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REVIEW ARTICLE

CANCER THERAPY AND MUCOSITIS

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ABSTRACT:
Radiation therapy is commonly used to treat cancers of the head and neck, most often with radiosensitizing concomitant chemotherapy. Oral mucositis is among the most frequent, symptomatic and regimen-limiting toxicities associated with chemoradiation protocols. Severe mucositis has a major impact on patient daily functioning, well-being, and quality of life. It can also compromise a patient's ability to tolerate planned therapy, resulting in missed doses or dose reductions. Changes occur in the resident oral flora (commensal) throughout cancer treatment that may have an influence on the development of mucosal toxicity associated with cancer treatment. The complex pathogenesis of mucositis has only recently been appreciated and reflects the dynamic interactions of all of the cell and tissue types that comprise the epithelium and submucosa. The identification of the molecular events that lead to treatment-induced mucosal injury has provided targets for mechanistically based interventions to prevent and treat mucositis. There is a potential interaction between the oral environment and the development of mucositis.

Key words: mucositis, oral flora, chemoradiation

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INTRODUCTION

Mucositis is the painful inflammation and ulceration of the mucous membranes lining the digestive tract, usually as an adverse effect of chemotherapy and radiotherapy treatment for cancer. Mucositis can occur anywhere along the gastrointestinal (GI) tract, but oral mucositis refers to the particular inflammation and ulceration that occurs in the mouth. Oral mucositis is a common and often debilitating complication of cancer treatment.

Oral mucositis is a well-known side effect of cancer chemotherapy, and it is associated with a number of complications, varying from pain and discomfort to potentially life-threatening systemic infections. The pathophysiology of the condition is still undefined, but recently the hypothesis has been put forward that mucositis is the result of a complex interaction of a number of factors, occurring in different phases. Many cytostatic drugs, including methotrexate, doxorubicin, and 5-fluorouracil, have a direct toxic effect on rapidly dividing oral mucosal cells, resulting in inflammation and epithelial damage (noninfectious mucositis).[1]

Consequently, the damaged mucosal epithelium may become infected: local defense mechanisms are impaired, and there may be alterations in the flow rate and the composition of saliva. Furthermore, many chemotherapeutic regimens used to treat cancer are myelosuppressive and/or immunosuppressive, increasing the patient's susceptibility to bacterial, viral or fungal infection. Disrupted oral tissues may act as a portal of entry for systemic spread of these infections. Similarly, the duration of hospitalization and levels of infection are increased by the presence of chemotherapy-induced oral mucositis in patients with solid tumours and also mucositis results in an increase in cost of treatment.[1]

There is also a potential interaction between the oral microenvironment and the development of mucositis. Changes occur in the resident oral flora throughout cancer treatment, and it is conceivable that these organisms and changes that occur may have an influence on the development of mucosal toxicity associated with cancer treatment.[2] Mucositis also threatens the efficacy of treatment plans by necessitating breaks in radiation therapy, reductions in doses of drugs used in chemotherapy and modifications in the selection of antineoplastic agents.[3]

A large number of bacterial species have been detected in the oral cavity, and it has previously been estimated that over 620 species are accommodated in the oral cavity, although with molecular techniques widely used, the number may actually be greater. The bacterial population varies between sites within the oral cavity. The microflora of the lips is thought to consist of facultative anaerobes, predominantly those of the Streptococcus genus.[3] Other microbes have been detected in relatively low numbers and include Veillonella, Neisseria and Candida (if underlying damage is present). The cheek and tongue harbour a number of Streptococcus species, as well as Actinomyces and Haemophilus. The microbes inhabiting the teeth consist of Streptococcus, Actinomyces and Haemophilus, with the obligate anaerobes found in oxygen-poor gingival crevice. Bacteria are also present in the saliva, with the predominant genera shown to be Prevotella, Streptococcus and Veillonella. The variation in microbial populations between regions is due to variations in the availability of nutrients, adherence capabilities and redox potential. Viruses have also been detected in a number of scenarios.[4]

