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INVITED MEDICAL REVIEW

Oral complications in the treatment of cancer patients

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While treatment for cancer in terms of chemotherapy and radiation therapy have evolved significantly since their inception, both of these cancer treatment modalities, especially if used in combination (e.g., as with head and neck cancers), have a very real potential to result in painful and debilitating adverse effects that clearly decrease quality of life and, potentially, increase mortality due to cancer. Herein, we discuss the prevalence and etiology of three broad categories of oral complications found during the treatment of cancer patients: mucositis, dysgeusia, and infectious disease. Lastly, we present therapeutic options that may be helpful in ameliorating these uncomfortable and, sometimes, life-threatening oral complications.

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Introduction

Cancer treatment has evolved significantly since the 1940s when folic acid antagonists and nitrogen mustards were first used as treatments for leukemia and lymphomas, respectively, with increases in both efficacy and tolerability. Likewise, radiation therapy (RT) has been in use for cancer treatment for more than 100 years, and has similarly evolved in terms of sophistication, efficacy, and reduction of undesirable side effects. Both cancer treatment modalities, however, especially if used in combination (e.g., as with head and neck cancers), have a very real potential to result in painful and debilitating adverse effects that clearly decrease quality of life and, potentially, increase mortality due to cancer. Herein, we discuss three broad categories of oral complications found during the treatment of cancer patients: mucositis, dysgeusia, and infectious disease. These topics are sufficiently large that we cannot discuss in full detail all of the clinical and pathophysiologic information that is known about these conditions. Instead, we cite references that individually discuss each of these broad areas in greater detail. Our intent is to present these three topics together in order to emphasize that (1) cancer treatment all too commonly results in one or more oral complications (adverse effects) and (2) that some complications (individually) may contribute to the development of another oral complication (such as Candida infection to dysgeusia). We present some therapeutic options that may be helpful in ameliorating some of these painful and, sometimes, life-threatening oral complications of modern chemotherapy (CT) and RT.

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Mucositis

One of the most clinically visible manifestations of cancer CT, mucositis, affects all portions of the integument ranging from the mouth to the anus of cancer patients. Mucositis refers to lesions of the gastrointestinal tract ranging from erythematous patches to infection-prone ulcerations (Sonis, 2007). Clinically, mucositis is a common side-effect of several chemotherapeutic drugs, including methotrexate, that are utilized in the treatment of cancer (Table 1) (Zackheim *et al*, 2003). Although mucositis in general is likely underreported, a retrospective study by Elting *et al,* examined 599 patients undergoing CT for solid tumors, including lymphomas, and discovered that 37% of patients developed mucositis and 11% developed severe World Health Organization (WHO) grade 3 or 4 oral mucositis at some point in treatment (Elting *et al*, 2003). In patients undergoing RT or chemoradiation for head and neck cancers, even low cumulative doses (10 Gy) may lead to mucositis (Sonis, 2007). The development and severity of mucositis in cancer patients is a major factor in nutritional deficiency secondary to mucositis-associated pain and infection. Understanding the etiology and treatment of mucositis can help clinicians make their cancer patients more comfortable as well as reduce morbidity and mortality during cancer therapy (Sonis, 2010). In addition, prevention and/or treatment of mucositis can decrease the use of parental nutrition,

Table 1 Common chemotherapeutic drugs that induce mucositis (Kostler *et al*, 2001)

Antimetabolites	*DNA-interactive drugs*	*Anti-mitotic drugs*
Cytarabine	Actinomycin D	Docetaxel
5-Fluorouracil	Amsacrin	Vinblastine
Floxuridine	Bleomycin	Vindesine
Methotrexate	Doxorubicin	
Thioguanin	Etoposide	
	Mitoxantron	

reduce emergency room use and unplanned hospitalizations, and reduce the need for drug dose de-escalation due to this complication.

Mucositis in cancer patients can negatively affect the patient's quality of life (QOL) (Elting *et al*, 2008), including the ability to maintain adequate oral intake and sufficient body weight. Mucositis development can be associated with alteration in taste (dysgeusia), hyposalivation, and, in severe cases, dysphagia (Cheng, 2007a). Clinically, oral mucositis severity is graded on several different scales, but the most widely used is the World Health Organization (WHO) 5-step grading scale (Table 2). From a nutritional standpoint, patients experiencing grade 3 mucositis tolerate little solid foods and are limited to a predominately liquid diet. When a patient progresses to WHO grade 4 mucositis, oral alimentation is often impossible and patients are at the greatest risk for nutritional and infectious complications (Scully *et al*, 2006). At this level of severity, nutritional support through parenteral nutrition or placement of a gastrointestinal tube is necessary in a high percentage of patients.

Historically, the etiology of mucositis was thought to be related to epithelial injury that was elicited by the preferential effect of chemotherapeutic agents on proliferating basal cells, which resulted in eventual loss and ulceration of the epithelium. Bacterial colonization and/or secondary infection of ulcers were/was also believed to increase the duration of ulcers or prevent healing. Recent hypotheses and clinical data, however, suggest that infection is not a central element in the development of mucositis (Sonis, 2007, 2010). While chemotherapeutic agents certainly target rapidly dividing normal tissues, including those of the oral mucosa and GI tract (Pico *et al*, 1998), new data suggest that damage to components of the submucosa is apparent well before injury to the overlying epithelium can be appreciated (Sonis, 2010). Specifically, injury and eventual apoptosis of fibroblasts and vascular endothelial cells appear to precede epithelial injury. Mechanistically, injury to endothelial cells results in loss of secreted epithelial growth factors such as keratinocyte growth factor (KGF), which may explain dysregulation of the normal growth patterns of the mucosal epithelium (Wearing and Sherratt, 2000). Others have shown that basic fibroblast growth factor can prevent endothelial apoptosis, thus protecting animals from radiation-induced epithelial injury (Paris *et al*, 2001). Other critical factors leading to ulceration may include the early release of inflammatory cytokines and reactive oxygen species in mucosal tissue, resulting in activation of transcription factors such as NF-κB that induce up-regulation of specific genes (tumor necrosis factor, IL-6, and IL1) which then trigger apoptosis and the cascade of events that lead to epithelial ulceration (Sonis, 2007).

