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*This series aims to enhance the healthcare team's awareness of the importance of early detection by recognizing signs and symptoms of orofacial cancers and their management , and of prevention. It discusses treatment complications from surgery, radiotherapy (RT) and chemotherapy (CTX), summarizing the outcomes of a meeting on 'Oral Healthcare in People Living with Cancer' held in 2010, attended by 300 delegates from 33 countries – dentists, specialists, and Dental Care Professionals (DCPs), and the cancer support team. There is a considerable body of literature on oral cancer but very little is written on healthcare aspects of people living with cancer and a particular focus of this meeting was caring for survivors. The Faculty included European leaders in the field who have authored the series. The full peer-reviewed papers from the meeting are published in Oral Oncology 2010;* ***46****; 485–570.*

## Oral Cancer: Comprehending the Condition, Causes, Controversies, Control and Consequences

# 14. Mucositis

Oral mucosal keratinocytes have a high mitotic rate and are, like cancer cells, targets of RT and cancer cytotoxic CTX agents. Mucosal damage is one of the most common adverse effects of CTX and of RT to the head and neck , with a prevalence ranging from 10–100%. Cancer therapy thus produces collateral damage. Mucositis is the result of a complex series of biological events that ultimately lead to ulceration and is often a dose-limiting toxicity. Thus, while other toxicities of cancer therapy may be declining following, for example, the introduction of Intensity Modulated Radiation Therapy (IMRT), mucositis remains an area of concern to both patients and clinicians. Even newer agents may produce oral ulceration or enhance toxicity of RT and of CTX. These include:

- mTOR inhibitors, such as rapamycin and temsirolimus;
- EGFR inhibitors, such as cetuximab;
- Erlotinib, in combination with gemcitabine.

## Radiotherapy-induced mucositis

RT is most often administered in small fractions over several weeks and to a localized area. Radiation-induced mucositis is invariable within the radiated field of mucosa and typically begins at cumulative doses of about 15 Gy (ie after around 10 days) and reaches full severity at 30 Gy, persisting for weeks or months (Figure 1). Tissues such as the soft palate, and the lateral borders and ventral surface of the tongue and floor of the mouth, which have a good vascular supply or a higher cell turnover rate, are more susceptible to radiation mucositis. Risk factors for radiation mucositis, apart from the radiation dose and fractionation include:

- Concurrent chemotherapy;
- Younger age;
- Alcohol;
- Poor oral hygiene;
- Dental disease;
- Genetic factors.

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## Chemotherapy-induced mucositis

Chemotherapy is administered over a short time, so the injury to mucosae tends to be acute and affects the whole gastrointestinal tract. Most patients on high-dose CTX develop severe oral mucositis which usually appears within 4–7 days after initiation of treatment and peaks within 2 weeks.

Risk factors for CTX mucositis include:

- Type and dose of CTX;
- Concurrent RT;
- Age;
- Body mass index;
- Female gender;
- Salivary hypofunction;
- Poor oral health;
- Mucosal trauma;
- Co-morbidities (eg diabetes mellitus, impaired renal function);
- Genetic determinants including genes that:
  - regulate the availability of active chemotherapy drug metabolites (eg folate-metabolizing enzymes may help to identify patients at greater risk for methotrexate toxicity; dihydropyrimidine dehydrogenase (DPYD) variants may identify those at risk with fluorouracil);
  - are involved in the direct cell response to the drug;
  - are associated with the expression of inflammatory mediators.

## Pathobiology

The damage induced by CTX is a complex phenomenon that affects both epithelium and lamina propria. There are several stages in mucositis:

- Initiation – the production of reactive oxygen species, direct cellular damage.
- Activation of transcription factors (eg nuclear factor-kappa B; NF-κB) leading to a local increase in pro-inflammatory cytokines (eg interleukin (IL)-6, and tumour necrosis factor (TNF)).
- Feedback mechanisms resulting in amplification and acceleration of the process, which finally leads to ulceration.
- Following cessation of the process, there is healing.