MICROBIOTA AND MUCOSITIS

Chemoradiation in head and neck cancers induces mucositis and other clinical debilitating effects which have been highlighted in Fig.1. This cytotoxic therapy alters the ecological balance in the oral cavity, by damaging non-keratinised surfaces and reducing the number of neutrophils. The depleted barrier function can allow some of the resident microbes to initiate pathogenic processes.[5] Mucus secretion is highly impaired after radiotherapy by a depletion and dysfunction of the salivary glands. Hyposalivation after radiotherapy contributes considerably to disruption of the natural barrier of the oral mucous membranes.[6] In 1970s, Brown and coworkers clearly demonstrated the impact of hyposalivation on the microbial population dynamics in various oral microenvironments.

The most prominent changes following radiotherapy were increase in Streptococcus mutans, Lactobacillus spp., C. albicans, and Staphylococcus spp. and decrease in Streptococcus sanguis, Neisseria spp. and Fusobacterium spp. (Brown et al, 1975). These shifts persist during the duration of xerostomia and are probably due to a reduced clearing of microbiota due to lower salivary flow (Guobis et al, 2011). The relationship between hyposalivation and a shift in the oral microbiome was further investigated by Shao et al (2011) using intensity-modulated radiotherapy (IMRT) or conventional radiotherapy. The data showed that preservation of the salivary flow and the stability of the oral microbiome were significantly higher after IMRT.[6]

Apart from the direct effects of the anti-cancer therapies on the structure and functionality of the oral mucosal layer, excessive degradation of mucins by mucolytic microbiota may contribute to the severity of mucositis as it disturbs the protective function of the mucosa. A number of mucolytic species have been identified in the oral cavity and include Streptococcus mitis, Streptococcus mutans, Streptococcus oralis, Streptococcus sanguinis, and Streptococcus sobrinus (Derrien et al, 2010). Recent clinical evidence suggests that mucolytic Streptococci play a role during chemotherapy-(Olczak-Kowalczyk et al, 2012) and radiotherapy-induced mucositis (Tong et al, 2003).[7]

Mucin degradation requires the subsequent activities of microbial enzymes, mainly glycosidases, each having the specificity to degrade a specific glycoside linkage. Streptococcus spp. produce one, several, or all mucin-degrading enzymes (Derrien et al, 2010). Although it is unclear at what stage and extent Streptococcus spp. play a role in the pathogenesis of mucositis, they have definitely the potential to have detrimental effects by targeting different types of mucins present in the mucus layer. Due to their high abundance on every surface in the oral cavity, it is likely that Streptococcus spp. has an impact on both the composition and thickness of the oral mucus layer and can easily cause infections. Indeed, commensal Streptococcus spp. have been shown to be able to shift to a pathogenic phenotype under certain circumstances. For example, S. mitis, a normal commensal of the human oropharynx, has been shown to cause a variety of infectious complications including infective endocarditis in vulnerable immune-compromised patients (reviewed by Mitchell, 2011). [7]

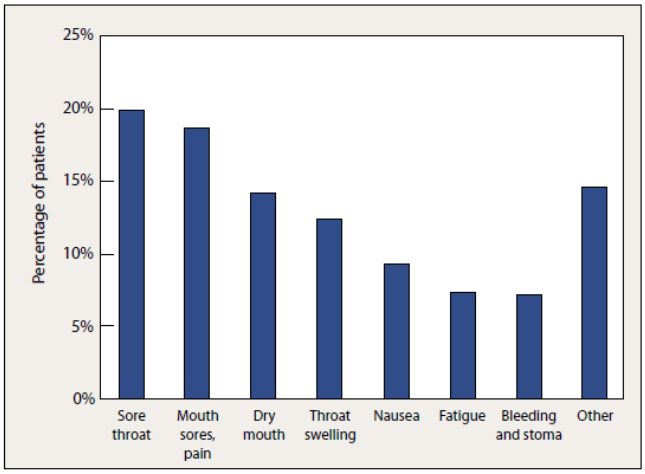

Figure 1: (Rank Order of Debilitating Side Effects) The negative impact of oral mucositis in patients receiving therapy for head and neck cancer can be seen in this histogram. Mucositis and other oral complications lead the ranking of adverse events in terms of debilitating effects reported by patients.[8]

