

Mucositis from Radiotherapy to the Head and Neck: an Overview

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Mucositis is an important consequence of radiotherapy to the head and neck. Effective management can make a difference both to patients’ quality of life and to the chance of a treatment course being completed. This article will explore the management of the patient with mucositis and will examine some interventions aimed at reducing the incidence and severity of mucositis.

Mucositis, characterised by inflammation and denudation of the affected mucosa, is an inevitable and important consequence of radiotherapy to the head and neck. It is acutely painful, adversely affecting patients’ quality of life, and can be the dose-limiting toxicity of radiotherapy regimes. In the most severe cases, notably when chemotherapy is given concurrently, mucositis can be life threatening, either because of reduced oral intake or because of superimposed infection causing septicaemia. Occasionally the severity of the mucosal reaction requires that treatment is interrupted or even discontinued, with detrimental consequences for tumour control. The management of mucositis is therefore an important part of the patient’s care, and health-care professionals need to be aware of potential problems and how to address them. This article will explore the development and management of mucositis in patients receiving radiotherapy to the head and neck and will describe some interventions for its prevention and treatment.

Pathophysiology

Radiotherapy causes a reduction in the rapidly dividing stem cells in the basal epithelial layer of the mucosa, preventing regeneration and affecting the integrity of the epithelium. At the molecular level, mucositis is a multi-stage process, initiated by mucosal injury [1]. Radiation causes DNA strand-breaks and production of reactive oxygen species which cause further cellular damage, leading to apoptosis, in the epithelium. There is increased production of inflammatory

cytokines such as tumour necrosis factor alpha, interleukin 6 and interleukin 1-beta, which cause direct mucosal damage and initiate positive feedback loops, thereby prolonging tissue damage.

Clinically, the first sign is inflammation and erythema of the mucosa within the treatment field. This is followed by production of a white pseudomembrane of fibrin, which eventually becomes confluent and covers the entire treatment field. Ultimately ulceration and breakdown of the mucosal barrier occurs, allowing the possible entry of pathogenic organisms. Bacterial colonisation causes further production of cytokines thereby perpetuating the whole process [2].

Severity of Mucositis

Various patient- and treatment-related factors can affect the severity and healing of the mucositis as summarised in Table 1.

Table 1: Factors Increasing Severity and/or Duration of Mucositis
• Higher radiotherapy total dose
• Large treatment volume
• Shorter overall treatment time
• Concurrent administration of chemotherapy
• Decreased neutrophil count / immunosuppression
• Individual factors – sensitivity to radiation
• Tobacco, alcohol and other mucosal irritants
• Superimposed mucosal infection

Grading of Mucositis

The development of mucositis follows a predictable pattern according to the dose of radiation received. It is important to determine whether the grade of mucositis is appropriate to the stage of the patient’s treatment. In addition, recording the grade of mucositis accurately is vital to allow comparisons between the acute radiation effects from different treatment regimes, particularly in the context of clinical trials. A variety of scales for grading mucositis is available, although for users of a given scale there may still be some inter-rater variability [3]. Commonly used scales include those from the National Cancer Institute [4], the Radiation Therapy Oncology Group [5] and the World Health Organisation [6]. Scoring is based on the appearance of the mucosa, but many scales also include analgesic requirements and functional effects such as impairment of oral intake, as shown in the generalised scale in Table 2.

On-treatment Assessment

Assessment of mucositis grade, oral hygiene, analgesic needs and nutritional status should be made at least weekly in all patients by health-care personnel experienced in such



Figures 1 and 2 show confluent (Grade 3) mucositis in patients receiving radiotherapy for oropharyngeal carcinoma.

examinations. More vulnerable patients may require closer monitoring. Using a good light source, the mucosa within the treatment field is inspected, noting the grade of mucosal reaction and the cleanliness of the oral cavity. Signs of bacterial or fungal infection are sought, often indicated by production of increased amounts of discoloured saliva. Other parameters to note are the patient's weight and oral intake (if not already tube-fed). Dietary advice and supplementation should be given accordingly, with instigation of tube feeding if indicated.

The patient's psychological well-being should also be taken into account. Many patients have few or mild symptoms prior to their radiotherapy and the pain from the effects of treatment may far outweigh any current problems from their cancer. Ongoing support and education are essential to reassure patients that this reaction can be expected. Those best placed to deliver this support are often the head and neck specialist nurse, ward nurses and the therapy radiographers who see the patient daily.

