chemotherapy- and radiotherapy-induced stomatitis: a randomized double-blind trial. *Oral Surg Oral Med Oral Pathol* **69:** 331–338.

Fidler P, Loprinzi CL, O'Fallon JR *et al* (1996). Prospective evaluation of a chamomile mouthwash for prevention of 5-FU-induced oral mucositis. *Cancer* **77:** 522–525.

Foote RL, Loprinzi CL, Frank AR *et al* (1994). Randomised trial of a chlorhexidine mouthwash for alleviation of radiation-induced mucositis. *J Clin Oncol* **12:** 2630–2633.

Franzen L, Henriksson R, Littbrand B, Zackrisson B (1995). Effects of sucralfate on mucositis during and following radiotherapy of malignancies in the head and neck region. A double-blind placebo-controlled study. *Acta Oncol* **34:** 219–223.

Gabrilove JL, Jakubowski A, Scher H *et al* (1988). Effect of granulocyte colony-stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. *N Engl J Med* **318:** 1414–1422.

Garfunkel AA (2004). Oral mucositis–the search for a solution. *N Engl J Med* **351:** 2649–2651.

Garfunkel AA, Tager N, Chausu S, Chausu G, Haze C, Galili D (1994). Oral complications in bone marrow transplantation patients: recent advances. *Isr J Med Sci* **30:** 120–124.

Genot MT, Klastersky J (2005). Low-level laser for prevention and therapy of oral mucositis induced by chemotherapy or radiotherapy. *Curr Opin Oncol* **17:** 236–240.

Gordon B, Spadinger A, Hodges E, Ruby E, Stanley R, Coccia P (1994). Effect of granulocyte-macrophage colony-stimulating factor on oral mucositis after hematopoietic stem-cell transplantation. *J Clin Oncol* **12:** 1917–1922.

Greenberg MS, Cohen SG, McKitrick JC, Cassileth PA (1982). The oral flora as a source of septicemia in patients with acute leukemia. *Oral Surg Oral Med Oral Pathol* **53:** 32–36.

Grotz KA, Henneicke-von Zepelin HH, Kohnen R *et al* (1999). Prospective double-blind study of prophylaxis of radioxerostomia with Coumarin/Troxerutine in patients with head and neck cancer. *Strahlenther Onkol* **175:** 397–403.

Grotz KA, Wustenberg P, Kohnen R *et al* (2001). Prophylaxis of radiogenic sialadenitis and mucositis by coumarin/troxerutine in patients with head and neck cancer – a prospective, randomized, placebo-controlled, double-blind study. *Br J Oral Maxillofac Surg* **39:** 34–39.

Gujral MS, Patnaik PM, Kaul R *et al* (2001). Efficacy of hydrolytic enzymes in preventing radiation therapy-induced side effects in patients with head and neck cancers. *Cancer Chemother Pharmacol* **47** (Suppl.)**:** S23–S28.

Guo H, Seixas-Silva JA Jr, Epperly MW *et al* (2003). Prevention of radiation-induced oral cavity mucositis by plasmid/liposome delivery of the human manganese superoxide dismutase (SOD2) transgene. *Radiat Res* **159:** 361–370.

Herrstedt J (2000). Prevention and management of mucositis in patients with cancer. *Int J Antimicrob Agents* **16:** 161–163.

Hickey AJ, Toth BB, Lindquist SB (1982). Effect of intravenous hyperalimentation and oral care on the development of oral stomatitis during cancer chemotherapy. *J Prosthet Dent* **47:** 188–193.

Ibrahim EM, al Mulhim FA (1997). Effect of granulocyte-macrophage colony-stimulating factor on chemotherapy-induced oral mucositis in non-neutropenic cancer patients. *Med Oncol* **14:** 47–51.

Kannan V, Bapsy PP, Anantha N *et al* (1997). Efficacy and safety of granulocyte macrophage-colony stimulating factor (GM-CSF) on the frequency and severity of radiation mucositis in patients with head and neck carcinoma. *Int J Radiat Oncol Biol Phys* **37:** 1005–1010.

