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Current Concepts on the Pathogenesis and Management of Radiation-Induced Oral Mucositis: A Literature Review

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ABSTRACT

Radiation-induced mucositis (RIM) is a significant complication of cancer treatment, particularly for patients undergoing radiation therapy for head and neck cancers. Radiation-induced oral mucositis (RIOM) causes severe pain, difficulty in swallowing, and may lead to dose reduction or treatment delays, adversely impacting patient outcomes. This review compiles current literature on the pathophysiology, prevention, and management of RIOM, with a focus on pharmacologic, non-pharmacologic, and emerging therapeutic interventions. Understanding these concepts is essential for advancing care strategies and improving patient quality of life during treatment.

Key Words: *Radiation induced mucositis, RIOM, complications of radiation, head and neck cancer*

INTRODUCTION

Head and Neck Cancers (HNC) are common and represent about 4% of all cancer types. In 2018, about 0.7 million new cases and 0.35 million deaths around the world. Surgery, radiation therapy, and chemotherapy are multidisciplinary approaches in the treatment of HNC [1] HNC constitutes a heterogeneous group of tumors including, among others, malignant neoplasms of lips, oral cavity, pharynx (usually divided into naso-, oro- and laryngopharynx), larynx, paranasal sinuses, or salivary glands [2] The most frequently used radiotherapy (RT) techniques in modern radiotherapy departments include Intensity-Modulated Radiation Therapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) with a total cumulative dose of 70 Gy (gray) by 2.0 Gy per day delivered over 7 weeks in definitive treatment and/or 60–66 Gy by 2.0 Gy over 6 to 6.5 weeks in adjuvant treatment [2]

Radiation-induced oral mucositis (RIOM) is one of the common toxic reactions from ionizing radiation and normal tissue injuries as a complication from RT or a combination of RT and CT [3]. It is an acute inflammatory, ulcerative condition of the oral mucosa. [4] Typically, RIOM occurs 2.5 weeks after the start of RT and lasts for 2–3 weeks after the procedure is completed. The labial, buccal, and soft palate mucosa, as well as the floor of the mouth and the ventral surface of the tongue are the most common sites. [2] The type of oral mucosa impacts RIOM risk as it typically effects the movable or thin mucosa but spares the more

keratinized tissue. [5] It affects up to 80% of patients undergoing radiotherapy for head and neck cancers, manifesting as painful inflammation and ulceration of the mucosal lining of the mouth and throat. [6] This condition severely impairs eating, speaking, and overall quality of life and manifests with xerostomia, dysphagia, dysarthria, odynophagia, and various secondary infections often necessitating interruptions or modifications to cancer therapy. [1, 7]

Despite the use of modern highly sophisticated RT techniques, such as IMRT or VMAT, which allow reduction of the radiation dose to healthy surrounding tissues, this complication still poses many problems in clinical practice. [2]

Clinical features and Classification of RIOM

Acute complications of RIOM develop during the early stages of radiotherapy and continue into the immediate post-treatment period (2-3 weeks), while chronic complications can manifest at any time, thereafter from weeks to years after treatment. [8] The initial clinical signs of RIOM include mucosal erythema and superficial sloughing that may occur with a cumulative radiation dose of 20 to 30 Gy, which is accompanied by the beginning of the breakdown of the intact mucosa followed by ulceration. It has been reported that HNC patients with nasopharyngeal or oropharyngeal tumors who receive cumulative radiation doses >50 Gy are more likely to develop mucositis. [9] Mucositis results in the loss of oral mucosal integrity, imbalance of the oral flora and hyposalivation leading to increased susceptibility to oral infections, including oropharyngeal candidiasis and viral infections such as herpes simplex virus, pronounced sensitivity to dental caries, gingivitis and periodontitis [4] Ultimately, severe RIM can even lead to hospitalizations and mortality [4]

The factors in the assessment of RTOM could be classified into two classes: patient-related and treatment-related. Patient-related factors include age, gender, nutritional status, comorbidities, oral hygiene habits, smoking, oral disease history and genetic factors, etc.