Table 2 World Health Organization (WHO) oral toxicity grading scale to clinically assess low (grade 1, 2) and high (grade 3, 4) oral mucositis (Scully *et al*, 2006)

Grade 0	Normal mucosa
Grade 1	Mild oral mucositis (OM), soreness ± mild erythema
Grade 2	Moderate OM, oral erythema, and ulceration
Grade 3	Severe OM, extensive erythema, and severe ulceration
Grade 4	Life-threatening OM, necrosis, and extensive bleeding

Ulcerative lesions in concurrence with CT-induced neutropenia can predispose the patient to the development of bacterial or fungal infections and further mucosal destruction. Therapeutic intervention at the ulcerative stage of mucositis is critical to avoiding concurrent infection. Regular tooth brushing, flossing and chlorhexidine-containing mouthwash use can help prevent bacterial colonization in ulcerative mucositis lesions (Keefe *et al*, 2007) although their effects on preventing mucositis are questionable (Sonis, 2007). In addition, prevention of hyposalivation by maintaining proper oral hydration through consistent water intake, use of artificial saliva substitutes or cholinergic agonists such as pilocarpine (Salagen®; MGI Pharma Inc., Bloomington, MN, USA), civimeline, or bethanechol (when pilocarpine is ineffective) to stimulate saliva production can help to preserve mucosal integrity (Sonis and Fey, 2002; Lalla *et al*, 2008).

While no medication has proven to successfully eliminate mucositis, management of painful symptoms can help alleviate oral discomfort and improve patient quality of life. Pain control, to encourage eating, is an important part of the management strategy of CT-induced oral mucositis (Cheng, 2007b). The management of oral mucositis-associated pain commonly includes the use of an oral solution mixture also known as 'Magic Mouthwash' that contains, in varying amounts, diphenhydramine, viscous lidocaine, bismuth subsalicylate, and corticosteroids (Chan and Ignoffo, 2005). Magic mouthwash relieves acute pain and decreases inflammation, allowing greater ease of alimentation. The severity of pain positively correlates with mucositis grade. High-grade mucositis pain is commonly relieved with potent analgesic medications, including opioids (Keefe *et al*, 2007).

Relatively new therapeutic interventions are currently under investigation to determine their effectiveness in minimizing the development of severe, high-grade mucositis and reducing the duration of mucositis lesions. Several growth factors and cytokines involved in the biological process of mucosal destruction are being studied as potential therapies (von Bultzingslowen *et al*, 2006). One widely studied drug, palifermin (Kepivance®; Amgen, Thousand oaks, CA, USA), a recombinant human keratinocyte growth factor, acts to stimulate mucosal epithelial cell proliferation. In a study

by Spielberger *et al* (2004), patients who were treated with intravenous (IV) palifermin 3 days before and following CT developed high-grade (WHO grade 3 or 4) mucositis 35% less frequently when compared to placebo controls. In addition, palifermin-treated patients exhibited shorter mucositis duration, diminished use of parenteral nutrition and higher scores for physical and functional well-being. Side effects of palifermin included rash, puritis and erythema. The percentage of palifermin-treated patients developing adverse events, however, did not differ greatly from those treated with placebo. Side effects of palifermin were generally mild and were not severe enough to discontinue therapy in any patients (Spielberger *et al*, 2004). In a smaller study done exclusively on patients being treated with methotrexate, the authors also concluded that palifermin is a beneficial preventative therapy for mucositis (Schmidt *et al*, 2008). Even a single dose of palifermin given before and after CT cycles can help prevent severe mucositis and may provide similar levels of efficacy, thus minimizing prophylactic medical costs. Interestingly, this study noted taste alteration as a palifermin side-effect (Vadhan-Raj *et al*, 2010).

Several practical therapies for mucositis are also available but have less evidence-based data to prove their effectiveness. The use of oral cryotherapy (i.e., application of ice chips to the mouth prior to and every 30 min following CT) is widely used by oncologists to reduce oral mucositis. Oral cryotherapy is thought to act by acutely constricting the blood vessels in the oral cavity, preventing release of the chemotherapeutic drugs to the mucosal epithelium (Lalla *et al*, 2008). The potential benefit of low level laser therapy (LLLT) may be an additional effective preventative measure (Lalla *et al*, 2008; Silva *et al*, 2010). Use of LLLT, utilizing an InGaAlP diode laser at a wavelength of 660-nm, on chemotherapy patients with various cancers, including non-Hodgkin's Lymphoma, showed lower rates of severe grade WHO mucositis (Silva *et al*, 2010). Other experimental approaches include the hormone, leptin, which may accelerate enterocyte turnover and has been shown to beneficially impact the development of mucositis in rats treated with methotrexate (Sukhotnik *et al*, 2009b).

Another potential preventative therapy is focused around the amino acid L-glutamine, which has low toxicity but may induce mild nausea (Noe, 2009). In clinical trials, a novel formulation of oral glutamine, Saforis™, was shown to significantly decrease the percentage of patients who developed WHO grade 2 or higher mucositis (38.7%) *vs* placebo (49.7%) with an adverse effect profile that was similar to placebo (Peterson *et al*, 2007). In a methotrexate-treated rat model, oral glutamine supplementation has been shown to increase gastrointestinal mucosal proliferation and prevent epithelial cell apoptosis by down-regulating inflammatory molecules and modulating intracellular redox potential (Noe, 2009; Sukhotnik *et al*, 2009a). Immunomodulatory agents may also have an impact on preventing RT and CT-induced mucositis. For example, gamma-D-glutamyl-L-tryptophan (SCV-07), an investigational peptide, reduced the duration and severity of oral mucositis in Syrian hamsters exposed to cisplatin and RT (Watkins *et al*, 2010).

Due to the high prevalence of mucositis in cancer patients and the extensive burden on quality of life, the interest in developing more effective treatments continues to be a focus of modern research. The complex pathobiology of mucositis involves multiple signaling pathways that warrant further investigating as future therapeutic targets. Efforts to prevent severe mucositis using drugs such as palifermin will likely decrease the incidence of painful mucosal toxicity and may permit the use of more aggressive (and possibly more effective) chemotherapeutic regimens.

Dysgeusia

Dysgeusia, referring to distorted or impaired ability to taste (Cowart, 2011), is a common clinical problem faced by cancer patients. By some estimates, 50–75% of cancer patients receiving CT, RT or both are affected (Hovan *et al*, 2010). Interestingly, RT patients (mostly for head and neck cancers) have worse dysgeusia than CT patients, and the severity is highly correlated with cumulative radiation dose. Indeed, 15% of RT patients continue to have altered taste even after completing their treatment (Hovan *et al*, 2010). While mild dysgeusia is tolerated fairly well, dysgeusia at any level has the potential to affect patient appetite, thus reducing caloric intake, inducing weight loss, and ultimately affecting nutritional status. While the origins of dysgeusia are multifactorial, there are straightforward ways, including dietary counseling, treatment of oral infection, and altering drug schedules, to minimize its impact on the patient (Ohrn *et al*, 2001).

