Oral Mucositis in Head and Neck Cancer: Risk, Biology, and Management

Stephen T. Sonis, DMD, DMSc

OVERVIEW

Of the toxicities associated with conventional forms of treatment for head and neck cancers, probably none has such a consistent legacy as oral mucositis.[1] Despite the fact that mucosal injury was noted as far back as Marie Curie's first forays into therapeutic radiation, an effective intervention has yet to be developed. In addition to its historic link to radiation, new therapeutic strategies including induction chemotherapy often produce mucositis, and targeted therapies appear to alter mucositis risk and its severity and course.[2] The symptomatic effect of oral mucositis is profound. Disabling oral and oropharyngeal pain prevents patients from eating normally, requires opiate analgesics, and in some cases results in alteration or discontinuation of anticancer therapy.[3] Furthermore, the health and economic consequences of oral mucositis are far from trivial. The incremental cost of oral mucositis in patients with head and neck cancer exceeds $17,000 (USD).[4]

Although the incidence of mucositis has been described as almost ubiquitous among patients with head and neck cancer treated with conventional chemoradiation regimens, there are clearly differences in the frequency and severity of its manifestations. The lack of uniform scoring criteria, variability of reporting thresholds (some studies only report grades 3 or 4), differences in the biologic challenge as a consequence of variations in chemoradiation treatment regimens, radiation fields, and tumor location have resulted in inconsistent incidence reporting. Furthermore, there continues to be a disconnect between health care professionals and patients relative to their assessments of the presence, severity, and effect of mucositis. The rate, symptom severity, and influence of mucositis on quality of life is routinely perceived as being greater among patients than the medical literature would suggest.[3] This might reflect the common and understandable attitude among those charged with treating the cancer that a marginally tolerable level of collateral damage to normal tissue is an acceptable price for tumor eradication. It is unclear what the acceptable level is from a patient's perspective, and it probably varies from patient to patient. Couple all of this with the realization that not all patients are at equal risk for mucositis, and it becomes easier to understand the reported range of mucositis frequency from as low as 30% to 40% to almost 100% when all severities of mucositis are evaluated.[5,6]

Mucositis incidence data surrounding intensity-modulated radiation therapy (IMRT) is illustrative of the lack of consistent reporting.[7-9] Many studies report mucositis incidence in patients being treated for head and neck cancers. While some reports are limited to cancers of the mouth, others are less restrictive in their inclusion criteria and include patients with cancers of the nasopharynx, sinuses, hypopharynx, and larynx as well as the mouth and oropharynx. Interpretation of results must account for this variation because it appears that the risk of significant (this definition varies from including all ulcerative mucositis to only grades 3 and 4) mucositis is markedly influenced by tumor location, as it affects the volume of oral mucosa that is exposed to radiation. The use of concomitant chemotherapy, now the standard of care, enhances mucositis risk and apparently, so does the concomitant use of targeted agents.

Regardless of the criteria used to assess the presence of mucositis in patients with head and neck cancers, it is clear there is a cohort of patients who go through treatment relatively unscathed by the toxicity. This observation has fueled speculation and studies on the topic of mucositis risk determinants. Approximately 30% of radiation therapy-induced side effects are attributable to therapy-related or patient-specific factors. A radiation dose–response analysis recently described by Bhide et al demonstrated the effect of different dose-response schedules on the development of mucositis.[10] In general, the volume of oral mucosa that receives weekly cumulative doses of 9.5Gy to 10Gy is likely to determine overall mucositis risk among susceptible patients. But even at this dose, about one-third of patients will not develop the condition. Likewise, among patients receiving cycled induction chemotherapy, almost one-half develop ulcerative

From the Biomodels, LLC, Brigham and Women's Hospital, and the Dana-Farber Cancer Institute, Boston, MA.

Author's disclosures of potential conflicts of interest are found at the end of this article.