Treatment-related factors include radiation dose, technique, and site, [10] The severity of RIOM is influenced by radiation-related factors: fractional dose, total cumulative dose, total volume of irradiated tissues. [2]

Oral mucositis has various classification systems;

The World Health Organization (WHO) scale is the most widely used system for measuring the anatomical, symptomatic, and functional elements of oral mucositis, while the Western Consortium for Cancer Nursing Research scale only describes the anatomical changes associated with oral mucositis [11]. The Radiation Therapy Oncology Group (RTOG) scale assesses the criteria for acute radiation therapy morbidity for mucous membranes [11]. Another scale that can be used to assess the severity of OM is The National Cancer Institute (NCI)-General Toxicity Criteria (CTC version 4.0), the European Organization for Cancer Research and Treatment (EORTC), and the Oral Mucositis Assessment Scale (OMAS) [1, 11] Additionally, research-dedicated scales, such OMI (Oral Mucositis Index) provide highly quantitative outputs based on a set of parameters that are narrowly defined. Another scale used is Dische's scale, which combines the assessment of clinical signs with symptoms [12]. Common Terminology Criteria Adverse Event (CTCAE V5.0, November 27, 2017) scale distinguishes different cases, from asymptomatic ones which do not require any medical intervention, to more serious cases requiring urgent nutritional and/or medical intervention or leading to the death of the patient. [13]

Pathogenesis of Radiation-Induced Oral Mucositis

RIOM pathogenesis consists of parallel, sequential, and staggered molecular events occurring in a temporal dimension. [14] The

pathogenesis is complex and involves a sequence of events beginning with radiation-induced DNA damage, followed by cellular and tissue-level responses that contribute to mucosal breakdown. The main stages include: initiation, primary damage with signal amplification, ulceration, followed by healing and fibrosis.

Initiation:
Radiation causes DNA and cellular damage in mucosal cells, producing reactive oxygen species (ROS). via ionization of intracellular water. [15] Radiation-induced oxidative stress has the potential to spread from targeted cells to non-targeted bystander cells through intercellular communication mechanisms. [2]

Signaling:
Radiation and ROS leads to the activation of at least 14 pathways that alternate biological control mechanism and are associated with the development of RIOM. [2] Damaged cells release damage-associated molecular patterns (DAMPs) such as cytokines (e.g., TNF-α, IL-1, IL-6), that bind receptors, amplifying an inflammatory cascade and increasing cell death. [16] It is currently believed that the most important and one of best-known mechanisms is the NF-*k*B pathway. In normal cells, activation of NF-*k*B pathways leads to apoptosis due to upregulating maximum 200 genes (including proinflammatory cytokine genes, i.e., cyclooxygenase-2, interleukin-1B, interleukin-6, inducible NO-synthase, superoxide dismutase and adhesion factors .[17] NF-*k*B activation also leads to the production of anti-apoptotic and pro-apoptotic factors (i.e., BCL-2 gene family (B-cell lymphoma 2)—BAX (Bcl-2-associated X protein), BCL-X1 (B-cell lymphoma/leukemia-x long)), which determines changes in normal mucosa tissue. Radiation can disturb balance and cause overexpression of pro-apoptotic BAX and put healthy cells on the programmed cell death pathway [5] Radiation also affects submucosal cells. Activation of activator protein 1 (AP1) leads to secretion of metalloproteinase (MMP), which damages collagenous subepithelial matrix and epithelium base membrane and potentially exacerbates injury and allows the promotion and dissemination of other pro-inflammatory and pro-apoptotic signals [5]

Amplification:
A positive feedback loop of inflammation further damages mucosal cells and tissues. Transcription factors induced in primary damage response can positively or negatively affect the local cellular response. Pro-inflammatory cytokines such as TNFα not only lead to programmed cell death but also create a positive-feedback loop and amplify other processes that are part of RIOM. [18]

Ulceration:
Mucosal surfaces break down, leading to painful ulcerations and susceptibility to infection by the action of action of MMPs triggered by DNA damage [19] Event cascade and accumulation of biological changes initiated through radiation delivery leads to clinically relevant mucosal injury. It occurs as ulceration extending to the submucosa and in many cases covered with pseudomembrane composed mainly of fibrinous excaudate [2] Due to mucosal damage, nerve endings are exposed, resulting in pain and loss of function. Simultaneously, ulceration becomes the portal of entry for microorganisms, such as bacteria or fungi, and it causes a higher relative risk of septicaemia. In animal studies, in the inflamed epithelium, the number of pathogenic bacteria is 300 times higher than in a healthy epithelium [5]. Bacterial colonization plays an essential role in the pathogenesis of RIOM. Lipopolysaccharides, lipoteichoic acid, cell wall antigens, and-glucans released from the bacterial cell wall can stimulate further secretion of proinflammatory cytokines by macrophages located in submucosa [20].