Karthaus M, Rosenthal C, Huebner G *et al* (1998). Effect of topical oral G-CSF on oral mucositis: a randomised placebo-controlled trial. *Bone Marrow Transplant* **22:** 781–785.

Kim JH, Chu FC, Lakshmi V, Houde R (1986). Benzydamine HCl, a new agent for the treatment of radiation mucositis of the oropharynx. *Am J Clin Oncol* **9:** 132–134.

Kostler WJ, Hejna M, Zielinski CC (2005). Palifermin and chemotherapy-induced oral mucositis. *N Engl J Med* **352:** 1264–1265 (author reply).

Koukourakis MI (2002). Amifostine in clinical oncology: current use and future applications. *Anticancer Drugs* **13:** 181–209.

Krijanovski OI, Hill GR, Cooke KR *et al* (1999). Keratinocyte growth factor separates graft-versus-leukemia effects from graft-versus-host disease. *Blood* **94:** 825–831.

Kuhrer I, Kuzmits R, Linkesch W, Ludwig H (1986). Topical PGE2 enhances healing of chemotherapy-associated mucosal lesions. *Lancet* **1:** 623.

Labar B, Mrsic M, Pavletic Z *et al*, (1993). Prostaglandin E2 for prophylaxis of oral mucositis following BMT. *Bone Marrow Transplant* **11:** 379–382.

Laine PO, Lindqvist JC, Pyrhonen SO, Strand-Pettinen IM, Teerenhovi LM, Meurman JH (1992). Oral infection as a reason for febrile episodes in lymphoma patients receiving cytostatic drugs. *Eur J Cancer B Oral Oncol* **28B:** 103–107.

Lalla RV, Peterson DE (2005). Oral mucositis. *Dent Clin North Am* **49:** 167–184.

van der Lelie H, Thomas BL, van Oers RH *et al* (2001). Effect of locally applied GM-CSF on oral mucositis after stem cell transplantation: a prospective placebo-controlled double-blind study. *Ann Hematol* **80:** 150–154.

Levy-Polack MP, Sebelli P, Polack NL (1998). Incidence of oral complications and application of a preventive protocol in children with acute leukemia. *Spec Care Dentist* **18:** 189–193.

Lockhart PB, Brennan MT, Kent ML *et al* (2005). Randomized controlled trial of pilocarpine hydrochloride for the moderation of oral mucositis during autologous blood stem cell transplantation. *Bone Marrow Transplant* **35:** 713–20.

Lopez I, Goudou C, Ribrag V, Sauvage C, Hazebroucq G, Dreyfus F (1994). Treatment of mucositis with vitamin E during administration of neutropenic antineoplastic agents. *Ann Med Interne (Paris)* **145:** 405–408.

Loprinzi CL, Cianflone SG, Dose AM *et al* (1990). A controlled evaluation of an allopurinol mouthwash as prophylaxis against 5-fluorouracil-induced stomatitis. *Cancer* **65:** 1879–1882.

Loprinzi CL, Ghosh C, Camoriano J *et al* (1997). Phase III controlled evaluation of sucralfate to alleviate stomatitis in patients receiving fluorouracil-based chemotherapy. *J Clin Oncol* **15:** 1235–1238.

Lucas VS, Beighton D, Roberts GJ, Challacombe SJ (1997). Changes in the oral streptococcal flora of children undergoing allogeneic bone marrow transplantation. *J Infect* **35:** 135–141.

MacBurney M, Young LS, Ziegler TR, Wilmore DW (1994). A cost-evaluation of glutamine-supplemented parenteral nutrition in adult bone marrow transplant patients. *J Am Diet Assoc* **94:** 1263–1266.

Maciejewski B, Zajusz A, Pilecki B *et al* (1991). Acute mucositis in the stimulated oral mucosa of patients during radiotherapy for head and neck cancer. *Radiother Oncol* **22:** 7–11.

Magrath IT, Janus C, Edwards BK *et al* (1984). An effective therapy for both undifferentiated (including Burkitt's) lymphomas and lymphoblastic lymphomas in children and young adults. *Blood* **63:** 1102–1111.