Dysgeusia can result in cancer patient from multiple causes (see Table 3). Direct injury to mucosal epithelium, nerves, taste buds, or olfactory receptors in the mouth and nose from CT or RT is a major source of dysgeusia in cancer patients due to the normal rapid turnover of these tissues. This often occurs in the setting of mucositis (see section on Mucositis) in which there is sufficient damage to taste and olfactory receptors to decrease numbers of receptors, alter their function, or disturb transmission of receptor signals to the brain. Treatment options for mucositis are discussed in the Mucositis portion of this review.

Many antineoplastic agents themselves have an unpleasant taste and enter the mouth from plasma by diffusion through capillaries. Other drugs such as antibiotics or analgesics used in the treatment of cancer patients in order to manage side effects may result in loss of taste [e.g., palifermin for treatment of mucositis (Spielberger *et al*, 2004)] or distorted taste.

Certain CT agents such as the histone deacetylase (HDAC) inhibitors can directly affect taste sensation without inducing mucositis. For instance, grade I and II dysgeusia were reported in nearly one-fourth of patients treated with vorinostat (Zolinza®; Merck & CO., Whitehouse station, NJ, USA) for cutaneous T-cell lymphoma (CTCL) (Duvic *et al*, 2007). Many patients complain of a metallic taste or hypersalted taste in

Table 3 Causes and treatment for dysgeusia

Causes of dysgeusia	*Potential therapy*
Chemo- and radiation therapy related mucositis (i.e., direct injury)	Ice chips during chemotherapy to constrict blood vessels and decrease release of chemotherapeutic drugs in the oral cavity; better techniques for radiation therapy that spare oral mucosa, including avoidance of the tip of the tongue in the field of treatment during RT (Yamashita *et al*, 2006)
Drugs that directly affect taste and smell receptors (e.g., histone deacetylase inhibitors)	Dosage reduction if possible; dietary consult; vitamin D (Fink, 2010)
Candidiasis (e.g., thrush)	Nystatin suspension swish and swallow or lozenges 4–5 times a day; gentian violet solution (do not swallow); clotrimazole lozenges; amphotericin B swish and swallow
Nutritional deficiency (decreased Zn, Cu, Ni), malabsorption, urinary losses	Variable but dietary consult essential; alternations in skin texture and/or skin dermatitis and scaling may be signs of true nutritional deficiency (Doerr *et al*, 1997; Chan *et al*, 1998)
Poor dentition, gingivitis	Dental consultation
Viral infection	Anti-viral medication

foods, leading to decreased appetite. Nearly identical proportions of patients in multicenter clinical trials for the CTCL agent, romidepsin (Istodax®; Celgene Corp, Warren, NJ, USA), another HDAC inhibitor, showed similar mild-to moderate symptoms of dysgeusia (Whittaker *et al*, 2010), suggesting that HDAC inhibitors as a drug class may trigger dysgeusia without significant mucositis. Fortunately, significant taste alteration noted by some patients can be improved by reducing the dosage of HDAC inhibitors without substantially decreasing HDAC efficacy.

Infections of the mouth (as discussed in Infections section) from bacterial (e.g., gingivitis), fungal (candidiasis/thrush), and viral (herpes simplex virus) agents can all lead to dysgeusia. Appropriate identification of some oral infections (e.g., severe herpes simplex, see section on Infections) can be challenging due to similarities in clinical appearance between mucosal infection and mucositis. Once a cause has been identified, treatment should be aggressive while keeping in mind that drug-resistant strains of pathogens may be seen in cancer patients (Pereira *et al*, 2010).

Several treatment strategies have been proposed for ameliorating the debilitating effects of dysgeusia. Zinc supplementation has been used as a management strategy because this element may be structurally important for proteins involved in the regulation of taste bud pores. The clinical efficacy of zinc supplementation has been quite variable, with some studies suggesting that zinc gluconate may improve appetite and general mood of patients suffering from idiopathic dysgeusia in a non-cancer population (Halyard, 2009). However, in a randomized trial assessing the efficacy of TID dosing of zinc sulfate in RT patients, some of whom were receiving CT, there was no significant difference in the two groups in terms of dysgeusia (Halyard *et al*, 2007). Amifostine (Ethyol®; Medimmune Inc., Gaithersburg, MD, USA), a cytoprotective agent (antioxidant), has also been tested for efficacy in dysgeusia in CT patients. While this agent may decrease the severity and occurrence of gastrointestinal toxicity (e.g., mucositis), it does not appear to decrease the incidence of dysgeusia and may paradoxically increase it (Komaki *et al*, 2004).

Intriguingly, Fink *et al* have reported that vitamin D supplementation markedly benefited two patients with chemotherapy-induced dysgeusia (Fink, 2010). The two patients had been treated with different chemotherapy regimens, but both had measured vitamin D insufficiency (4.9 and 6.3 ng ml^{-1}, respectively,) prior to vitamin D supplementation at 2000 U (cholecalciferol) per day. Remarkably, one of these patients reported a clear improvement of dysgeusia within a week of initiating vitamin D. The other patient had also suffered from severe oral mucositis and acral dermatitis, both of which improved after vitamin D supplementation.

Depending on the cause of dysgeusia, there are a few simple steps that nutritionists advise for symptomatic patients (Hovan *et al*, 2010). First, patients should be advised to drink plenty of fluids while eating (unless medically contraindicated). This simple step allows for dissolution of various taste components and facilitates their translocation to taste buds. Next, patients should be counseled to chew food slowly, releasing more flavors and, importantly, increasing saliva production. The latter is particularly important because many cancer treatments can lead to decreased saliva production and subsequent dry mouth. Without sufficient saliva, most foods are virtually tasteless. Artificial saliva and other treatment options can thus be beneficial to those patients with insufficient saliva production (Diaz-Arnold and Marek, 2002). Second, nutritionists advise patients to switch foods during meals to prevent adaptation of taste receptors. In addition, many patients will naturally switch to foods that are not as dramatically altered in taste, but care should be taken to make sure that balanced meals are eaten. In this situation, consultations with a nutritionist or a sensory psychologist are quite helpful to first establish dysgeusia and to offer treatment and dietary advice to alleviate it (Cowart, 2011). Overall dietary counseling appears to have more impact on long-term dysgeusia compared to acute dysgeusia (Ravasco *et al*, 2005a), but may additionally improve patient outcome (Ravasco *et al*, 2005b)

and quality of life (Ravasco *et al*, 2007) in certain cancer populations.

