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Oral Mucositis: A Crucial Problem during Radiation Therapy

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Abstract

Nonsurgical cancer treatments are often limited by the presence of side effects and oral mucositis is the most common of these. The current model of mucositis involves a complex mechanism of molecular, cellular, and tissue-based changes. A variety of assessment tools exist to monitor symptoms during treatment and multidisciplinary approach is vital to prevent mucositis. Patients require support to deal with the symptoms of mucositis without losing their quality of life. Some agents and protocols may be helpful in the treatment, but most pharmacological approaches remain controversial.

Keywords: Mucositis; Radiotherapy; Head and neck cancer

Introduction

Radiation Therapy (RT) is used for the treatment of head and neck cancer since radiation has been used as a therapeutic modality. Although this treatment is applied for improving the patient's quality of life, it is also associated with several side effects. The head and neck is a complex region composed of dissimilar structures and these all have different responses to RT. Radiotherapy may cause acute changes in these tissues such as mucosa, salivary glands and skin. Mucositis, inflammation of the oral mucosa, is one of the acute adverse effect of RT. Symptoms due to mucositis may vary from pain and discomfort to intolerance of food or fluids [1]. The incidence and severity of mucositis have been increased with the use of altered schedules and concurrent chemotherapy. Mucosal toxicity is regarded as the main dose – limiting toxicity in radical treatments [2]. Many reviews and clinical studies have been published in order to define the best clinical protocol for prophylaxis or treatment of mucositis, but a consensus has not been obtained yet.

The radiation-induced mitotic death of basal cells in the oral mucosa is resulted with acute oral mucositis [3]. If the radiation dose is delivered as equivalent as the ability of mucosal regeneration, severe reactions will not appear. When the dose is increased slightly, damage at the mucosa will be confluent mucositis. Severe mucositis can compromise the delivery of optimal RT doses or treatment schedules to the target volumes. The patient may no longer be able to continue RT; treatment is then usually interrupted. These disruptions at treatment due to oral complications can directly affect the patient's survival.

The aim of this paper is presenting the recent status of radiation induced oral mucositis.

Pathophysiology

Mucosal cells have a high capacity of cellular turnover which is the cause of irradiation sensitivity. During RT the basal layer cells of the mucous membranes are damaged and resulted with inflammation of mucosal tissue, and this is called as mucositis [4]. Mucositis is associated with severe pain that necessitates opiates during the RT. Sonis et al. emerged a model for the development of mucositis which includes four phases of mucositis [5].

Phase I is the inflammatory or vascular phase that seen soon after the administration of RT. Cytokines like tumor necrosis factor-α and interleukin-1 are responsible from this phase. They released from the epithelial and connective tissues within the radiation field and cause local tissue damage. Also they increase the vascular permeability, which enhances the cell killing effect of the ionizing radiation.

Phase II is the epithelial phase in which the direct effect of RT on the basal epithelial layer is seen. The cytotoxic effects of ionizing radiation on the rapidly dividing cells of the basal epithelium causes to reduced cell renewal,

induced cell death, atrophy and ulceration. Also cytokines continue to release during this phase. The mucosa will appear erythematous that is the result of vascularity increase and epithelial atrophy.

Phase III is the ulcerative or bacterial phase. Full-thickness erosion is seen at this stage and a fibrinous pseudomembrane occurs. It looks like a whitish and opalescent layer on top of the ulcerated mucosa. Bacterial colonisation of the complex microflora within the mouth can stimulate further cytokine release, thus causes more severe mucositis, as well as causing secondary infection. Candida and Gram-negative infections are particularly common, especially at patients who suffer from dry mouth during RT or who continue to smoke and drink alcohol during treatment [6].

Phase IV is the healing phase. This phase is the process of epithelial proliferation and differentiation is renewed and the normal microflora which is able to reestablish homeostasis. It is difficult to predict exactly when this will occur following RT, as the dose and fractionation schedule will influence the healing process, as will the condition of the patient. However, Singh et al. reported that healing usually occurs by 3 weeks after the end of treatment, as surviving epithelial cells are stimulated into dividing more rapidly as a result of radiation damage [6]. In patients who receive concomitant chemotherapy, healing time is likely to take much longer.

Clinical Syndroms and Assessment of Mucositis

The pain of mucositis can be extremely intense – patients describe

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	1	2	3	4
WHO	Painless ulcers Edema Mild soreness	Painful erythema Ulcers Able to eat	Unable to eat	Parenteral or enteral support
NCI- CTCv4	Asymptomatic or mild symptoms İntervention not indicated	Modarate pain Not interfering with oral intake Modified diet indicated	Severe pain İnterfering with oral intake	Life-threating consequences Urgent intervention indicated
RTOG	Erythema Mild Pain No analgesics	Patchy mucositis (<1/2 mucosa) Modarate pain requiring analgesia	Fibrinous mucosa (>1/2 mucosa) Severe pain requiring narcotic	Ulceration Hemorrhage Necrosis

Table 1: Grading Scales for Mucosal Changes.

the inside of their mouth or throat as feeling like it has been prodded with a red-hot poker. Patients with severe mucositis often find it difficult to open their mouths and become reluctant to speak. Patients avoid from drinking liquids or swallowing their saliva due to the fear of the pain and discomfort they may cause. This acute pain and discomfort are intensified by severe mucosal dryness.