Mahood DJ, Dose AM, Loprinzi CL *et al* (1991). Inhibition of fluorouracil-induced stomatitis by oral cryotherapy. *J Clin Oncol* **9:** 449–452.

Martin MV (1993). Irradiation mucositis: a reappraisal. *Eur J Cancer B Oral Oncol* **29B:** 1–2.

Mascarin M, Franchin G, Minatel E *et al* (1999). The effect of granulocyte colony-stimulating factor on oral mucositis in head and neck cancer patients treated with hyperfractionated radiotherapy. *Oral Oncol* **35:** 203–208.

Matejka M, Nell A, Kment G *et al* (1990). Local benefit of prostaglandin E2 in radiochemotherapy-induced oral mucositis. *Br J Oral Maxillofac Surg* **28:** 89–91.

Mazokopakis EE, Vrentzos GE, Papadakis JA, Babalis DE, Ganotakis ES (2005). Wild chamomile (*Matricaria recutita* L.) mouthwashes in methotrexate-induced oral mucositis. *Phytomedicine* **12:** 25–27.

McCarthy GM, Skillings JR (1992). Orofacial complications of chemotherapy for breast cancer. *Oral Surg Oral Med Oral Pathol* **74:** 172–178.

Mead GM (2002). Management of oral mucositis associated with cancer chemotherapy. *Lancet* **359:** 815–816.

Meloni G, Capria S, Proia A, Trisolini SM, Mandelli F (1996). Ice pops to prevent melphalan-induced stomatitis. *Lancet* **347:** 1691–1692.

Nakamura K, Natsugoe S, Kumanohoso T *et al* (1996). Prophylactic action of allopurinol against chemotherapy-induced stomatitis – inhibition of superoxide dismutase and proteases. *Anticancer Drugs* **7:** 235–239.

Nemunaitis J, Rosenfeld CS, Ash R *et al* (1995). Phase III randomized, double-blind placebo-controlled trial of rhGM-CSF following allogeneic bone marrow transplantation. *Bone Marrow Transplant* **15:** 949–954.

Nes AG, Posso MB (2005). Patients with moderate chemotherapy-induced mucositis: pain therapy using low intensity lasers. *Int Nurs Rev* **52:** 68–72.

Nikoletti S, Hyde S, Shaw T, Myers H, Kristjanson LJ (2005). Comparison of plain ice and flavoured ice for preventing oral mucositis associated with the use of 5 fluorouracil. *J Clin Nurs* **14:** 750–753.

Oblon DJ, Paul SR, Oblon MB, Malik S (1997). Propantheline protects the oral mucosa after high-dose ifosfamide, carboplatin, etoposide and autologous stem cell transplantation. *Bone Marrow Transplant* **20:** 961–963.

Orazi A, Du X, Yang Z, Kashai M, Williams DA (1996). Interleukin-11 prevents apoptosis and accelerates recovery of small intestinal mucosa in mice treated with combined chemotherapy and radiation. *Lab Invest* **75:** 33–42.

Palmieri C, Vigushin D (2005). Palifermin and chemotherapy-induced oral mucositis. *N Engl J Med* **352:** 1264–1265 (author reply).

Parulekar W, Mackenzie R, Bjarnason G, Jordan RC (1998). Scoring oral mucositis. *Oral Oncol* **34:** 63–71.

Perch SJ, Machtay M, Markiewicz DA, Kligerman MM (1995). Decreased acute toxicity by using midline mucosa-sparing blocks during radiation therapy for carcinoma of the oral cavity, oropharynx, and nasopharynx. *Radiology* **197:** 863–866.

Peterson DE (2006). New strategies for management of oral mucositis in cancer patients. *J Support Oncol* **4:** 9–13.

Pico JL, Avila-Garavito A, Naccache P (1998). Mucositis: its occurrence, consequences, and treatment in the oncology setting. *Oncologist* **3:** 446–451.

Porta C, Moroni M, Nastasi G (1994). Allopurinol mouthwashes in the treatment of 5-fluorouracil-induced stomatitis. *Am J Clin Oncol* **17:** 246–247.