The oral microflora is considered to play only a secondary role in the pathogenesis of mucositis.

| Guidelines from | References |
|---|---|
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**Table 1.** Clinical guidelines on management of mucositis.

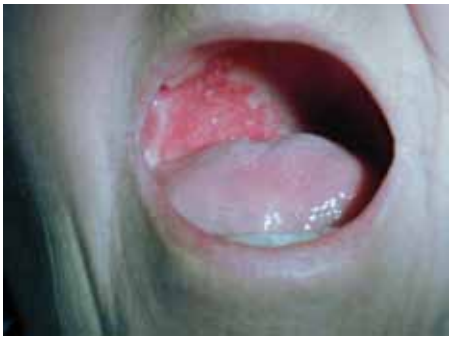

**Figure 1.** A 64-year-old lady with tonsillar cancer after three weeks of chemo-radiation with cisplatin + taxotere and 2 Gy/day. (Courtesy of Dr Andrei Barasch.)

## Clinical features

Oral mucositis is defined as inflammation of the mucosa resulting from cancer therapy and typically presents as erythema, ulceration, swelling and atrophy. Mucositis may be exacerbated by local factors, such as trauma from teeth, or microbial colonization. Since chemotherapy-induced damage affects the entire alimentary tract mucosae, terms such as alimentary mucositis and mucosal barrier injury are also then used.

## The effect of mucositis on quality of life

Many patients report oral mucositis as the most debilitating and troublesome adverse effect of cancer therapy, and that opioid analgesics did not always adequately relieve pain, but instead led to other issues such as dry mouth and constipation. Mucositis is also associated with poorer treatment outcomes and increased financial burdens, a longer hospital stay, and an increased use of narcotics and nutritional support. In some patients, mainly those undergoing myeloablative haematopoietic stem cell transplant (HSCT, or bone marrow transplant), mucositis predisposes to fever and infections, and occasionally mortality.

## Diagnosis

Lesions in the cancer patient that can complicate the diagnosis include:

- Fungal and viral infections; ulcerations induced by herpes simplex virus reactivation for example can confuse, but differs clinically from mucositis in that they may also involve the tongue dorsum, the gingivae and the hard palate.
- Acute Graft Versus Host Disease (aGVHD) after HSCT may present as lichenoid lesions, desquamation and ulceration that may be difficult to distinguish from mucositis.
- Neutropenic ulcers in myelo-suppressed patients, are usually well-defined and painful. Typically, microbiological tests are then negative.

## Quantification

A number of instruments is available to evaluate the observable, subjective and functional dimensions of oral mucositis (eg World Health Organization, National Cancer Institute Common Terminology Criteria for Adverse Events, or Eilers' Oral Assessment Guide for a more comprehensive oral assessment).

Nevertheless, the incidence of mucositis is widely under-reported. Clinician-based scorings of toxicities often fail to coincide with targeted mucosal evaluation or patients' reporting of symptoms. For example, while incidence of oral mucositis reported by oncologists was about 15% in patients receiving CTX for colorectal cancer, over 70% of the patients being treated reported significant mouth or throat soreness.

## Management

Unfortunately, there are few

*Basic oral care and good clinical practices*

1. Multidisciplinary development and evaluation of oral care protocols, and patient and staff education in the use of such protocols to reduce the severity of oral mucositis from chemotherapy and/or radiation therapy. Use of a soft toothbrush that is replaced on a regular basis. Elements of good clinical practice should include the use of validated tools to regularly assess oral pain and oral cavity health. The inclusion of dental professionals is vital throughout treatment and follow-up phases.
2. Patient-controlled analgesia with morphine as the treatment of choice for oral mucositis pain in patients undergoing haematopoietic stem cell transplantation (HSCT). Regular oral pain assessment using validated instruments for self-reporting is essential.