Healing and Fibrosis:

In most cases, RIOM heals spontaneously 4–12 weeks after treatment is completed. [18]. After radiation ends, the body initiates wound healing, marked by cell proliferation and tissue repair by signaling from the extracellular matrix (ECM) and anti-inflammatory cytokines. However, these processes may be delayed or incomplete. [19]

Nowadays, it is believed that submucosal signaling promotes proliferation, migration and differentiation of the epithelial cells, in which the most important is the activation of intrinsic tyrosine kinase [5,21]. The structure of the reconstituted submucosa is not identical to that of the submucosa prior to mucotoxic disruption, even after the epithelium has been fully replenished [22].

This cascade underscores the need for interventions at various stages, particularly to reduce inflammation and promote healing.

A hypothetical argument suggests that ROM pathogenesis describes the cumulative effect of two distinct pathways which occur in a semi-staggered sequence. The first pathway, the immediate injury pathway, induces direct damage to basal stem cells, whereas injury induced by the second pathway, the indirect pathway, reflects the failure of normal host defence mechanisms to keep up with biological challenges imparted by accumulating radiation doses. The two occur in parallel, but their contribution to RIOM pathogenesis is staggered andnot equivalent. [14]

The immediate pathway is responsive to radiation dose and schedule, but not markedly impacted by intrinsic response modifiers such as genetics. However, the indirect pathway is responsible for most of the acute and chronic tissue effects associated with RIOM [14].

Current Management Strategies

Current management of RIOM focuses on symptom relief, maintaining nutritional intake, and preventing infections. As treatment modalities and supportive care evolve, there is an increasing focus on evidence-based approaches for preventing and managing RIM.

Modern RT techniques, like intensity-modulated radiotherapy (IMRT), have outperformed the conventional RT techniques, in attempting to alleviate radiation-induced toxicities. Nonetheless, it has been reported that IMRT does not decrease the incidence of RIOM; especially in patients with nasopharyngeal cancer (NPC). Accurate prediction of RIOM can assist clinicians for early intervention. There are some guidelines for prophylaxis of mucositis such as patient education, use of non-medicated saline rinses, hydration, nutritional support, infection control, non-pharmacologic and pharmacologic options that could be implemented for patients if we predict it before radiotherapy [23].

Many studies have indicated that use of artificial intelligence such as radiomics can be a valuable tool to facilitate precision diagnosis, treatment planning, and predicting outcomes [24]. In recent years, it has been shown that integrating quantitative medical imaging biomarkers into clinical and dosimetric data has improved the prediction of radiation-induced toxicities in the treatment of various cancers [23].

Despite its clinical relevance, a standardized strategy for preventing and treating RIOM has not been defined yet. [13]

Since 2004, the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) cooperative group published their recommendations on the prevention and treatment of RIOM. Similarly, the European Society of Medical Oncology (ESMO) has periodically published its recommendation since 2009, while an Italian working group endorsed by Associazione Italiana di Radioterapia ed Oncologia Clinica (Gruppo AIRO Inter-regionale Lazio-Abruzzo-Molise) did it in 2019 [13].

A multi-disciplinary approach is recommended for prevention and management of RIOM

1. Preventive Approaches

Preventive strategies aim to mitigate mucositis onset and severity, often by protecting mucosal integrity or reducing radiation-induced inflammation.

- Oral Cryotherapy: The application of cold to the oral cavity during radiation sessions reduces blood flow, potentially minimizing mucosal exposure to radiation. Studies suggest a benefit in reducing mucositis incidence, particularly for patients undergoing chemotherapy-radiotherapy combinations [25].
- Low-Level Laser Therapy (LLLT): LLLT, also called photobiomodulation therapy, uses low-energy light to stimulate cell repair and reduce inflammation. Recent trials support its efficacy in preventing and alleviating mucositis severity, making it a recommended option in certain patient populations [26].
- Amifostine: This radio-protective agent acts as a scavenger of free radicals generated by radiation. While effective, its use is limited by potential side effects, including nausea and hypotension. [27]

2. Pharmacologic Management

Managing RIM pharmacologically involves the use of agents to reduce inflammation, pain, and infection risk.

- Anti-inflammatory Agents: Corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) can reduce mucosal inflammation, but their efficacy is limited by side effects and short-term benefit [28].
- Pain Management: Pain control remains critical, typically achieved through:
- Topical anesthetics (e.g., lidocaine), which provide short-term relief but must be applied frequently.
- Analgesics such as opioid or non-opioid pain medications, administered systemically for moderate-to-severe mucositis.
- Antimicrobials: Prophylactic and therapeutic use of antimicrobials, including antiseptic mouthwashes and antifungal agents, help prevent secondary infections in ulcerated mucosal tissue [29].
- Palifermin: A recombinant keratinocyte growth factor that stimulates epithelial cell proliferation, shown to reduce the severity and duration of mucositis in patients receiving radiation therapy for hematologic malignancies. However, its efficacy is limited in solid tumors, and further studies are required to optimize its use. [30]

3. Non-Pharmacologic Interventions

Non-pharmacologic approaches provide supportive care to improve comfort and facilitate healing.