Different grading systems for mucositis have been introduced, but only a few of them are standardized (Table 1). World Health Organisation (WHO), National Cancer Institute Common Toxicity Criteria version 4 (NCI-CTCv4) and Radiation Therapy Oncology Group (RTOG) toxicity scales are commonly used for the evaluation of mucositis [7,8]. Although the grading is necessary to document its degree, most of these scoring systems can be applied only for clinically visible mucositis.

Prevention and Management of Mucositis

Once damage has occured, there are relatively few interventions of value. Only a few drugs' efficacy on prevention and treatment of radiation-induced mucositis has been observed in literature [9-16]. The care should be given to the reduction of potential trauma to the irradiated mucous membranes. Potential trauma may be caused by two etiologies. First one is the mechanical trauma which consists by the damages of foods, drinks, dentures or teeth, or even opening the mouth when mucous membranes are dry and stuck together. The second one is bacterial, caused by abnormal microflora in the mouth which may colonise and invade the already erythematous or ulcerated mucosa.

Regular and systematic oral hygiene is fundamental for the prevention of mechanical or bacterial trauma. A moist and clean mucosa is less likely to be traumatized by daily routine functions. The frequent of mouth care is probably more important than the used mouth care agent. Studies suggested that pretreatment oral care instructions can delay the onset of mucositis and reduce its severity [17-19]. Simple mouth washing agents such as sterile water with 0,9% saline and sodium bicarbonate solution was advocated by most protocols [20-22].

The care of teeth and dentures is also a vital component of basic mouth care. Assessment and treatment like dental extractions of teeth prior to RT have an essential importance in order to prevent osteoradionecrosis. Twice-daily tooth-brushing with a fluorided toothpastes and soft toothbrushes are recommended throughout treatment. Mouth washing with chlorhexidine may be used for its antiplaque effect, although this may need to be attenuated and should only be used twice a day [6].

Pain management of oral mucositis has a leading role at the supportive care of patients who receive RT to the head and neck. Regular assessment and mouth care with the administration of adequate and timely analgesia are the basis of the management of a patient with the risk of mucositis. So patients can provide their fluid and dietary intake and hospitalisation for parenteral nutrition can often be prevented. Fentanyl pectin nasal sprey is one of the effective drug for breakthrough pain seen at this kind of mucositis [23]. Dietary care also helps to reduce potential trauma. Taking soft and bland foods should be suggested rather than spicy foods, spirits and smoking. One essential component is the involvement of the dietician at this multidiscipline treatment team of head and neck cancers [24].

Sutherland and Bowman's meta-analysis showed that; the overall risk of severe mucositis can be reduced by preventive treatments [25]. However, this result was obtained from physicians assessments, none of the interventions appeared to reduce patients'symptoms due to oral mucositis.

The strategies proposed to treat radiation-induced mucositis include the use of antimicrobials, antifungals, prostaglandin, radio-protectors and specific cytokines, including granulocyte macrophage colony-stimulating factor (GM-CSF) and Keratinocyte Growth Factor (KGF).

Antibiotic treatment has a role on preventing severe mucositis with elimination of microbial flora. For myelosupressed and seropositive patients, topical and systemic acyclovir treatment may help to control of oral herpetic lesions [26].

Prostaglandin E2, the cytoprotective enzyme, is reported to have great protective influence on the rapidly dividing epithelium, but has not shown promising results in reducing mucositis degree [27].

Thiol compound WR-2721 (Amifostine) is a radio-protector agent. The systemic administration of this agent has shown to decrease symptoms of mucositis at patients [28]. Randomized trials required to conclude its efficacy in preventing mucositis.

Cytokines have a great role at the inflammation phase of mucositis and expected to be effective on prevention. Systemic administration of granulocyte colony-stimulating factor (G-CSF) and granulocyte -macrophage colony stimulating factor (GM-CSF) are usually combined with chemotherapy regimes and remains uncertain at the mucositis treatment. Several studies with topical usage as mouthwashes reported beneficial effects [29,30]. Although others including RTOG study showed none [31]. In two randomized trials conducted in head and neck cancer patients, KGF administration was decreased severe oral mucositis [32,33]. However patient-reported outcomes related to mouth and throat soreness and to treatment breaks or compliance were not significantly different between arms in either trial.

Nowadays some marketing products try to find place in the management of mucositis, like mucoadhesive hydrogel (MuGard) or

Caphosol, a preparation comprising two separately packaged aqueous solutions, a phosphate solution (Caphosol A) and a calcium solution (Caphosol B) [34,35]. Better results with these were demonstrated in randomised prospective trials. However, there is no widespread use of any for standart treatment of mucositis.

Conclusion

The oral side effects of RT can be particularly severe and may have a profound impact fundamental aspects of quality of life. Main toxicity is mucositis and prevention or treatment of mucositis remains an unsolved problem. Simply assessment of the oral mucosa before the treatment is essential to minimize side effects. Adequate management with a multidisciplinary team provides best supportive care to the patients suffering from disease and side effects of treatment modalities.

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