Management of Mucositis

The management of mucositis currently focuses on maintaining oral hygiene and pain control. Good oral hygiene promotes patient comfort and helps to prevent superimposed infection. Adequate analgesia is essential both to control pain and to ensure maximum possible oral nutritional intake.

a) Oral Hygiene

The aim of oral hygiene is to keep the mucosa clean and moist in order to promote patient comfort and facilitate oral intake. A good intake of fluids is essential to maintain hydration. Frequent saline mouthwashes help to keep the mucosa clean by removing debris and keeping it moist. The addition of sodium bicarbonate to the mouthwash may help to lessen the thick, stringy saliva that distresses patients so much, often producing a feeling of nausea. In the early stages of treatment, saline mouthwashes should be done at least four times daily, increasing to 2-hourly when mucositis becomes more severe. Chlorhexidine (Corsodyl™) is commonly used within oral care protocols, although it is not useful for prevention of mucositis [7] and may be detrimental [8]. Dentate patients should continue to brush their teeth frequently, preferably with fluoride toothpaste and using a soft 'baby' toothbrush where necessary. If the mucosa becomes too sore for this, foam sponges can be used although they have been shown to be less effective for prevention of

both plaque and caries [7]. Edentulous patients should be encouraged to remove their dentures when not using them for eating and to keep them scrupulously clean.

b) Analgesia

Analgesia should make the patient comfortable and allow the patient to maintain his/her weight through oral intake, if not tube-fed already. All medications should preferably be in liquid or soluble form and should not be irritant to the inflamed mucosa. For those that are, patients should be encouraged to dilute the measured dose till comfortable.

The World Health Organisation guidelines for pain relief [9] can be followed. Paracetamol, particularly in the form of mucilage which coats the inflamed mucosa, can be useful in the early stages and is often helpful in conjunction with stronger analgesia as mucositis worsens. Codeine or dihydrocodeine can be useful as intermediate analgesics but in many cases of mucositis patients will require strong opiates such as morphine. This should initially be a short-acting preparation, but once analgesic needs are established, a long-acting opiate, such as sustained release morphine or fentanyl transdermal patches, can be started. It is important to remember that, in the weeks after treatment, the pain will gradually decrease so patients should have a regime in place for reducing their long-acting opiate. At any stage in the pathway, non-steroidal anti-inflammatory drugs (NSAIDs) may be added, if not contra-indicated. Benzydamine

Table 2: Grading of Mucositis

Grade	Appearance of Mucosa	Functional effects
I	Mild erythema	Slight alteration in diet; mild analgesia may be required
II	Bright erythema with patchy fibrin	Mild to strong analgesia required; significant alteration of diet
III	Confluent fibrin (Figures 1 and 2)	Able to take liquid diet only; may require tube feeding; strong narcotic analgesia required
IV	Ulceration, spontaneous haemorrhage, necrosis	Alimentation impossible; needs tube feeding; strong narcotic analgesia required
V	Some scales include Grade V, representing toxicity-related death	

Table 3: Interventions for Mucositis	
Intervention	Action / rationale
Amifostine	Cytoprotective. May prevent mucositis.
Growth factors: eg Palifermin, Granulocyte macrophage – colony stimulating factor	May act directly on epithelial cells or have an effect secondary to an increased neutrophil count.
Low level laser therapy (LLLT)	Evidence that LLLT is helpful in the prevention and treatment of mucositis. Requires specialised operators and expensive equipment
Antibiotic lozenges	Exploit possible link between oral microflora and severity of mucositis. No conclusive evidence.
Honey	Antibacterial properties may reduce incidence of superimposed infection.
Gelclair	Barrier across irradiated mucosa. May help to reduce pain.
Sucralfate	Forms a barrier over the mucosa. No conclusive evidence to support its use.
Chlorhexidine	Antibacterial, antiplaque. Irritant to mucosa. Not recommended as a preventive measure. May be detrimental.
Benzylamine	Useful as an analgesic and possibly for anti-inflammatory properties
Saline mouthwash (± sodium bicarbonate)	Very effective when used frequently.

(Diffiam™) mouthwash can provide a degree of analgesia but at full strength may sting unpleasantly and can be diluted 50:50. Some patients also find aspirin mouthwashes helpful. Topical anaesthetics such as lidocaine, although effective at pain relief, tend to be short acting and may predispose to local trauma due to anaesthetised mucosa [10]. The presence of infection can dramatically increase the intensity of the patient's pain so, while it is good prescribing practice to await the results of culture and sensitivity tests, it may be in the patient's best interest to treat clinically obvious infection with a broad spectrum antibiotic or antifungal.

c) Interventions for the Prevention or Treatment of Mucositis

A full discussion of the range of the interventions proposed for prevention and treatment of mucositis is beyond the scope of this article. They fall into two categories – those that target the process of development or healing of mucositis and those which are largely symptomatic therapy. Useful overviews include those by Barasch and Peterson [11] and Scully *et al* [12] and a systematic review by Worthington *et al* [13]. Guidelines for the prevention and treatment of cancer-therapy-induced mucositis were produced in 2004 by The Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology [7] and have since been updated [14]. Table 3 summarises some of the interventions under investigation for mucositis due to chemotherapy or radiotherapy.

Conclusions

Mucositis is an important and unpleasant consequence of radiotherapy to the head and neck. Its management still centres around the control of symptoms such as pain and on the promotion of good oral hygiene using nothing more sophisticated than saline mouthwashes. Much research has been done into interventions to prevent or treat mucositis from both radiotherapy and chemotherapy. Conclusive proof of any reliable method is lacking, however, often due to

studies which are flawed through being underpowered or lacking suitable controls [6,7]. Robust research is urgently needed to reduce the impact of mucositis and to allow clinicians to maximise the efficacy of cancer therapies thus improving the quality of life of patients undergoing radiotherapy to the head and neck.

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