Potten CS (1996). Protection of the small intestinal clonogenic stem cells from radiation-induced damage by pretreatment with interleukin 11 also increases murine survival time. *Stem Cells (Dayt)* **14:** 452–459.

Rahn R, Adamietz IA, Boettcher HD, Schaefer V, Reimer K, Fleischer W (1997). Povidone-iodine to prevent mucositis in patients during antineoplastic radiochemotherapy. *Dermatology* **195** (Suppl. 2)**:** 57–61.

Rapoport AP, Miller Watelet LF, Linder T *et al* (1999). Analysis of factors that correlate with mucositis in recipients of autologous and allogeneic stem-cell transplants. *J Clin Oncol* **17:** 2446–2453.

Rice DH, Gill G (1979). The effect of irradiation upon the bacterial flora in patients with head and neck cancer. *Laryngoscope* **89:** 1839–1841.

Rocke LK, Loprinzi CL, Lee JK *et al* (1993). A randomized clinical trial of two different durations of oral cryotherapy for prevention of 5-fluorouracil-related stomatitis. *Cancer* **72:** 2234–2238.

Rodu B, Gockerman JP (1983). Oral manifestations of the chronic graft-v-host reaction. *JAMA* **249:** 504–507.

Rosso M, Blasi G, Gherlone E, Rosso R (1997). Effect of granulocyte-macrophage colony-stimulating factor on prevention of mucositis in head and neck cancer patients treated with chemo-radiotherapy. *J Chemother* **9:** 382–385.

Roth BJ, Sledge GW Jr, Williams SD, Meyer SC, Ansari R, Fisher WB (1991). Methotrexate, vinblastine, doxorubicin, and cisplatin in metastatic breast cancer. A phase II trial of the Hoosier Oncology Group. *Cancer* **68:** 248–252.

Rubenstein EB, Peterson DE, Schubert M, Keefe D *et al* (2004). Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. *Cancer* **100** (Suppl.)**:** 2026–2046.

Ruescher TJ, Sodeifi A, Scrivani SJ, Kaban LB, Sonis ST (1998). The impact of mucositis on alpha-hemolytic streptococcal infection in patients undergoing autologous bone marrow transplantation for hematologic malignancies. *Cancer* **82:** 2275–2281.

Samaranayake LP, Robertson AG, MacFarlane TW *et al* (1988). The effect of chlorhexidine and benzydamine mouthwashes on mucositis induced by therapeutic irradiation. *Clin Radiol* **39:** 291–294.

Schloerb PR, Skikne BS (1999). Oral and parenteral glutamine in bone marrow transplantation: a randomized, double-blind study. *JPEN J Parenter Enteral Nutr* **23:** 117–122.

Schubert MM, Sullivan KM, Morton TH *et al* (1984). Oral manifestations of chronic graft-v-host disease. *Arch Intern Med* **144:** 1591–1595.

Scully C, Epstein J, Sonis S (2003). Oral mucositis: a challenging complication of radiotherapy, chemotherapy, and radiochemotherapy. Part 1, pathogenesis and prophylaxis of mucositis. *Head Neck* **25:** 1057–1070.

Scully C, Epstein J, Sonis S (2004). Oral mucositis: a challenging complication of radiotherapy, chemotherapy, and radiochemotherapy. Part 2, diagnosis and management of mucositis. *Head Neck* **26:** 77–84.

Ship JA, Eisbruch A, D'Hondt E, Jones RE (1997). Parotid sparing study in head and neck cancer patients receiving bilateral radiation therapy: one-year results. *J Dent Res* **76:** 807–813.

Sinzinger H, Porteder H, Matejka M, Peskar BA (1989). Prostaglandins in irradiation-induced mucositis. *Lancet* **1:** 556.

Sironi M, Milanese C, Vecchi A *et al* (1997). Benzydamine inhibits the release of tumor necrosis factor-alpha and monocyte chemotactic protein-1 by *Candida albicans*-stimulated human peripheral blood cells. *Int J Clin Lab Res* **27:** 118–122.

Sonis ST (1998). Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. *Oral Oncol* **34:** 39–43.

