

# Mucositis—Supportive Care During Radiotherapy or Chemoradiotherapy of Head and Neck Cancer

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## Abstract

Painful ulcers and sores and related dysphagia, thick saliva, taste impairment, and weight loss significantly affect the quality of life of head and neck cancer patients undergoing radiation treatment with or without concomitant chemotherapy. The available data for mucositis prophylaxis and treatment could be heterogeneous for clinical interpretation. In this editorial, we will describe what is already known and to outline the most important aspects of mucositis care.

## Keywords

Chemoradiotherapy, head and neck cancer, mucositis, radiotherapy, supportive care

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The majority of patients undergoing radiation therapy for head and neck (HN) cancer will develop oral mucositis, which is a clinical syndrome characterized by erythema, ulcerations, and odynophagia (see *Table 1*). It is almost universal and more severe among patients with oral cavity, oropharynx, and nasopharynx primaries.<sup>1–3</sup> Although therapeutic ratio and outcomes are improved by concomitant chemotherapy<sup>4,5</sup> or altered fractionation,<sup>6</sup> both are related to dose-limiting mucositis and increase the risk for consequential dysphagia. Finally, mucositis is associated with unplanned breaks in radiation therapy, hospital admissions for pain management or insertion of enteral feeding tube,<sup>3</sup> and is associated with increased costs.<sup>7</sup> Reducing mucositis could be achieved by different means. This editorial will describe the available data and future perspectives in mucositis management.

## Mouth Hygiene and Preventive Dental Care

Basic oral care protocols including daily topical fluoride, flossing, and frequent mouth rinses can be helpful for preventing and alleviating of mucositis.<sup>8,9</sup> The evidence to support this approach is not strong, yet maintaining oral hygiene is supported by the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) Clinical Practice Guidelines.<sup>10</sup> Although different mouthwash preparations are available (normal saline, sodium bicarbonate, calcium phosphate), none of them had been consistently recommended by the gathered evidence-based data, but the panel suggested that they might be considered for oral care. The only rinse that the MASCC/ISOO recommended against was chlorhexidine mouthwash.<sup>10</sup>

Pretreatment dental care reduces risk for osteoradionecrosis.<sup>11</sup> In addition, designing dental protective stents to prevent electron back-scatter off metal caps/bridges into the neighboring soft tissue could be beneficial for mucositis risk reduction.<sup>12–14</sup>

## Reducing Mucositis by Antiviral/Antibacterial/Mucosal Coating Agents

Different preparations including acyclovir, nystatin, fluconazole, sucralfate, and aluminum salt of sulfated sucrose were evaluated by multiple (mostly conflicting) studies. None of the above can be recommended to reduce chemoradiotherapy mucositis.<sup>15</sup>

Newer mucosal protectants are available for HN cancer patients. Keratinocyte growth factor (palifermin) stimulates differentiation of mucosal cells. Two randomized studies have shown reduction of likelihood and median duration of severe mucositis, but narcotic use, patient-reported pain, and chemoradiotherapy compliance were not different from placebo.<sup>16,17</sup> Marketed mucoadhesive hydrogel has been reported to significantly reduce patient-reported oral soreness and mucositis World Health Organization (WHO) score on the last day of radiation therapy compared with placebo,<sup>18</sup> but it was not evaluated versus other preparations.

## Pain Management

Pain is the main debilitating symptom of mucositis. Topical anesthetics, narcotics, and antidepressants could control it. While the former could not be advocated based on the available data,<sup>15</sup> both topical morphine<sup>19,20</sup> and

transdermal fentanyl<sup>15,21</sup> had been shown as highly effective in producing pain relief. In addition, long-acting opioid patches reduce the need for immediate-release opiates and provide lengthier freedom from pain.

Tricyclic antidepressants reduce patient-reported symptoms without affecting the severity of mucositis. A randomized, double-blind, cross-over study<sup>22</sup> of oral solution containing doxepin had shown significantly reduced mucositis pain compared with placebo, it was associated with more burning, unpleasant taste, and greater drowsiness, but most patients elected to continue doxepin during radiotherapy (RT) after the double-blind part of the study was completed.