Corresponding author: Stephen T. Sonis, DMD, DMSc, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115; email: ssonis@partners.org.

mucositis, while the other half survive three cycles of treatment with no appreciable mucosal injury. Consequently, one must conclude that risk is largely a function of patient-related, not treatment-related, factors.[11]

The pursuit of understanding patient-related mucositis risk factors is not new. Historically, it has centered on gender, body mass, age, comorbidities, and lifestyle.[12] Although there is some data to support each of these, it is sparse and far less convincing than one might expect given the discrepancies in mucositis frequency. More recently, the potential role of genetics has surfaced as a more likely explanation.[11]

Genetic risk factors for regimen-related mucositis have been primarily studied in patients with non-head and neck cancer. Both individual and clusters of pathway-related single nucleotide polymorphisms (SNPs) have been reported to increase mucositis risk. In contrast, to date, studies of genetic risk of mucositis in head and neck cancer have been limited to evaluating radiosensitivity and its relationship to DNA repair. The genome-wide association study methodology or more sophisticated forms of analysis have not yet been applied. Rather, candidate gene/SNP studies have been the norm and have identified polymorphism associated with the XRCC1 as being predictive of mucosal injury.[13,14] Given the successes of SNP-based toxicity risk prediction studies in patients undergoing stem cell transplant or cycled chemotherapy, it seems likely that a broader look at both genes and SNPs that takes into account gene/SNP interacting networks should be fruitful in identifying actionable elements of mucositis risk prediction.

THE ORAL ENVIRONMENT AND MUCOSITIS

The pathogenesis of mucositis is a study of multiple sequential biologic events coupled with the influence of the oral environment and microbiome.[1] The majority of pathways that lead to mucositis are the same whether the initiating event is chemotherapy (as in induction), radiation, or concomitant chemoradiation. However, the schedule of biologic challenges is clearly different. Whereas patients being treated with cycled chemotherapy receive an acute challenge that is administered systemically, patients undergoing radiation receive a succession of fragmented (fractionated) radiation doses, which, even in small increments, trigger a cascade of biologic events. Although radiation is considered to be focally administered (vs. systemic), the biologic events it triggers are detectable systemically with resulting constitutional effects. In both cases, what has been described as 'bystander" events result in collateral injury when products or signals from one cell (potentially the targeted tumor) negatively affect normal adjacent cells.[15]

The oral mucosa shares its neighborhood with a multitude of microorganisms: bacteria, viruses, and fungi. Although the modulating influence of microbes has been studied relative to cancer regimen–related toxicities in other areas of the gastrointestinal tract, studies of their effect on oral mucositis have been largely limited to descriptions of quantitative or qualitative changes.[1,16] Mucositis is not an infectious disease. Its frequency is not affected by decolonization or antimicrobial strategies. The kinetics of bacterial colonization follows, rather than precedes, mucositis development.[1] Although there are changes in the composition of the bacterial flora in patients who are myelosuppressed and were first described almost 40 years ago, modifying the oral bacterial composition has not proven to be an effective mucositis deterrent. Furthermore, antibacterial strategies for mucositis interventions have been ineffective.[17]

The role of viruses, particularly herpes simplex (HSV), in the etiology of radiation-induced mucositis remains questionable. Advocates for such a relationship cite observations of culturable HSV in a limited proportion of patients who have clinically significant oral mucositis.[18] They also suggest that treatment with standard antiviral therapy favorably affects the subsequent course of mucositis. Since over one-half of patients have latent HSV-1 infection, it is not unexpected that virus, activated by radiation or local tissue injury, would be detectable in some patients with mucositis. Consequently, although not a primary driver of mucositis, HSV-1 presence in a secondary infection could affect the course of the condition. The effectiveness of prophylactic administration of antiviral medication to patients who are seropositive and on radiation-induced mucositis has not been adequately investigated.

The oral environment is also unique relative to the presence of saliva. The fluid is a rich mix of enzymes, antibodies, and proteins that play an important role in maintaining the homeostasis of the oral mucosa and limiting microbial colonization. Because patients being treated with head and neck radiation routinely demonstrate signs of xerostomia, it was not unreasonable to suspect that a change in either the quantity or quality of saliva might affect the course of mucositis. However, this does not appear to be the case to any significant extent and certainly not in the context of a potential interventional strategy. In fact, the course of mucositis has been unaffected when saliva production–stimulating agents have been tested.[19,20]

Nonetheless, additional studies are probably justified to determine the true effect of saliva on tissue. For example, are patients with preexisting conditions that lead to xerostomia more likely to develop mucositis?

KEY POINTS

- Oral mucositis is among the most common toxicities of standard chemoradiation regimens used to treat head and neck cancers.
- Risk of mucositis is largely determined by genetic factors.
- The pathobiology of mucositis is complex. The mechanistic complexity of mucositis provides targets for intervention.
- Mucositis in patients being treated for head and neck cancer remains a substantive, unmet clinical need.