In summary, dysgeusia is a common side-effect of the CT and RT in cancer patients, particularly when the two are combined in head and neck cancer patients. There are many etiologies of dysgeusia, some of which are treatable (e.g., infection,) but others are poorly amenable to therapy. Technological advances in RT have resulted in ways of sparing sensitive taste areas (e.g., tip of the tongue). Drug therapy (amifostine and zinc supplementation) for dysgeusia resulting from CT and RT, however, have largely been disappointing in stringent clinical trials, thus other avenues for treatment such as vitamin D supplementation should be investigated. Until then, dietary counseling combined with relatively simple interventions such as artificial saliva may relieve the impact of dysgeusia. It is important that physicians take the time to ask their patients simple questions that might reveal that the patient is indeed experiencing symptomatic taste alternations (e.g., Do foods taste normal to you? How is your appetite? Are you losing weight?) that would trigger an appropriate referral to someone familiar with the chemosensory problems that cancer patients face.

Infectious disease complications

As a result of the above described effects on the oral mucosa, both CT and RT lead to opportunistic infections which contribute to morbidity and mortality in cancer patients receiving treatment (Miller and Kearney, 2001).

Candidiasis

Candida albicans and related fungi are commensal organisms that routinely inhabit the oral cavity. Under normal circumstances they co-exist with the other oral microorganisms of the oral cavity and do not cause disease. Colonization and infections do occur under circumstances where the systemic or local environment is altered, including the immunosuppression, hyposalivation, tissue damage, and/or imbalance of flora observed in cancer patients undergoing treatment. In a review of the literature by Lalla *et al*, the prevalence of oral fungal infection in all cancer treatments including chemotherapy and head and neck radiation was about 7.5% before treatment, 40% during treatment, and 30% after treatment. Rates of colonization approached 70% during and after treatment. Pseudomembranous candidiasis (thrush), erythematous candidiasis, and angular chelitis are the most common clinical presentations (Figure 1). Chronic hyperplastic candidiasis is rarely reported. Sepsis can occur through oral infection and can be fatal if unrecognized, especially with non-albicans species such as *Candida tropicalis* (Lalla *et al*, 2008).

A Cochrane review meta-analysis published in 2007 concluded that there is insufficient evidence to make a recommendation for or against treating oral candidiasis with antifungal agents in cancer patients receiving cancer treatment, emphasizing the need for more placebo-controlled trials (Worthington *et al*, 2010). However, in practice, oral candidiasis in immunocompromised patients calls for treatment to reduce morbidity and prevent systemic infection.

Topical antifungal agents have a lower risk of side effects and drug interactions, but there is inconsistent evidence supporting their efficacy in patients receiving cancer therapy (Lalla *et al*, 2010). The Infectious Disease Society of America (IDSA) guidelines suggest clotrimazole troches or nystatin pastilles as first line therapy for mild oropharygeal candidiasis (Pappas *et al*, 2009). In their review of oral fungal infections in cancer patients, Lalla *et al* point out that troches/pastilles are difficult to use and are traumatic in circumstances such

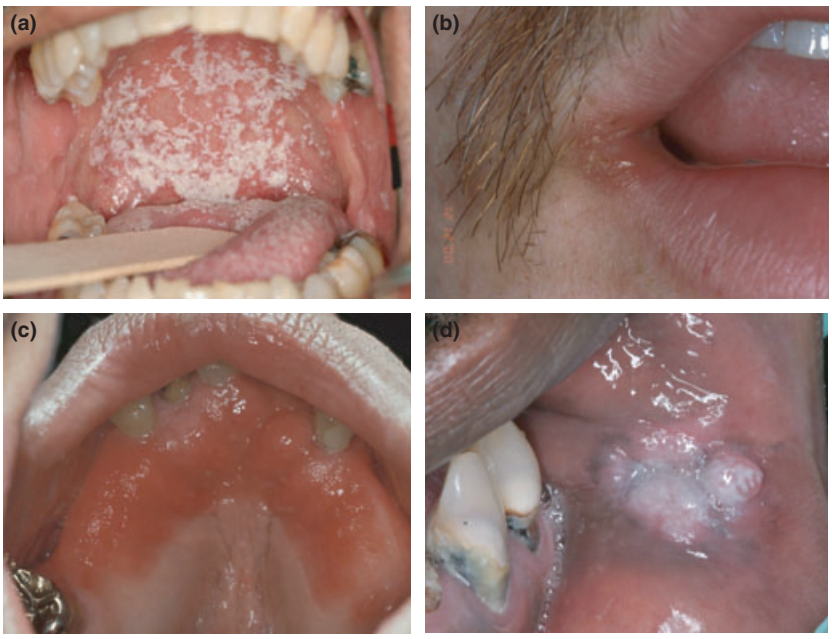

Figure 1 Presentations of oral candidiasis. (**a**) Pseudomembranous (thrush) – white pseudomembranes that can be removed with gentle scraping, (**b**) Erythema, fissuring, and crusting of the commissures of the lips, (**c**) Erythematous (atrophic) – intensely red, inflamed areas often on denture-bearing mucosa, (**d**) Chronic hyperplastic (candidal leukoplakia) – hyperkeratotic white patch which cannot be removed with scraping

as hyposalivation due to head and neck radiation and/or mucositis from chemotherapy. In these situations, nystatin rinses may be the better option (Lalla *et al*, 2010).

Although topical agents offer some advantages, they are associated with a high relapse rate. Thus, systemic (usually oral) antifungal agents are preferred for treatment of oral candidiasis (Meis and Verweij, 2001). Systemic fluconazole (Diflucan®; Pfizer Labs, New York, NY, USA) is recommended for moderate-to-severe disease according to IDSA guidelines (Pappas *et al*, 2009) and may be of particular benefit when hyposalivation is a contributing factor. Oral fluconazole (100–200 mg day^{-1} for 2 weeks) is as effective and is better tolerated than itraconazole (Sporonox®; PriCara, Raritan, NJ, USA) (Martin, 2000, Meis and Verweij, 2001; Lalla *et al*, 2010). Long-term use of fluconazole, however, for treatment and/or prevention can lead to the emergence of resistant strains (Martin, 2000; Meis and Verweij, 2001). In fluconazole resistant cases, itraconazole capsules (200 mg day^{-1} for 2–4 weeks) or itraconazole oral solution (200 mg day^{-1} for 2 weeks) is usually effective (Lalla *et al*, 2010). IDSA guidelines also mention posaconazole (Noxafil®; Merck & CO., Whitehouse station, NJ, USA) as second line treatment (Pappas *et al*, 2009). In refractory disease, voriconazole (Vfend®; Pfizer Labs, New York, NY, USA) and capsofungin (Cancidas®; Merck & CO., Whitehouse station, NJ, USA) can be used as they are more potent with a broader spectrum of action. Voriconazole, however, is associated with severe photosensitivity and, possibly, an increased risk of skin cancer (Vazquez, 2003, Pappas *et al*, 2009). Although it is limited by its systemic side effects, Amphotericin B (Fungizone®; Bristol-Myers Squibb Co., Princeton, NJ, USA) is an option for severe refractory cases of oral candidiasis (Lalla *et al*, 2010). If the enteric route is not available, most of these drugs can be used in intravenous form.