Sonis ST (2002). The biologic role of nuclear factor-$\kappa\beta$ in disease and its potential involvement in mucosal injury associated with antineoplastic therapy. *Crit Rev Oral Biol Med* **13:** 300–309.

Sonis ST (2004a). The pathobiology of mucositis. *Nat Rev Cancer* **4:** 277–284.

Sonis ST (2004b). Pathobiology of mucositis. *Semin Oncol Nursing* **20:** 11–15.

Sonis ST, Fey EG (2002). Oral complications of cancer therapy. *Oncology* **16:** 680–686.

Sonis HT, Haley JD (1996). Pharmcological attenuation of chemotherapy-induced oral mucositis. *Exp Opinon Invest Drugs* **5:** 1155–1162.

Sonis S, Kunz A (1988). Impact of improved dental services on the frequency of oral complications of cancer therapy for patients with non-head-and-neck malignancies. *Oral Surg Oral Med Oral Pathol* **65:** 19–22.

Sonis S, Muska A, O'Brien J, Van Vugt A, Langer-Safer P, Keith J (1995). Alteration in the frequency, severity and duration of chemotherapy-induced mucositis in hamsters by interleukin-11. *Eur J Cancer B Oral Oncol* **31B:** 261–266.

Sonis ST, Eilers JP, Epstein JB *et al* (1999a). Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. Mucositis Study Group. *Cancer* **85:** 2103–2113.

Sonis S, Edwards L, Lucey C (1999b). The biological basis for the attenuation of mucositis: the example of interleukin-11. *Leukemia* **13:** 831–834.

Sonis ST, Elting LS, Keefe D *et al* (2004a). Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer* **100** (Suppl.)**:** 1995–2025.

Sonis ST, Elting LS, Keefe D *et al* (2004b). Perspectives on cancer therapy-induced mucosal injury. *Cancer* **100** (Suppl.)**:** 1995–2025.

Spielberger R, Stuff P, Bensinger W *et al* (2003). Use of recombinant human keratinocyte growth factor (rHuKGF) can reduce severe oral mucositis in patients with hematologic malignancies using peripheral blood progenitor transplantation after radiation-based conditioning–results of phase 3 trial. ASCO Proc., Abstract 3642.

Spielberger R, Stiff P, Bensinger W *et al* (2004). Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med* **351:** 2590–2598.

Spijkervet FK, Sonis ST (1998). New frontiers in the management of chemotherapy-induced mucositis. *Curr Opin Oncol* **10** (Suppl. 1)**:** S23–S27.

Spijkervet FK, van Saene HK, Panders AK *et al* (1989a). Effect of chlorhexidine rinsing on the oropharyngeal ecology in patients with head and neck cancer who have irradiation mucositis. *Oral Surg Oral Med Oral Pathol* **67:** 154–161.

Spijkervet FK, Van Saene HK, Panders AK *et al* (1989b). Effect of chlorhexidine rinsing on the oropharyngeal ecology in patients with head and neck cancer who have irradiation mucositis. *Oral Surg Oral Med Oral Pathol* **67:** 154–161.

Sprinzl GM, Galvan O, de Vries A *et al* (2001). Local application of granulocyte-macrophage colony stimulating factor (GM-CSF) for the treatment of oral mucositis. *Eur J Cancer* **37:** 2003–2009.

Suntharalingam M, Jaboin J, Taylor R *et al* (2004). The evaluation of amifostine for mucosal protection in patients with advanced loco-regional squamous cell carcinomas of the head and neck (SCCHN) treated with concurrent weekly carboplatin, paclitaxel, and daily radiotherapy (RT). *Semin Oncol* **31** (6 Suppl. 18)**:** 2–7.

Sutherland SE, Browman GP (2001). Prophylaxis of oral mucositis in irradiated head-and-neck cancer patients: a proposed classification scheme of interventions and meta-analysis of randomized controlled trials. *Int J Radiat Oncol Biol Phys* **49:** 917–930.

Symonds RP (1998). Treatment-induced mucositis: an old problem with new remedies. *Br J Cancer* **77:** 1689–1695.