- Nutritional Support: Ensuring adequate nutrition through dietary modifications or tube feeding is essential, as mucositis can severely limit oral intake. Nutritional intervention has been linked to improved outcomes and tolerance of cancer treatment. [10]
- Oral Hygiene: Maintaining oral hygiene with saline rinses and gentle brushing can reduce the risk of infection. Although hygiene does not directly reduce mucositis incidence, it minimizes secondary complications. Basic Oral Care: Maintenance of good oral hygiene, pre-treatment dental evaluation, Saline solution, sodium bicarbonate, benzidamine mouthwash have been recommended. [l,13]
- •Cessation of smoking prior to commencement of radiation therapy [31]
- Mucosal Coating Agents: Sucralfate and other coating agents form a protective barrier over mucosal surfaces, offering temporary pain relief and helping to prevent further damage [32].

- Natural products like honey are efficacious in mitigating mucosistis [33]

4. Emerging Therapies

Advancements in understanding RIM pathophysiology have led to novel therapeutic strategies, though many remain experimental.

- Growth Factor Therapies: Agents targeting epithelial growth, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), are being investigated for their potential to accelerate mucosal repair. Preliminary data indicate promise, though large-scale trials are needed for validation [34]
- Gene Therapy and Cytokine Modulation: Modulating cytokines involved in RIM, such as TNF-α and IL-1, may offer targeted treatment. However, the complexity of cytokine signaling limits the clinical application of these approaches, as unintended immunosuppression could increase infection risks. [33]
- Targeted Molecular Agents: Agents targeting specific molecular pathways involved in inflammation and cell damage, such as NF-κB inhibitors, are under investigation. These therapies hold potential but require further safety and efficacy validation.[35]

Evidence-Based Guidelines for RIOM Management

Professional organizations, including the Multinational Association of Supportive Care in Cancer (MASCC) and the American Society of Clinical Oncology (ASCO), have developed evidence-based guidelines to optimize the management of radiation-induced mucositis. Their recommendations emphasize a multimodal approach, which includes:

1. Low-Level Laser Therapy (LLLT): LLLT is recommended for both prevention and management of RIM due to its demonstrated efficacy in reducing the severity and duration of mucositis.
2. Oral Cryotherapy: Especially beneficial during chemotherapy and radiation, oral cryotherapy is recommended to reduce mucositis incidence by minimizing mucosal blood flow and limiting tissue exposure to radiation.
3. Topical Anesthetics and Systemic Analgesics: These are essential for pain control, with topical anesthetics providing immediate relief and systemic analgesics prescribed based on pain severity.
4. Palifermin: MASCC and ASCO guidelines support palifermin use for hematologic cancer patients undergoing high-dose radiation therapy, though its efficacy in solid tumors remains under investigation.

These guidelines reflect the value of evidence-based, individualized care, prioritizing interventions that minimize RIOM severity, improve treatment adherence, and enhance patient well-being and quality of life during cancer therapy [29].

Challenges and Future Directions

Managing RIOM effectively is complex, with variability in patient responses and an ongoing need for effective, personalized interventions. Future research focuses on identifying biomarkers for susceptibility and developing targeted therapies that address individual patient profiles. Additionally, further clinical trials are needed to establish the long-term efficacy and safety of emerging therapies such as cytokine modulators, gene therapy, and novel molecular agents.

Therefore, analysis and clarification of the main risk factors have certain significance for clinical implementation of individualized clinical nursing measures, reduction of the incidence rate of RIOM, reduction of disease incidence, improvement of patients' quality of life, and reduction of patients' physical and mental burden. [36]

CONCLUSION

Radiation-induced mucositis is a significant, quality-of-life-impacting side effect of cancer treatment, particularly for patients with head and neck cancers. Current management emphasizes a multimodal approach that integrates both preventive and therapeutic strategies to alleviate symptoms and ensure cancer treatment adherence. Advances in understanding RIOM pathophysiology are fostering the development of novel interventions, offering potential for improved patient outcomes. Ongoing research and refinement of clinical guidelines are essential to addressing the evolving needs of patients affected by RIM.

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