PATHOBIOLOGY

Earlier models have postulated that only the epithelium is involved in the development of mucositis and that mucositis therapy directed solely at epithelial stem cells would be beneficial. However, it has become clear that mucositis is a more complex process than originally believed and involves a complex interaction between the components of the epithelium and the submucosa.[9] Other mucosal components, such as the endothelium,

extracellular matrix, and connective tissue, also play a role. This process can be thought of as occurring in five stages or phases: initiation, message generation, signal amplification, ulceration, and healing. Such a model can serve as a new paradigm for increasing our understanding of the pathogenesis of mucositis and for developing agents directed against components of these pathways. This working model is still evolving, so the exact subdivisions between stages and the molecular interactions occurring remain to be more precisely defined.[8]

The initiation phase (Fig. 2) involves direct damage to DNA and other cellular components that occur immediately following exposure to radiation or chemotherapy. These treatments generate reactive oxygen species (ROS), free radicals that can cause DNA strand breaks in the epithelium and submucosa and initiate a cascade of other downstream biological events.[10]The microbiota at this stage comprises of increased levels of Streptococcus mitis, Streptococcus salivarius, and Lactobacilli, while there is a decrease in levels of Streptococcus sanguis. The most frequent etiology of the infection at this stage is Candida albicans, followed by Candida glabrata, Candida krusei and Candida tropicalis.[7]

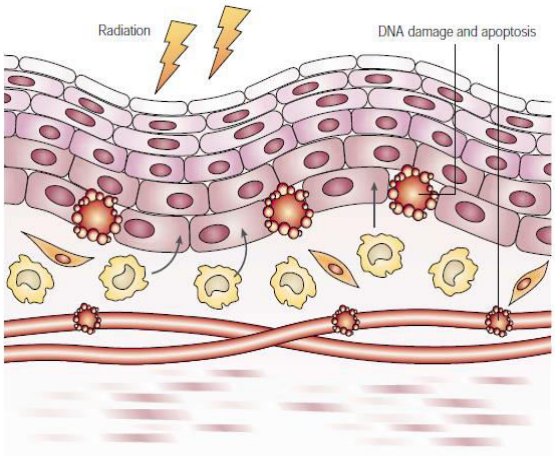

Figure 2: Primary damage response and signal amplification**.** Mucositis is initiated by direct injury to basal epithelial cells and this causes the activation of transcription factors Nuclear factor-kappa B (NF-κB) and NRF2 leading to the upregulation of genes modulating the damage response. Immune cells produce cytokines tumor necrosis factor(TNF-α) and interleukin 6, which causes further tissue injury.[11]

In the next stage—upregulation and message generation—transcription factors are activated that affect a number of genes controlling protein synthesis and cell signaling. Of the numerous transcription factors involved, one of the most important is nuclear factor-kappa B (NF-κB). This regulatory molecule controls nearly 200 genes involved with mucositis, including those encoding pro-inflammatory cytokines and cell adhesion molecules. Increased synthesis of the cytokines interleukin (IL)-1β and IL-6 can also be seen in the mucosa.[12] Other enzymes activated by radiation, chemotherapy, and ROS include ceramide synthase and sphingomyelinases that can increase the rate of apoptosis. Together, these transcription factors and other substances serve to trigger a variety of destructive processes that can be lethal to epithelial cells and surrounding fibroblasts.[10] Significant increase is seen in levels of Candida spp. Specific increase in E. coli, P. aeruginosa, Enterobacter species, and K. pneumoniae continue to contribute to exacerbation of mucositis.[7]

Signal amplification, the third stage, consists of feedback loops that further increase the number and level of activating signals. Pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), which are secreted following radiation or chemotherapy damage, not only directly result in tissue injury but also further increase the activity of other signaling factors such as NF-κB and mitogen-activated protein kinase (MAPK)[13] (Fig. 3). The net result is an ongoing cycle of amplification of injury that persists well after the initial insult of radiation therapy or chemotherapy. Interestingly, despite all these cellular changes occurring during the initial stages of mucositis, few symptoms are apparent.[10] In cases of chemotherapy, predominance of Gemella haemolysans and S. mitis was found. The total number of species per patient increased and a shift to a more complex oral bacterial profile is also found.[7]