Symonds RP, McIlroy P, Khorrami J *et al* (1996). The reduction of radiation mucositis by selective decontamination antibiotic pastilles: a placebo-controlled double-blind trial. *Br J Cancer* **74:** 312–317.

Tejedor M, Valerdi JJ, Arias F *et al* (2000). Hyperfractionated radiotherapy concomitant with cisplatin and granulocyte-macrophage colony stimulating factor (Filgrastim) for laryngeal carcinomas. *Cytokines Cell Mol Ther* **6:** 35–39.

Thurmond JM, Brown AT, Sims RE *et al* (1991). Oral *Candida albicans* in bone marrow transplant patients given chlorhexidine rinses: occurrence and susceptibilities to the agent. *Oral Surg Oral Med Oral Pathol* **72:** 291–295.

Trotti A, Bellm LA, Epstein JB *et al* (2003). Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. *Radiother Oncol* **66:** 253–262.

Tsavaris N, Caragiauris P, Kosmidis P (1988). Reduction of oral toxicity of 5-fluorouracil by allopurinol mouthwashes. *Eur J Surg Oncol* **14:** 405–406.

Verdi CJ, Garewal HS, Koenig LM, Vaughn B, Burkhead T (1995). A double-blind, randomized, placebo-controlled, crossover trial of pentoxifylline for the prevention of chemotherapy-induced oral mucositis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **80:** 36–42.

Vissink A, Jansma J, Spijkervet FK *et al* (2003). Oral sequelae of head and neck radiotherapy. *Crit Rev Oral Biol Med* **14:** 199–212.

Vokurka S, Bystricka E, Koza V *et al* (2005). The comparative effects of povidone-iodine and normal saline mouthwashes on oral mucositis in patients after high-dose chemotherapy and APBSCT–results of a randomized multicentre study. *Support Care Cancer* **13:** 554–558.

Wadleigh RG, Redman RS, Graham ML, Krasnow SH, Anderson A, Cohen MH (1992). Vitamin E in the treatment of chemotherapy-induced mucositis. *Am J Med* **92:** 481–484.

Wahlin YB (1989). Effects of chlorhexidine mouthrinse on oral health in patients with acute leukemia. *Oral Surg Oral Med Oral Pathol* **68:** 279–287.

Wardley AM, Scarffe JH (1996). Role of granulocyte-macrophage colony-stimulating factor in chemotherapy-induced oral mucositis. *J Clin Oncol* **14:** 1741–1743.

Wardley AM, Jayson GC, Swindell R *et al* (2000). Prospective evaluation of oral mucositis in patients receiving myeloablative conditioning regimens and haemopoietic progenitor rescue. *Br J Haematol* **110:** 292–299.

Weisdorf DJ, Bostrom B, Raether D *et al* (1989). Oropharyngeal mucositis complicating bone marrow transplantation: prognostic factors and the effect of chlorhexidine mouth rinse. *Bone Marrow Transplant* **4:** 89–95.

Wijers OB, Levendag PC, Harms ER *et al* (2001). Mucositis reduction by selective elimination of oral flora in irradiated cancers of the head and neck: a placebo-controlled double-blind randomized study. *Int J Radiat Oncol Biol Phys* **50:** 343–352.

Wingard JR, Merz WG, Rinaldi MG, Johnson TR, Karp JE, Saral R (1991). Increase in Candida krusei infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. *N Engl J Med* **325:** 1274–1277.

Woo SB, Lee SJ, Schubert MM (1997). Graft-vs.-host disease. *Crit Rev Oral Biol Med* **8:** 201–216.

World Health Organization (1979). *Handbook for reporting results of cancer treatment*. World Health Organization: Geneva, Switzerland, pp. 15–22.

Worthington. (2004). *Cochrane Database Syst Rev*: CD001973.

Wright J, Feld R, Knox J (2005). Chemotherapy-induced oral mucositis: new approaches to prevention and management. *Expert Opin Drug Saf* **4:** 193–200.

Wymenga AN, van der Graaf WT, Hofstra LS *et al* (1999). Phase I study of transforming growth factor-beta3 mouthwashes for prevention of chemotherapy-induced mucositis. *Clin Cancer Res* **5:** 1363–1368.