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Strategies for Managing Radiation-Induced Mucositis in Head and Neck Cancer

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Radiation-induced mucositis (RIM) is a common toxicity for head and neck cancer (HNC) patients. The frequency has increased because of the use of more intensive altered radiation fractionation and concurrent chemotherapy regimens. The extent of the injury is directly related to the mucosal volume irradiated, anatomic subsite exposed, treatment intensity, and individual patient predisposition. The consequences of mucositis include pain, dysphagia including feeding tube dependency, dehydration, micronutrient deficiencies, weight loss, and potentially life-threatening aspiration. Currently, there is no Food and Drug Administration–approved cytoprotective agent that reliably prevents RIM for HNC, but several are under investigation. Strategies to limit the extent of mucositis and to manage its symptoms include basic oral care and supportive medications. Limiting the use of aggressive treatments to truly high-risk cancers and special attention to radiation therapy planning techniques can also help restrict the scope of the problem. This review focuses on mucositis recognition, patient treatment selection, and RIM symptom-management strategies.

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Mucositis is an acute injury to the mucosal lining of the head and neck (HN) region associated with cancer treatment. Although radiation therapy (RT) potentially affects any mucosal surface exposed, from lips to cervical esophagus, chemotherapy-induced mucositis (also known as “stomatitis” or “oral” mucositis) most commonly involves the anterior oral cavity (buccal pads, lips, and lateral oral tongue). Chemotherapy-induced stomatitis is typically less severe and of shorter duration (3-12 days) than that associated with RT (3-12 weeks). The use of concurrent chemotherapy with RT shortens the onset, exacerbates the severity, and prolongs the duration of mucositis. Mucositis has become more widely problematic over the last 5 to 10 years as intensive chemoradiation regimens have become more commonplace.

In moderate to aggressive treatment programs, mucosal inflammation and epithelial cell loss lead to the interruption of the integrity of the mucosal barrier. The clinical recognition of mucosal changes range from mild erythema to deep mucosal ulceration.¹ The ulcers are typically covered by ex-

udates composed of cells, serum, and debris, so this more advanced stage is interchangeably referred to as “ulcerative,” “fibrinous,” or “pseudomembranous” mucositis. This spectrum of mucosal changes and associated symptom clusters is referred to as radiation-induced mucositis (RIM).

RIM-associated symptoms arising during RT/radiochemotherapy (CRT) for head and neck cancer (HNC) include “mouth and throat sores”; difficulty swallowing; pain; lost or altered taste (dysgeusia); excessive secretions that may lead to gagging, nausea, and vomiting; loss of appetite; fatigue; weight loss; and aspiration.^{2,3} The problem of excessive, viscid mucus in the mouth and throat is seldom reported but has been shown to be one of the most burdensome symptoms for many patients with high-grade RIM.⁴⁻⁶ Xerostomia is the most prevalent late effect of RT for HNC but also may be an early-phase component contributing to acute mucositis.⁷⁻⁹ Salivary mucins protect the surface integrity of the mucosa, and salivary antimicrobial effects and growth factors foster healthy, mature mucosa.¹⁰⁻¹³ Paradoxically, it is not uncommon for patients to complain both about dry mouth and excessive throat mucus.

The duration of mucositis is proportional to the degree of mucosal stem cell depletion. RIM may take weeks to months to heal depending on mucosal stem cell recovery. Excessive depletion may prevent healing and lead to a chronic open wound recognized as “soft-tissue necrosis.” This may be referred to as a “consequential late effect.”^{14,15} Other conse-

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quential late effects include mucosal scarring (healing by secondary intention) and loss of mucosal compliance, contributing to chronic dysphagia.

Risk Factors

The risk for developing mucositis and its severity and duration involves patient and treatment factors. Patient factors include age, sex, genetic predisposition, oral health, normalcy of saliva, use of tobacco and alcohol, and comorbidities. Treatment risk factors include the specific locations and surface area/volume of the head and neck mucosa irradiated, the rate of radiation dose accumulation (fractionation), the specific concurrent chemotherapy agent(s) used, and their dose schedules.

Strategies for Managing RIM

There is no current Food and Drug Administration (FDA)-approved intervention for the prevention of RIM. Current therapy consists of symptom management. Thus, mucositis has become one of the main areas of focus in HN symptom research and for the development of management guidelines.^{16,17} Published recommendations for mucositis interventions now include Multinational Association of Supportive Care in Cancer (MASCC),¹⁸ National Comprehensive Cancer Network (NCCN),¹⁶ and a Cochrane review.¹⁹

Treatment Selection as a Mucositis-Management Strategy

Limiting treatment intensification to selected patients most likely to benefit from it prevents those who will not benefit from suffering unnecessary toxicity. Chemoradiation has become the standard of care over the last decade based on clinical trials that focused on stage III and IV disease. However, there is sufficient heterogeneity among patients with stage III/IV disease that favorable subgroups can be identified for whom there would be no meaningful likelihood for locoregional control or survival benefit as a result of treatment intensification.

An argument has been made that chemoradiation is not the treatment of choice for all patients with stage III or IV HNC.²⁰ Locoregional control in oropharynx cancer, for example, is driven primarily by T stage. Results from the University of Texas M. D. Anderson Cancer Center indicate that patients with primary tumors <4 cm treated with RT alone \pm neck dissection for residual enjoy a 2-year locoregional control rate of 94% independent of N stage.²¹ Patients with a single node under 3 cm or 2 small nodes under 3 cm aggregate, for example, are likely to do well with RT alone. Patients with T4 primaries and/or true N2 or greater neck disease are appropriate to be considered on an individual basis for the addition of chemotherapy.