As in treatment of oral candidiasis, prophylaxis with topical agents has the advantage of fewer side effects and unwanted drug interactions, but their efficacy has been questioned and topical agents can be difficult to use. Little has been written about the relative cost-effectiveness systemic *vs* topical prophylaxis for oral fungal infection (Lalla *et al*, 2010). Specifically, does prophylaxis of oral fungal infection in mild-to-moderate risk cancer patients who are receiving cancer therapy, but not receiving systemic antifungal prophylaxis, improve quality of life and nutritional intake leading to better outcomes?

Systemic prophylaxis against fungal infections in cancer patients receiving treatment is expected to prevent oral fungal infections. A Cochrane review did conclude that there is good evidence from randomized-controlled trials that drugs absorbed from the GI tract prevent candidiasis in cancer patients (Worthington *et al*, 2010). A review of 17 studies reported that the prophylactic use of fluconazole during cancer therapy reduces the prevalence of all clinical fungal infections, including systemic infections, to 1.9% (Lalla *et al*, 2010). Other studies using itraconazole, posaconazole, and intravenous micafungin (Mycamine®; Astellas Pharma US, Inc., Deerfield, IL, USA) have also demonstrated efficacy and, possibly, more cost effectiveness than fluconazole (Collins *et al*, 2008; Schonfeld *et al*, 2008; Stam *et al*, 2008; Sohn *et al*, 2009; de la Camara *et al*, 2010). The cost/benefit of prophylaxis of invasive fungal infections with any antifungal drug is most favorable in severely immunosuppressed and/or neutropenic patients.

Viral infections

Oral viral infections, including herpes simplex virus (HSV), varicella zoster virus (VZV), Epstein–Barr virus (EBV), and cytomegalovirus (CMV), are often complications of cancer treatment. Severe infections may lead

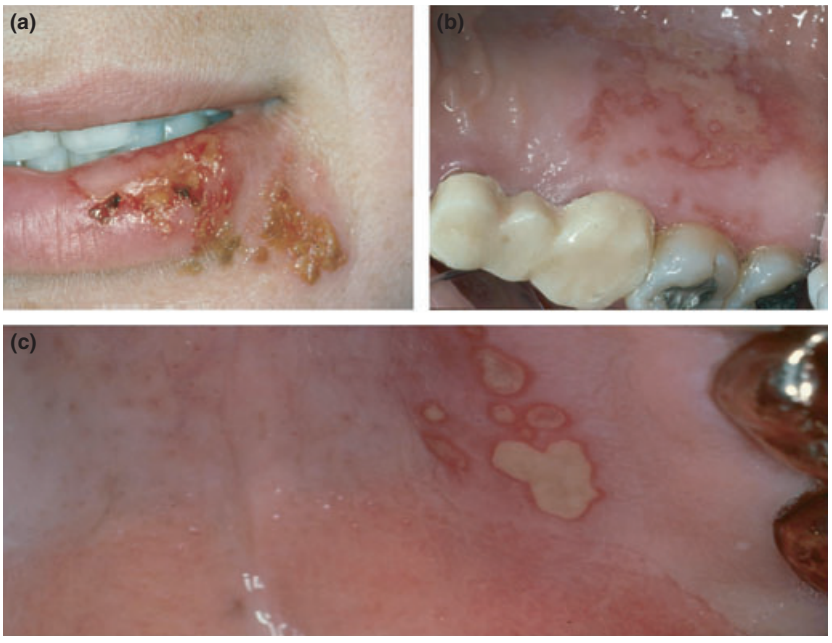

Figure 2 Oral HSV. (**a**) Clustered vesicles and crusted ulcers on vermilion border and peri-oral skin, (**b**) Sharply demarcated ulcer on the hard palate, (**c**) Coalescing shallow, round ulcers with scalloped borders on the hard palate

to dehydration and malnutrition, and life-threatening complications include encephalitis and disseminated infection. HSV is especially prevalent in the population at large and is the focus of most prophylaxis and treatment of viral infections in patients undergoing cancer therapy. In immunocompromised patients, however, the presentation of HSV may be atypical and can be confused with mucositis or apthous ulcers, as noted above. Therefore, testing for HSV should be considered for acute, painful oral ulcerations that are otherwise unexplained or persistent (Figure 2).

In most cases, HSV infection results from re-activation of latent virus. Elad *et al* (2010) reported that the prevalence of HSV infection in neutropenic patients with oral ulcers during treatment for hematologic malignancies approaches 50%. HSV was found in one-third of all patients, including those without mucosal ulcers. In patients receiving radiation therapy for head and neck cancer the prevalence of HSV was near 0%. In patients receiving combined radiation and chemotherapy, however, the prevalence increased to nearly 40%. These data suggest that immunosuppression due to chemotherapy is the main contributive factor. Neutropenic patients with hematologic malignancies are at the highest risk. There is very little literature assessing the prevalence of other viral infections such as VZV (Elad *et al*, 2010).

Acyclovir (Zovirax®; GlaxoSmithKline Pharmaceuticals, Research Triangle Park, NC, USA) and valacyclovir (Valtrex®; GlaxoSmithKline Pharmaceuticals, Research Triangle Park, NC, USA) have both been shown to be effective for prevention of oral HSV infection in immunosuppressed HSV seropositive patients. Oral prophylaxis can be achieved with an acyclovir dose of 200–800 mg TID or a valacyclovir of 500 mg BID (Reusser, 2002; Arduino and Porter, 2006; Glenny *et al*, 2009). A Cochrane review published in 2009 found no evidence that valacyclovir was more efficacious than acyclovir for prevention or for treatment of HSV. Furthermore, higher doses of valacyclovir were no more efficacious than lower doses of valacyclovir during prophylaxis. During treatment, acyclovir was found to decrease viral shedding time as well as decrease time to resolution of pain and healing (Glenny *et al*, 2009). Acyclovir can be used in intravenous doses of 5 mg kg^{-1} every 8 h or oral administration of 200–400 mg 3–5×/day. Intravenous valacyclovir is not available; however, the oral dosing regimen is 500–1000 mg BID. Famciclovir (Famvir®Novartis Pharmaceuticals Corp, East Hanover, NJ, USA) is also an option. Some authors suggest that patient compliance is better with the valacyclovir-dosing regimen, allowing for adequate drug exposure time and concentration and leading to less resistance (Beutner, 1995; Arduino and Porter, 2006). In the case of drug resistance, intravenous foscarnet (Foscavir; AstraZeneca, Wilmington, NC, USA) and cidofovir (Vistide; Gilead Sciences, Inc., Foster City, CA, USA) are alternative therapies (Chilukuri and Rosen, 2003).