BIOLOGIC EVENTS THAT LEAD TO MUCOSAL INJURY AND EXAMPLES OF OPPORTUNITIES FOR MECHANISTICALLY BASED INTERVENTIONS

The conclusion that mucosal injury is the consequence of a multifactorial cascade of biologic events is relatively new.[21] In the realm of radiation injury, direct cell damage culminating in DNA strand breaks is still relevant, but it's not the only show in town. Although the basal cells of the epithelium are the consummate "end organ" leading to tissue destruction, the pathways that lead to their demise are multiple. Although the biologic stages originally noted to describe the sequence of mucositis remain fundamentally correct, accumulating data demonstrate that their complexity is more involved than was originally described. Also, although compartmentalization of the events associated with mucositis is undoubtedly a fantasy created for the convenience of explanation, the sequence can be divided into five stages: initiation, upregulation/activation, signal amplification, ulceration, and healing. The initiating biologic events that start the process were first attributed to oxidative stress and the generation of free radicals. Although still a critical event, we now know that activation of the innate immune response and Nrf2 provides alternative initiating pathways. Studies in which these pathways have been effectively interrupted demonstrate mitigation of downstream injury. From an interventional standpoint, the initiation phase is a ripe target as its attenuation affects the course of direct and indirect pathways of tissue damage.

The free-radical scavenger, amifostine, was among the first drugs used for mucositis intervention.[22] Originally developed for the military, the clinical utility of its radioprotective effects were applied to mollify salivary gland damage and consequent xerostomia. Its application as a mucoprotective has generated interesting but inconsistent results. Especially interesting is the observation that amifostine is capable of activating genes associated with superoxide dismutase, itself capable of attenuating oxidative stress. Supporting a potential therapeutic opportunity have been results of preclinical studies in which superoxide dismutase mimetics have been effective in diminishing the intensity and course of radiation-induced mucositis and novel gene transfer studies that have reached the same conclusion.[23] In a similar way, studies with n-acetyl cysteine—an established antioxidant with the ability to affect nuclear factor-kappa beta (NF-κB) activity—have demonstrated efficacy in both animal and human studies. Finally, as noted below, palifermin's (keratinocyte growth factor 1) ability to reduce radiation-induced mucosal damage is likely due, in part, to the molecule's effect on glutathione activity.[24] Additional support for this hypothesis is the finding of increased risk of mucositis among patients who express SNPs associated with gene mutations associated with glutathione synthesis.

Following initiation, another series of cell-based events is triggered. At least 14 canonical pathways have already been associated with the development of mucositis in patients being treated with concomitant chemoradiation for head and neck cancers.[25] Among the best studied is activation of the NF-κB pathway and consequent generation of proinflammatory cytokines.[26] Although tissue and peripheral blood levels of proinflammatory cytokines—such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α)—track well with the development of mucositis, it is unclear whether their role is one of mediating or messaging for injury or whether they are themselves true drivers of damage. This is especially true in the case of radiation-induced mucositis where repeated fractional challenges cause a challenge dynamic different from that associated with the acuity of chemotherapy. This is an area that requires more investigation, particularly in determining prevention and treatment strategies. Studies with agents known to mediate TNF production have been clinically tested with mixed results. Of potential importance is the finding that polymorphisms associated with TNF production are associated with chemotherapy toxicity risk prediction. It is well known that, in a variety of inflammatory diseases that result in mucosal injury (i.e., inflammatory bowel disease), an antagonistic group of cytokines—the anti-inflammatory cytokines such as IL-4, IL-10 and IL-11—likely have functional significance.[27] Given the complexities of mucositis, it would be naïve to not consider the potential role of these molecules in the overall pathogenesis of the condition. However, there current data is limited.