Different recipes for solutions (so-called magic mouthwash solutions) containing a mix of different antibiotics, antihistamines, local anesthetics, an antifungal (e.g. nystatin), a corticosteroid, and antacids are in use; unfortunately, there are no data to show any benefit in alleviation of mucositis.<sup>10</sup>

## Pharmacologic Prevention and Treatment of Mucositis

Amifostine is an organic thiophosphate that competes with oxygen binding to the free radicals, which is essential to their activity in damaging the DNA, exerting a protective effect. The pro-drug is activated by membrane alkaline phosphatase, the concentration of which is lower in the acidic environment of cancer, potentially resulting in preferential protection of normal tissues. Unfortunately, besides the side effects (hypotension, nausea if administered parenterally, and skin reaction; local pain and nausea if injected subcutaneously), three randomized studies<sup>23–25</sup> failed to show a definitive benefit of amifostine over placebo.

## Better Radiosensitizers?

Epidermal growth factor receptor (EGFR) is overexpressed in the majority of HN tumors, suggesting a potential benefit of EGFR signaling pathway inhibition. Indeed, in the randomized phase III study<sup>26</sup> RT concurrent with cetuximab (a monoclonal antibody to EGFR) resulted in improved tumor-control rates compared with RT alone with no difference in mucositis rates between the arms. Still, others<sup>27</sup> report that cetuximab can induce enhanced mucosal injury. This finding could be potentially explained by heterogeneity in EGFR expression found in mucosal cells in different patients.<sup>28</sup>

## Reduced Treatment Intensity

Human papillomavirus (HPV)-positive oropharyngeal cancer has a better prognosis, especially in patients without or with minimal smoking history.<sup>29</sup> Overall survival in this favorable cohort exceeds 80 %. This yielded the following hypothesis: can we keep high tumor control-rates in

**Table 1: World Health Organization Scale for Oral Mucositis**

Grade 0—No oral mucositis
Grade 1—Erythema and soreness
Grade 2—Ulcers; able to eat solids
Grade 3—Ulcers; requires liquid diet
Grade 4—Ulcers; alimentation not possible

these patients while reducing treatment intensity and toxicity? The phase II Eastern Cooperative Oncology Group (ECOG) 1308 study<sup>30</sup> was designed to answer this question. If complete remission (CR) was achieved in the primary tumor following induction chemotherapy, the dose to the primary tumor bed was reduced to 54 Gy (instead of the standard dose of 70 Gy), concurrent with cerituximab. Local-regional control rate in these patients was 95 %. The ongoing phase III Quarterback trial will provide us with definite answers on this topic.

## Mucositis-related Toxicity

Alterations in taste are dose dependent, and radiation to the anterior tongue and oral cavity seems to have the biggest effect.<sup>31</sup> Preliminary data suggest zinc sulfate may alleviate these symptoms. Unfortunately this hypothesis was refuted by findings of the negative phase III study.<sup>32</sup>

N-acetyl cystein is a mucolytic that breaks disulfide bonds in mucus.<sup>33</sup> We prescribe it after the completion of RT to patients who still suffer thick secretions, although data to support this recommendation are lacking.

Finally, to address complications related to significant weight loss caused by malnutrition, prophylactic insertion of percutaneous endoscopic gastrostomy (PEG) feeding tubes in all patients prior to RT start was compared with reactive feeding tubes in two randomized trials.<sup>34,35</sup> Both found that prophylactic PEG resulted in less weight loss, improved patient-reported quality of life (QOL), and lower long-term dysphagia. However, the benefit of prophylactic PEGs may come at the expense of longer dependence on PEG and increased late esophageal strictures requiring dilatation (30 % versus 6 %).<sup>36,37</sup>

## Conclusions

HN patients following RT are affected in different ways, many of them related to mucositis. Proper management of mucosal damage by prophylactic (maintaining of mouth hygiene and dental care) and active (pain management, dose reduction when possible, and nutritional care) steps can substantially improve treatment-related QOL. ■

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