*Radiotherapy: prevention*

3. Use of midline radiation blocks and three-dimensional radiation treatment to reduce mucosal injury.
4. Benzydamine for prevention of radiation-induced mucositis in patients with head and neck cancer receiving moderate-dose radiation therapy.
5. Chlorhexidine *not to be used* to prevent oral mucositis in patients with solid tumours of the head and neck who are undergoing radiotherapy.
6. Sucralfate *not to be used* for the prevention of radiation-induced oral mucositis.
7. Antimicrobial lozenges *not to be used* for the prevention of radiation-induced oral mucositis.

*Standard-dose chemotherapy prevention*

8. Patients receiving bolus 5-fluorouracil (5-FU) chemotherapy should undergo 30 minutes of oral cryotherapy to prevent oral mucositis.
9. 20 to 30 minutes of oral cryotherapy to decrease mucositis in patients treated with bolus doses of edatrexate.
10. Aciclovir and its analogues *not to be used* routinely to prevent mucositis.

*Standard-dose chemotherapy: treatment*

11. Chlorhexidine *not to be used* to treat established oral mucositis.

*High-dose chemotherapy with or without total body irradiation plus haematopoietic cell transplantation: prevention*

12. In patients with haematological malignancies receiving high-dose chemotherapy and total body irradiation with autologous stem cell transplant, keratinocyte growth factor-1 (palifermin) in a dose of 60 µg/kg/day for 3 days prior to conditioning treatment and for 3 days post-transplant for the prevention of oral mucositis.
13. Cryotherapy to prevent oral mucositis in patients receiving high-dose melphalan.
14. Pentoxifylline not to be used to prevent mucositis in patients undergoing HSCT.
15. GM-CSF mouthwashes *not to be used* for the prevention of oral mucositis in patients undergoing HSCT.
16. Low-level laser therapy (LLLT) to reduce the incidence of oral mucositis and its associated pain in patients receiving high-dose chemotherapy or chemoradiotherapy before HSCT, if the treatment centre is able to support the necessary technology and training.

**Table 2.** Summary of Evidence-based Clinical Practice Guidelines for Care of Patients with Oral Mucositis. (Keefe DM, Schubert MM, Elting LS, Sonis ST, Epstein JB, Raber-Durlacher JE, *et al*. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer* 2007; **109** (5): 820–831).

randomized controlled studies and the available prophylactic and therapeutic strategies are limited. Topical anaesthetic (Viscous lidocaine®) coating agents may be of some value, but the pain usually requires systemic analgesics for relief. Since infections may be associated, appropriate diagnosis and antimicrobial agents must be considered. Fungal or bacterial infections may be seen in either CTX or RT-induced mucositis but viral infections seem to be rare in patients with RT-induced mucositis.

Interventions which have some proven success include:

- Excellent oral care, including pre-treatment dental evaluation;
- Oral cryotherapy using ice;
- Exposure to soft laser;
- Systemic administration of keratinocyte growth factor (palifermin). The US Federal Drugs Administration (FDA) in 2004 approved palifermin for use in patients with haematologic malignancies receiving myelotoxic therapy requiring haematopoietic stem cell support. In this group of patients, it reduced the number of days suffering from mucositis, with no special adverse effects other than an occasional rash. The safety and efficacy of palifermin have not, however, been established in patients with non-haematologic malignancies such as oral cancer.

There are several clinical practice guidelines on mucositis available (recent ones shown in Tables 1 and 2).

There is limited evidence for the efficacy of a supersaturated calcium phosphate rinse for the prevention and treatment of mucositis.

New agents being trialed for the amelioration of mucositis include supplements (eg glutamine, zinc sulphate), enzymes involved in the detoxification of reactive oxygen species (eg glutathione-S-transferase) and antimicrobial peptides. In addition, epigenetic approaches aimed at modifying overexpression of pro-inflammatory cytokines seem promising.