Oral hairy leukoplakia (OHL) is a common manifestation of Epstein–Barr virus that is frequently seen in HIV infection as corrugated white plaques, primarily on the lateral borders of the tongue, although other mucosal sites may be affected (Figure 3). Occasionally, it can be confused with leukoplakias due to a variety of etiologies, e.g., chronic hyperplastic candidiasis (compare with Figure 1d). OHL can, however, present in patients who are HIV negative but who are immunocompromised for other reasons, such as cancer therapy. It has been reported in patients with acute myelogenous leukemia (AML), acute lymphocytic leukemia, and multiple myeloma undergoing chemotherapy (Syrjanen *et al*, 1989; Blomgren and Back, 1996; Nicolatou *et al*, 1999), as well as in a patient on prednisone for a gastrointestinal stromal tumor (Piperi *et al*, 2010). It has even been reported as a presenting sign of AML in an undiagnosed, untreated 15-year-old boy (Cho *et al*, 2010). No universal therapy exists, but OHL has been effectively and safely treated with high dose oral valacyclovir (Walling *et al*, 2003). Topical therapies

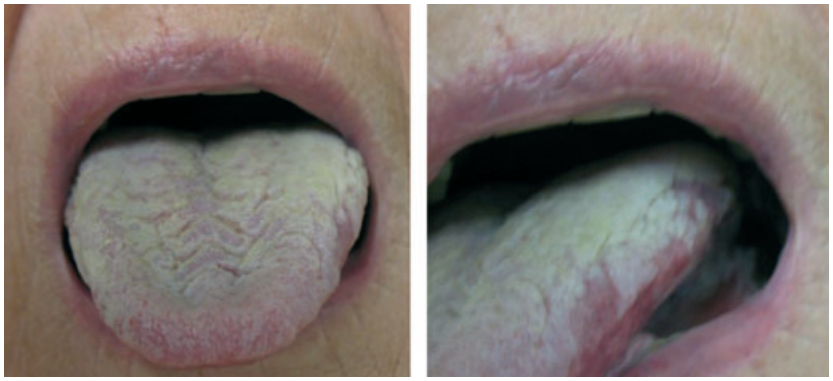

Figure 3 Presentation of oral hairy leukoplakia (OHL) in an immunosuppressed patient. It is often an asymptomatic non-painful white plaque along the lateral tongue borders; may vary in appearance from smooth, flat, small lesions to irregular 'hairy' or 'feathery' lesions with prominent folds or projections. It may be either continuous or discontinuous along both tongue borders, and they are often not bilaterally symmetric. Lesions are adherent, and only the most superficial layers can be removed by scraping. There is no associated erythema or edema of the surrounding tissue. OHL may also involve dorsal and ventral tongue surfaces, the buccal mucosa, or the gingiva. Occasionally, lesions may clinically resemble chronic hyperplastic candidiasis (compare with Figure 1**d**)

such as 25% podophyllin resin alone or combined with 5% topical acyclovir have also shown efficacy (Moura *et al*, 2007, 2010). Gentian violet has been reported as a safe, inexpensive treatment as well (Bhandarkar *et al*, 2008). Although it is rare, OHL can present in cancer patients, even those not currently undergoing chemotherapy, and it needs to be diagnosed and treated appropriately.

Bacterial disease

There are numerous bacteria which constitute normal oral flora, but which may become pathogenic with immune suppression. Rautemaa *et al* (2007) suggest that the possibility of oral infection should be considered for any sepsis of unknown origin in cancer patients. Viridans Strep, Prevotellae, *Fusobacterium, Actinobacillus, actinomycetemcomitans,* and *Actinomyces* species may cause oral mucosal infections. Such infections are usually localized and can be treated with a combination of penicillin and metronidazole, with subsequent dental procedures as necessary. Life-threatening complications such as endocarditis or Lemierre's syndrome, when infection spreads via the pharynx to the mediastinum causing sepsis, may also occur. Removal of bacteria from teeth by gentle brushing with a soft tooth brush, flossing, and use of an antimicrobial mouthwash may be helpful. If there is mucosal damage, vigorous use of a stiff-bristled tooth brush may lead to bacteremia. In this situation, a chlorhexidine-containing mouthwash is recommended (Hong *et al*, 2010).

Dental disease

Few clinical studies examine the impact of cancer therapies on dental disease such as caries and periodontal disease. Hong *et al* (2010) report that the weighted prevalence of dental infections/abscesses during CT is approximately 6% (Hong *et al*, 2010). Patients who had undergone RT for head and neck malignancies had the highest rate of decayed/missing/filled teeth among patients who have had antineoplastic therapies. Rautemaa *et al* suggest the use of fluoride products and chlorhexidine rinses in patients who are post RT, but stress the need for more clinical studies examining the pathophysiology of dental disease after RT and CT (Rautemaa *et al*, 2007).

Summary

Despite many improvements in CT and RT for cancer patients, oral complications are common, leading to discomfort, poor quality of life, and occasionally life-threatening problems such as severe malnutrition and infection. Fortunately, effective treatments do exist, ranging from antibiotics for bacterial and fungal infections to palifermin for chemotherapy-induced mucositis. On the other hand, other complications (e.g., dysgeusia secondary to chemotherapy) appear to have few effective remedies although anecdotal reports suggest that vitamin D may have beneficial effects in dysgeusia. Ongoing research is very much needed to find new therapeutic targets that will reduce these debilitating, severe side effects in patients undergoing cancer therapy.

Author contributions

D Mosel and R Bauer contributed equally to writing and editing. D Lynch provided photographs and edited the manuscript. ST Hwang contributed to writing, editing, and finalizing the manuscript.

References

Arduino PG, Porter SR (2006). Oral and perioral herpes simplex virus type 1 (HSV-1) infection: review of its management. *Oral Dis* **12:** 254–270.

Beutner KR (1995). Valacyclovir: a review of its antiviral activity, pharmacokinetic properties, and clinical efficacy. *Antiviral Res* **28:** 281–290.