In theory, pharmacologics or biologics that alter cytokine expression or levels represent a potential therapeutic approach, and a number have been evaluated. Benzydamine HCl (BZD) is an anti-inflammatory rinse that has been approved outside the United States for use in patients receiving radiation therapy. Its efficacy is modest and limited to patients receiving standard radiation regimens in the absence of concomitant chemotherapy.[6] BZD has been reported to have a range of biologic activities that interfere with mechanisms thought to be of importance in the pathogenesis of radiation-induced oral mucositis. A study in a hamster model of mucositis—in which the effect of topically applied BZD on selected morphologic and biologic parameters was studied in temporal fashion— demonstrated that BZD modified epithelial proliferation, but not differentiation, and that the observed changes correlated with a reduction in tissue levels of IL-1β and TNF-α, but not IL-6. Preferential antiapoptotic activity was seen in epithelium and connective tissue of BZD-treated animals.[28]

Another cytokine-based approach capitalized on the anti-inflammatory activities of IL-11. Subcutaneous injection of the cytokine favorably altered the course of mucositis induced by either chemotherapy (5-FU) or radiation in animal models. When studied in association with radiation-induced mucositis, it appeared that IL-11 suppressed the expression of genes associated with IL-1β, TNF-α, IL-2, and transforming growth factor-beta. Furthermore, the timing of modified gene expression corresponded with observed mucosal injury. Tissue levels of IL-1β and TNF-α were also suppressed in association with better clinical outcomes.[29] A clinical trial in patients receiving autologous stem cell transplantation for breast cancer was stopped before accrual could be completed.

Two agents known to inhibit TNF-α production have been evaluated in preclinical and clinical studies of mucositis associated with chemotherapy. Pentoxifylline was effective in delaying clinical manifestations of chemotherapy-induced oral and intestinal toxicity in animal models and also ameliorated oral mucositis associated with conditioning regimens for stem cell transplant.[30-32] However, it was also associated with a higher rate of infection, suggesting that the physiologic cost of such an approach in patients who are myelosuppressed may exceed its antimucositis benefit. Nonetheless, the observation does provide a glimpse of a potential intervention strategy.

Given the finding that multiple pathways simultaneously contribute to mucositis, it seems very likely that a truly effective agent will be characterized by mechanistic pleotropism.[24] Palifermin, keratinocyte growth factor-1, was approved for the prevention and treatment of oral mucositis in patients with hematologic malignancies who received stomatotoxic conditioning regimens for hematopoietic stem cell transplants and serves as a prototype for a pleotropic antimucostitis agent. The phase III trial on which palifermin's approval was based on the mandated use of total-body irradiation as a conditioning regimen component. Subsequent trials of palifermin's efficacy have not been as consistent, but in general, the overall trend speaks to its utility for a mucositis indication. For the purposes of this discussion, the collective biologic effects of the molecule are illustrative of a multitargeted biologic shotgun. As related to initiation, palifermin has the ability to upregulate enzymes associated with the disruption of reactive oxygen species. In particular, glutathione-S-transferase and glutathione peroxidase are favorably impacted. And indirectly, palifermin's ability to upregulate Nrf2—which itself has been shown to reduce oxygen free radical damage—has been observed. Palifermin likely affects clonogenic cell death by preventing DNA strand breaks through its activation of DNA polymerases and its antiapoptotic effects implemented during the upregulation phase (probably through NF-κB) through Bcl-2, Bax, and p53 enhanced cell survival. Although palifermin resonates as a growth factor, its ability to modulate both pro- and anti-inflammatory cytokines provides a means for it to actively attenuate the cytokine-mediated tissue-damaging and amplifying effects. There is also evidence to suggest that palifermin has the potential to mitigate the effect of reduced epithelial turnover, and this is manifested in reductions in the atrophic and ulcerative changes that characterize mucositis. As one would predict based on its fundamental growth factor activity, it appears likely that palifermin favorably affects events associated with epithelial injury. However, the inconsistencies reported in palifermin's clinical efficacy seem puzzling given its biologic robustness and point to some of the challenges in developing an effective mucositis intervention.

Clinical data for palifermin as a mucositis intervention now exist for conditioning regimens for both autologous and allogeneic hematopoietic stem cell transplantation; chemotherapy used for the treatment of colorectal cancer, head and neck cancer, and sarcoma; and a smattering of regimens for hematologic malignancies. Positive efficacy signals have been reported for most but not all. The variability of responsiveness is confusing and might reflect individual dose response, responsiveness to keratinocyte growth factor or a range of other possibilities. What seems clear is that, as shown with other mechanistically based approaches to mucositis treatment, not all patients respond in the same way, and to optimize efficacy, a personalized approach to intervention—understanding risk and response/nonresponse—is highly desirable.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked "L" indicate leadership positions. Relationships marked "I" are those held by an immediate family member; those marked "B" are held by the author and an immediate family member. Relationships marked "U" are uncompensated.