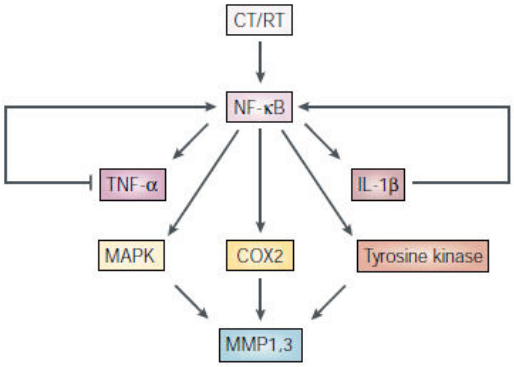

Figure 3: Signal amplification during mucositis.

Cancer therapy activates the transcription factor nuclear factor-κB (NF-κB) in epithelial, endothelial and mesenchymal cells and macrophages, leading to the upregulation of genes and the production of proinflammatory cytokines, such as tumour-necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). These signaling pathways lead to activation of matrix metalloproteinases (MMPs), which ultimately results in tissue injury.[14]

The fourth stage, ulceration, involves penetration through the epithelium into the submucosa. The ulcerated surface can then be colonized by oral bacteria, producing toxins and additional inflammatory cytokines (from activated macrophages) and angiogenic factors (Fig. 4a). This

ulcerative phase is primarily responsible for the main clinical symptoms of mucositis (pain, inflammation, and loss of function) and is associated with higher costs (increased drug use and hospitalization).[10] At this stage, the main cause of oral ulceration have been several gram-negative bacteria, Candida spp., a gram-negative anaerobic bacterium Porphyromonas gingivalis, anaerobes Parvimonas micra, Fusobacterium nucleatum, and Treponema denticola and yeasts C. glabrata and C. kefyr also have a positive predictive factor in oral ulcerations.

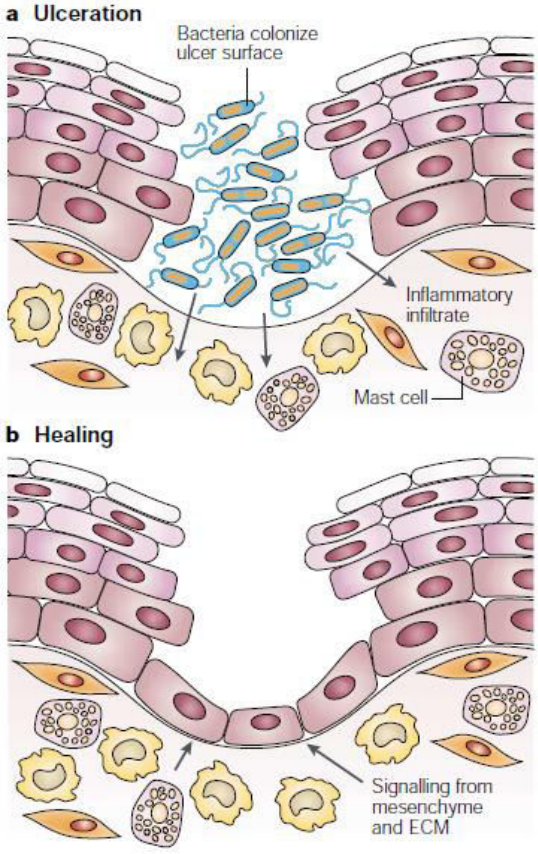

Figure 4a: Ulceration and healing. About 10 days after the cancer therapy, the integrity of the epithelium disintegrates and ulceration occurs. Oral bacteria colonization of ulcer causes release of cell-wall products that penetrate into the connective tissue to stimulate the release of other cytokines. The ulcer can be covered by a fibrinous, bacteria-laden exudate that is referred to as a 'pseudomembrane'. **Figure 4b** In most cases, spontaneous healing occurs about 2–3 weeks after the cessation of radiotherapy or by 3 weeks after the administration of chemotherapy. The epithelium migrates from the wound margins which determine proliferation, migration and differentiation.[11]