Bhandarkar SS, MacKelfresh J, Fried L, Arbiser JL (2008). Targeted therapy of oral hairy leukoplakia with gentian violet. *J Am Acad Dermatol* **58:** 711–712.

Blomgren J, Back H (1996). Oral hairy leukoplakia in a patient with multiple myeloma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **82:** 408–410.

von Bultzingslowen I, Brennan MT, Spijkervet FK *et al* (2006). Growth factors and cytokines in the prevention and treatment of oral and gastrointestinal mucositis. *Support Care Cancer* **14:** 519–527.

de la Camara R, Jarque I, Sanz MA *et al* (2010). Economic evaluation of posaconazole vs fluconazole in the prevention of invasive fungal infections in patients with GVHD following haematopoietic SCT. *Bone Marrow Transplant* **45:** 925–932.

Chan A, Ignoffo RJ (2005). Survey of topical oral solutions for the treatment of chemo-induced oral mucositis. *J Oncol Pharm Pract* **11:** 139–143.

Chan S, Gerson B, Subramaniam S (1998). The role of copper, molybdenum, selenium, and zinc in nutrition and health. *Clin Lab Med* **18:** 673–685.

Cheng KK (2007). Oral mucositis, dysfunction, and distress in patients undergoing cancer therapy. *J Clin Nurs* **16:** 2114–2121.

Chilukuri S, Rosen T (2003). Management of acyclovir-resistant herpes simplex virus. *Dermatol Clin* **21:** 311–320.

Cho HH, Kim SH, Seo SH *et al* (2010). Oral hairy leukoplakia which occurred as a presenting sign of acute myeloid leukemia in a child. *Ann Dermatol* **22:** 73–76.

Collins CD, Ellis JJ, Kaul DR (2008). Comparative cost-effectiveness of posaconazole versus fluconazole or itraconazole prophylaxis in patients with prolonged neutropenia. *Am J Health Syst Pharm* **65:** 2237–2243.

Cowart B (2011). Taste dysfunction: a practical guide for oral medicine. *Oral Dis* **17:** 2–6.

Diaz-Arnold AM, Marek CA (2002). The impact of saliva on patient care: a literature review. *J Prosthet Dent* **88:** 337–343.

Doerr TD, Prasad AS, Marks SC *et al* (1997). Zinc deficiency in head and neck cancer patients. *J Am Coll Nutr* **16:** 418–422.

Duvic M, Talpur R, Ni X *et al* (2007). Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). *Blood* **109:** 31–39.

Elad S, Zadik Y, Hewson I *et al*. (2010). A systematic review of viral infections associated with oral involvement in cancer patients: a spotlight on Herpesviridea. *Support Care Cancer* **18:** 993–1006.

Elting LS, Cooksley C, Chambers M, Cantor SB, Manzullo E, Rubenstein EB (2003). The burdens of cancer therapy. Clinical and economic outcomes of chemotherapy-induced mucositis. *Cancer* **98:** 1531–1539.

Elting LS, Keefe DM, Sonis ST *et al*. (2008). Patient-reported measurements of oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy: demonstration of increased frequency, severity, resistance to palliation, and impact on quality of life. *Cancer* **113:** 2704–2713.

Fink M (2010). Vitamin D deficiency is a cofactor of chemotherapy-induced mucocutaneous toxicity and dysgeusia. *J Clin Oncol* [Epub ahead of print].

Glenny AM, Fernandez Mauleffinch LM, Pavitt S, Walsh T (2009). Interventions for the prevention and treatment of herpes simplex virus in patients being treated for cancer. *Cochrane Database Syst Rev* **1:** CD006706.

Halyard MY (2009). Taste and smell alterations in cancer patients – real problems with few solutions. *J Support Oncol* **7:** 68–69.

Halyard MY, Jatoi A, Sloan JA *et al* (2007). Does zinc sulfate prevent therapy-induced taste alterations in head and neck cancer patients? Results of phase III double-blind, placebo-controlled trial from the North Central Cancer Treatment Group (N01C4). *Int J Radiat Oncol Biol Phys* **67:** 1318–1322.

Hong CH, Napenas JJ, Hodgson BD *et al* (2010). A systematic review of dental disease in patients undergoing cancer therapy. *Support Care Cancer* **18:** 1007–1021.

Hovan AJ, Williams PM, Stevenson-Moore P *et al* (2010). A systematic review of dysgeusia induced by cancer therapies. *Support Care Cancer* **18:** 1081–1087.

Keefe DM, Schubert MM, Elting LS *et al* (2007). Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer* **109:** 820–831.

Komaki R, Lee JS, Milas L *et al* (2004). Effects of amifostine on acute toxicity from concurrent chemotherapy and radiotherapy for inoperable non-small-cell lung cancer: report of a randomized comparative trial. *Int J Radiat Oncol Biol Phys* **58:** 1369–1377.

Kostler WJ, Hejna M, Wenzel C, Zielinski CC (2001). Oral mucositis complicating chemotherapy and/or radiotherapy: options for prevention and treatment. *CA Cancer J Clin* **51:** 290–315.

Lalla RV, Sonis ST, Peterson DE (2008). Management of oral mucositis in patients who have cancer. *Dent Clin North Am*. **52:** 61–77, viii.

Lalla RV, Latortue MC, Hong CH *et al*. (2010). A systematic review of oral fungal infections in patients receiving cancer therapy. *Support Care Cancer* **18:** 985–992.

Martin MV (2000). The use of fluconazole and itraconazole in the treatment of candida albicans infections: a review. *J Antimicrob Chemother* **45:** 555.

Meis JF, Verweij PE (2001). Current management of fungal infections. *Drugs* **61**(Suppl. 1)**:** 13–25.

Miller M, Kearney N (2001). Oral care for patients with cancer: a review of the literature. *Cancer Nurs* **24:** 241–254.

Moura MD, Guimaraes TR, Fonseca LM, de Almeida Pordeus I, Mesquita RA (2007). A random clinical trial study to assess the efficiency of topical applications of podophyllin resin (25%) versus podophyllin resin (25%) together with acyclovir cream (5%) in the treatment of oral hairy leukoplakia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **103:** 64–71.

Moura MD, Haddad JP, Senna MI, Ferreira e Ferreira E, Mesquita RA (2010). A new topical treatment protocol for oral hairy leukoplakia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **110:** 611–617.

Nicolatou O, Nikolatos G, Fisfis M *et al* (1999). Oral hairy leukoplakia in a patient with acute lymphocytic leukemia. *Oral Dis* **5:** 76–79.