Employment or Leadership Position: Stephen T. Sonis, Biomodels (L). **Consultant or Advisory Role:** Stephen T. Sonis, ActoGeniX; Axaxia Biologicals; Galera Therapeutics (U); Inform Genomics; Izun Pharmaceuticals; Merck; Novartis; Pfizer; Polymedix (U); ProCertus; SciClone. **Stock Ownership:** None. **Honoraria:** None. **Research Funding:** None. **Expert Testimony:** None. **Other Remuneration:** None.

References

1. Sonis ST. Mucositis: the impact, biology and therapeutic opportunities of oral mucositis. *Oral Oncol.* 2009;45:1015-1020.
2. Keil F, Selzer E, Berghold A, et al. Induction chemotherapy with docetaxel, cisplatin and 5-fluorouracil followed by radiotherapy with cetuximab for locally advanced squamous cell carcinoma of the head and neck. *Eur J Cancer.* 2013;49:352-359.
3. Elting LS, Keefe DM, Sonis ST, et al. Patient-reported measurements of oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy. *Cancer.* 2008;113:2704-2713.
4. Nonzee NJ, Dandade NA, Markossian T, et al. Evaluating the supportive care costs of severe radiochemotherapy-induced mucositis and pharyngitis: results from a Northwestern University Costs of Cancer Program pilot study with head and neck and nonsmall cell lung cancer patients who received care at a county hospital, a Veterans Administration hospital, or a comprehensive cancer care center. *Cancer.* 2008;113:1146-1152.
5. Mortensen HR, Overgaard J, Specht L, et al. Prevalence and peak incidence of acute and late normal tissue morbidity in the DAHANCA 6&7

randomised trial with accelerated radiotherapy for head and neck cancer. *Radiother Oncol.* 2012;103:69-75.