After a few days of mucositis, neutropenia develops and the microbiota at this stage also comprises of F. nucleatum. During cultivation C. albicans, C. tropicalis, and aspergillus are the commonest fungal isolates from oral mucositis. Other organisms isolated in patients with oral mucositis are Bacillus species, E. cloacae, K. pneumoniae, P. aeruginosa, S. aureus, E. coli, S. haemolyticus, S. epidermidis, and S. maltophilia.[15]

The final stage in the pathobiology of mucositis is healing (Fig 4b). Epithelial cells, under control of signals secreted by the extracellular matrix, migrate, grow, and differentiate to form a wound. These signals are then downregulated to avoid hyperplasia. With the healing process under way, symptoms begin to abate. High counts of Candida spp. and a significantly greater percentage of Lactobacillus spp. are seen during this stage.[7]

TREATMENT

Suppression of TNF-α production seems to correlate well with effective modulation of mucositis. IL-11 administration in an animal model had favourable results and was associated with a reduction of TNF-α gene expression. The ability of keratinocyte growth factors (KGFs) to modulate TNF-α levels have been noted. Benzydamine HCl showed efficacy in reducing the severity of mucositis and associated pain in patients who were being treated with radiation for cancers of the head and neck. Among its biological effects, benzydamine inhibits TNF-α production. So, modulation of the production or release of pro-inflammatory cytokines might be one effective strategy for anti-mucositis agents.[16] Another approach to mucositis intervention has focused on a possible role for cellular nutrition. In particular, a number of studies have evaluated the use of glutamine, a non-essential amino acid, which is required for cells to survive during periods of catabolic stress.[15]

Topical analgesics include 2% viscous lidocaine and 'magic' or 'miracle' mouthwash formulations that typically include a combination of lidocaine, benzocaine, diphenhydramine, kaolin, milk of magnesia and/or sucralfate. These agents are swished and expectorated, and can be safely used throughout the day as needed for the duration of mucositis symptoms. Such rinses can be especially beneficial when used prior to alimentation and oral hygiene.[17]

Systemic management with morphine and other opioid pain medications is effective and considered standard of- care therapy for severe cases, although breakthrough pain and dose-limiting toxicities are frequently encountered.[18]

Gelclair (Cambridge Laboratories, Dublin, Ireland) and Mucotrol (Cura Pharmaceutical, Eatontown, New Jersey, USA) are Food and Drug Administration-approved mucoadhesive agents that coat and adhere to the inside of the mouth, and are effective by physically blocking painful exposed nerve endings in the damaged ulcerated mucosa.[19] While safe and generally well tolerated, relief from these agents is variable with additional systemic pain management typically required.[8]

A new study reveals that GM-CSF enhances the cytotoxic and phagocytic behavior of macrophages and granulocytes in model systems. Evidence from recent clinical trials demonstrates that parenteral GMCSF therapy reduces the

incidence of chemotherapy induced mucositis; hence, it can be used effectively as well. [20]

As the haematological toxicities that are associated with many types of cancer therapy can now be effectively controlled by the administration of growth factors, the control of mucositis is becoming increasingly important.[19]

Although there is no approved therapy to prevent or treat the condition at present, the development of an effective intervention is seen as a high priority in oncological supportive care. Advances in understanding the pathobiology of mucositis have resulted in identification of a range of promising targets for treatment.[8]

CONCLUSION

Oral mucositis is a common and serious complication secondary to chemoradiotherapy for head and neck cancer that has a profound effect on morbidity, compliance and treatment outcomes. Recent advances in basic research have greatly expanded our understanding and appreciation of the complex and dynamic underlying pathophysiology of this condition. A number of currently available approaches and interventions can be utilized to minimize the pain and dysfunction associated with mucositis ulcers. In the near future, we can expect to see a number of new treatment modalities that likely in combination, due to multiple complementary and synergistic mechanisms, will be effective in reducing the severity and duration of mucositis and improve outcomes in patients undergoing therapy for head and neck cancer.

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