Noe JE (2009). L-glutamine use in the treatment and prevention of mucositis and cachexia: a naturopathic perspective. *Integr Cancer Ther* **8:** 409–415.

Ohrn KE, Wahlin YB, Sjoden PO (2001). Oral status during radiotherapy and chemotherapy: a descriptive study of patient experiences and the occurrence of oral complications. *Support Care Cancer* **9:** 247–257.

Pappas PG, Kauffman CA, Andes D *et al* (2009). Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. **48:** 503–535.

Paris F, Fuks Z, Kang A *et al* (2001). Endothelial apoptosis as the primary lesion initiating intestinal radiation damage in mice. *Science* **293:** 293–297.

Pereira CM, Souza CA, Correa ME (2010). Herpetic geometric glossitis: acyclovir resistant case in a patient with acute myelogenous leukemia. *Indian J Pathol Microbiol* **53:** 133–134.

Peterson DE, Jones JB, Petit RG 2nd (2007). Randomized, placebo-controlled trial of Saforis for prevention and treatment of oral mucositis in breast cancer patients receiving anthracycline-based chemotherapy. *Cancer* **109:** 322–331.

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

Piperi E, Omlie J, Koutlas IG, Pambuccian S (2010). Oral hairy leukoplakia in HIV-negative patients: report of 10 cases. *Int J Surg Pathol* **18:** 177–183.

Rautemaa R, Lauhio A, Cullinan MP, Seymour GJ (2007). Oral infections and systemic disease – an emerging problem in medicine. *Clin Microbiol Infect* **13:** 1041–1047.

Ravasco P, Monteiro-Grillo I, Marques Vidal P, Camilo ME (2005a). Impact of nutrition on outcome: a prospective randomized controlled trial in patients with head and neck cancer undergoing radiotherapy. *Head Neck* **27:** 659–668.

Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME (2005b). Dietary counseling improves patient outcomes: a prospective, randomized, controlled trial in colorectal cancer patients undergoing radiotherapy. *J Clin Oncol* **23:** 1431–1438.

Ravasco P, Monteiro Grillo I, Camilo M (2007). Cancer wasting and quality of life react to early individualized nutritional counselling!. *Clin Nutr* **26:** 7–15.

Reusser P (2002). Management of viral infections in immunocompromised cancer patients. *Swiss Med Wkly* **132:** 374–378.

Schmidt E, Thoennissen NH, Rudat A *et al* (2008). Use of palifermin for the prevention of high-dose methotrexate-induced oral mucositis. *Ann Oncol* **19:** 1644–1649.

Schonfeld W, Wang Cheng J, Tong KB, Seifeldin R (2008). Cost-effectiveness analysis of antifungal prophylaxis in patients undergoing hematopoietic stem cell transplantation. *Clin Ther* **30:** 964–973.

Scully C, Sonis S, Diz PD (2006). Oral mucositis. *Oral Dis* **12:** 229–241.

Silva GB, Mendonca EF, Bariani C, Antunes HS, Silva MA (2010). The prevention of induced oral mucositis with low-level laser therapy in bone marrow transplantation patients: a randomized clinical trial. *Photomed Laser Surg* **29:** 27–31.

Sohn HS, Lee TJ, Kim J, Kim D (2009). Cost-effectiveness analysis of micafungin versus fluconazole for prophylaxis of invasive fungal infections in patients undergoing hematopoietic stem cell transplantation in Korea. *Clin Ther*. **31:** 1105–1115; discussion 1066–1068.

Sonis ST (2007). Pathobiology of oral mucositis: novel insights and opportunities. *J Support Oncol* **5:** 3–11.

Sonis ST (2010). New thoughts on the initiation of mucositis. *Oral Dis* **16:** 597–600.

Sonis ST, Fey EG (2002). Oral complications of cancer therapy. *Oncology (Williston Park)* **16:** 680–686; discussion 686, 691–692, 695.

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.

Stam WB, O'Sullivan AK, Rijnders B *et al* (2008). Economic evaluation of posaconazole vs. standard azole prophylaxis in high risk neutropenic patients in the Netherlands. *Eur J Haematol* **81:** 467–474.

Sukhotnik I, Mogilner JG, Karry R *et al* (2009a). Effect of oral glutamine on enterocyte turnover during methotrexate-induced mucositis in rats. *Digestion* **79:** 5–13.

Sukhotnik I, Mogilner JG, Shteinberg D *et al* (2009b). Leptin accelerates enterocyte turnover during methotrexate-induced intestinal mucositis in a rat. *Cancer Biol Ther* **8:** 899–906.

Syrjanen S, Laine P, Niemela M, Happonen RP (1989). Oral hairy leukoplakia is not a specific sign of HIV-infection but related to immunosuppression in general. *J Oral Pathol Med* **18:** 28–31.

Vadhan-Raj S, Trent J, Patel S *et al* (2010). Single-dose palifermin prevents severe oral mucositis during multicycle chemotherapy in patients with cancer: a randomized trial. *Ann Intern Med* **153:** 358–367.

Vazquez JA (2003). Invasive oesophageal candidiasis: current and developing treatment options. *Drugs* **63:** 971–989.

Walling DM, Flaitz CM, Nichols CM (2003). Epstein-Barr virus replication in oral hairy leukoplakia: response, persistence, and resistance to treatment with valacyclovir. *J Infect Dis* **188:** 883–890.

Watkins B, Pouliot K, Fey E, Tuthill C, Sonis S (2010). Attenuation of radiation- and chemoradiation-induced mucositis using gamma-D-glutamyl-L-tryptophan (SCV-07). *Oral Dis* **16:** 655–660.

Wearing HJ, Sherratt JA (2000). Keratinocyte growth factor signalling: a mathematical model of dermal-epidermal interaction in epidermal wound healing. *Math Biosci* **165:** 41–62.

Whittaker SJ, Demierre MF, Kim EJ *et al* (2010). Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. *J Clin Oncol* **28:** 4485–4491.

Worthington HV, Clarkson JE, Khalid T, Meyer S, McCabe M (2010). Interventions for treating oral candidiasis for patients with cancer receiving treatment. *Cochrane Database Syst Rev* **2:** CD001972.

Yamashita H, Nakagawa K, Nakamura N *et al* (2006). Relation between acute and late irradiation impairment of four basic tastes and irradiated tongue volume in patients with head-and-neck cancer. *Int J Radiat Oncol Biol Phys* **66:** 1422–1429.

Zackheim HS, Kashani-Sabet M, McMillan A (2003). Low-dose methotrexate to treat mycosis fungoides: a retrospective study in 69 patients. *J Am Acad Dermatol* **49:** 873–878.