6. Keefe DM, Schubert MM, Elting LS, et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer.* 2007; 109:820-831.
7. Al-Mamgani A, van Rooij P, Verduijn GM, et al. The impact of treatment modality and radiation technique on outcomes and toxicity of patients with locally advanced oropharyngeal cancer. *Laryngoscope.* 2013; 123:386-393.
8. Wang ZH, Zhang SZ, Zhang ZY, et al. Protecting the oral mucosa in patients with oral tongue squamous cell carcinoma treated postoperatively with intensity-modulated radiotherapy: a randomized study. *Laryngoscope.* 2012;122:291-298.
9. Vlacich G, Diaz R, Thorpe SW, et al. Intensity-modulated radiation therapy with concurrent carboplatin and paclitaxel for locally advanced head and neck cancer: toxicities and efficacy. *Oncologist.* 2012;17:673-681.
10. Bhide SA, Gulliford S, Schick U, et al. Dose-response analysis of acute oral mucositis and pharyngeal dysphagia in patients receiving induction chemotherapy followed by concomitant chemo-IMRT for head and neck cancer. *Radiother Oncol.* 2012;103:88-91.
11. Filippi AR, Franco P, Ricardi U. Is clinical radiosensitivity a complex genetically controlled event? *Tumori.* 2006;92:87-91.
12. Vera-Llonch M, Oster G, Hagiwara M, et al. Oral mucositis in patients undergoing radiation treatment for head and neck carcinoma. *Cancer.* 2006;106:329-336.
13. Pratesi N, Mangoni M, Mancini I, et al. Association between single nucleotide polymorphisms in the XRCC1 and RAD51 genes and clinical radiosensitivity in head and neck cancer. *Radiother Oncol.* 2011;99:356-361.
14. Werbrouck J, De Ruyck K, Duprez F, et al. Acute normal tissue reactions in head-and-neck cancer patients treated with IMRT: influence of dose and association with genetic polymorphisms in DNA DSB repair genes. *J Radiot Oncol Biol Phys.* 2009;73:1187-1195.
15. Mothersill C, Seymour C. Are epigenetic mechanisms involved in radiation-induced bystander effects? *Front Genet.* 2012;3:1-6.
16. Stringer AM, Al-Dasoogi N, Bowen JM, et al. Biomarkers of chemotherapy-induced diarrhoea: a clinical study of intestinal microbiome alterations, inflammation and circulating matrix metalloproteinases. *Support Care Cancer.* Epub 2013 Feb 10.
17. Giles FJ, Rodriguez R, Weisdorf D, et al. A phase III, randomized, double-blind, placebo-controlled, study of iseganan for the reduction of stomatitis in patients receiving stomatotoxic chemotherapy. *Leuk Res.* 2004;28:559-565.
18. Nicolatou-Galitis O, Athanassiadou P, Kouloulias V, et al. Herpes simplex virus-1 (HSV-1) infection in radiation-induced oral mucositis. *Support Care Cancer.* 2006;14:753-762.
19. Lockhard PB, Brennan MT, Kent ML, et al. Randomized controlled trial of pilocarpine hydrochloride for the moderation of oral mucositis during autologous blood stem cell transplantation. *Bone Marrow Transplant.* 2005;35:713-720.
20. Scaratino C, LeVegue F, Swann RS, et al. Effect of pilocarpine during radiation therapy: results of RTOG 97-09, a phase III randomized study in head and neck cancer patients. *J Support Oncol.* 2006;4:252-258.
21. Sonis ST. The pathobiology of mucositis. *Nat Rev Cancer.* 2004;4:277-284.
22. Nicolatou-Galitis O, Sarri T, Bowen J, et al. Systematic review of amifostine for the management of oral mucositis in cancer patients. *Support Care Cancer.* 2013;21:357-364.
23. Murphy CK, Fey EG, Watkins BA, et al. Efficacy of superoxide dismutase mimetic M40403 in attenuating radiation-induced oral mucositis in hamsters. *Clin Cancer Res.* 2008;14:4292-4297.
24. Blijlevens N, Sonis S. Palifermin (recombinant keratinocyte growth factor-1): a pleiotropic growth factor with multiple biological activities in preventing chemotherapy- and radiotherapy-induced mucositis. *Ann Oncol.* 2007;18:817-826.
25. Sonis S, Haddad R, Posner M, et al. Gene expression changes in peripheral blood cells provide insight into the biological mechanisms associated with regimen-related toxicities in patients being treated for head and neck cancers. *Oral Oncol.* 2007;43:289-300.
26. Sonis ST. The biologic role for nuclear factor-kappaB in disease and its potential involvement in mucosal injury associated with anti-neoplastic therapy. *Crit Rev Oral Biol Med.* 2002;13:380-389.
27. Sultani M, Stringer AM, Bowen JM, et al. Anti-inflammatory cytokines: important immunoregulatory factors contributing to chemotherapy-induced gastrointestinal mucositis. *Chemother Res Pract.* 2012;2012: 490804.
28. Sonis ST, Watkins B, Fey E, et al. Mechanism of action of benzydamine in the treatment of oral mucositis. *J Clin Oncol.* 2005;23:8040.
29. Sonis ST, Peterson RL, Edwards LJ, et al. Defining mechanisms of action of interleukin-11 on the progression of radiation-induced oral mucositis in hamsters. *Oral Oncol.* 2000;36:373-381.
30. Lima V, Vidal FD, Rocha FA, et al. Effects of tumor necrosis factor-alpha inhibitors pentoxifylline and thalidomide on alveolar bone loss in short-term experimental periodontal disease in rats. *J Periodontol.* 2004; 75:162-168.
31. Melo ML, Brito GA, Soares RC, et al. Role of cytokines (TNF-alpha, IL-1beta and KC) in the pathogenesis of CPT-11-induced intestinal mucositis in mice: effect of pentoxifylline and thalidomide. *Cancer Chemother Pharmacol.* 2008;61:775-784.
32. Ferrà C, de Sanjosé S, Lastra CF, et al. Pentoxifylline, ciprofloxacin and prednisone failed to prevent transplant-related toxicities in bone marrow transplant recipients and were associated with an increased incidence of infectious complications. *Bone Marrow Transplant.* 1997;20: 1075-1080.

Biological markers Oral mucositis Head and neck cancer Radiotherapy Systematic review Meta-analysis. Electronic supplementary material. The online version of this article (doi: 10.1007/s00520-017-3783-8) contains supplementary material, which is available to authorized users.Â National Comprehensive Cancer Network. 2016 NCCN clinical practice guidelines in oncology: head and neck cancers (version 2). [Accessed 20 Dec 2016]. Avaliable in: http://www.nccn.org. 17.