The selection of systemic agents used as radiosensitizers has a major impact on rates and the severity of mucositis. The

following examples show the spectrum. Cisplatin is a cytotoxic agent that causes a relatively modest increase in mucositis with RT. Cisplatin can be delivered as a single agent in full systemic dose with RT and has been shown to improve survival in multiple phase III trials.²² Thus, cisplatin is the standard agent used in the Radiation Therapy Oncology Group (RTOG); 5-fluorouracil, on the other hand, has been largely abandoned as a concurrent agent because it strongly enhances RIM and leads to frequent dose reductions or unplanned RT treatment interruptions.²³ Cetuximab is a new targeted agent that has been shown to be an effective radiosensitizer that did not appear to worsen mucositis as compared with RT alone in its phase III registration trial.²⁴ The effect of cetuximab on mucositis will be further explored in phase IV trials and when it is added to chemoradiation, such as in the RTOG phase III trial 0522 (rtog.org).

Although altered fractionation is commonly used with concurrent chemotherapy and at least 6 randomized trials show that altered fractionation RT with concurrent chemotherapy is superior to altered fractionation alone, there is currently no level I evidence showing an advantage of altered over conventional fractionation RT in the setting of concurrent chemotherapy. The RTOG has completed a now maturing phase III trial (H0129) in which patients all received high-dose cisplatin and were randomized to standard or accelerated radiation fractionation.²⁵ If H0129 shows meaningful improved survival or locoregional control with acceptable toxicity as a result of accelerated radiation, then the risk-benefit tradeoff for treatment intensification can be justified for appropriately selected patients. For now, we recommend using conventional fractionation in the setting of concurrent chemotherapy for most patients in the nonclinical trial setting.

Basic Oral Care

MASCC and NCCN guidelines and a National Cancer Institute report recommend "basic oral care" as a standard practice to prevent infections and potentially help alleviate mucosal symptoms.^{18,26} Although it is accepted that basic oral care is important to maintain dental and mucosal health, there is little direct evidence that it significantly affects the incidence or severity of oral mucositis.²⁷ Nonetheless, basic oral care is considered a commonsense part of management. Pretreatment evaluation by dental specialists to consider restoration or extraction is mandatory.²⁸⁻³⁰ The maintenance of oral hygiene during and after radiation will reduce the risk for dental complications, including infections, caries, gingivitis, and osteoradionecrosis. Basic oral care during radiation involves brushing in a nontraumatic fashion with a soft brush, flossing as tolerated, and frequent rinsing with bland solutions such as normal saline with sodium bicarbonate (1 L water with 1/2 teaspoon baking soda and 1/2 teaspoon salt), the use of moisturizing agents, periodic dental evaluations and cleanings, and the use of lifelong daily dental fluoride prophylaxis.³¹

Pain Management

Pain management is the single most important aspect of symptom control during HN radiation. Most patients require both systemic and topical analgesics. Narcotic dose, frequency, and duration should be regularly adjusted to meet the intensity level of pain. Transdermal fentanyl is useful in HN patients who often have a limited ability to swallow solids. A recent symptom review study showed that too few HNC patients are given adequate narcotic analgesia.³² All patients on narcotics should receive concurrent stool softeners and dietary guides to prevent constipation and maintain daily regularity. Viscous lidocaine is commonly used as a topical anesthetic and is effective for the temporary relief of mucositis-related pain.

“Magic Mouthwash”

Antacids, diphenhydramine, and the topical antifungal nystatin are often combined with viscous lidocaine in various institutional formulas known as “magic mouthwash.” Although these are popular, there has been no formal testing of such combinations. Diphenhydramine is sedating and may carry unpleasant anticholinergic properties. Topical nystatin in our experience does little to prevent or control candidiasis that may be coexistent with RIM. We find that oral ketoconazole or fluconazole are more effective therapeutically for candidiasis in the setting of RT for HN cancer.

Coating Agents and Devices

There are multiple proprietary oral rinses and coating agents available for mucositis symptoms, but none has been sufficiently tested for efficacy in the HN radiation setting. Their use should be based on patient preference and perceived comfort/benefit.³¹ Both the MASCC and Cochrane groups agree that there is insufficient evidence for the use of sucralfate in the treatment of mucositis. The following swish and spit products have been approved by the FDA not as active pharmacologies but as devices to reduce oral mucositis symptoms: Gelclair (EKR Therapeutics, Inc., Cedar Knolls, NJ), Mugard (Milestone Biosciences, LLC, Altamonte Springs, FL), Mucatrof (Belcher Pharmaceuticals, Inc, Largo, FL), and Caphosol (EUSA Pharma, Princeton, NJ). There are currently insufficient efficacy data to make a recommendation for these agents for HN RIM.

Dysphagia Support

RIM often leads to severe dysphagia and odynophagia. Patients frequently require feeding tubes. The use of prophylactic feeding tubes is controversial. We prefer to avoid a prophylactic tube in most patients, but we recognize that some high-risk patients may benefit from proactive tube placement. This includes patients with a history of severe weight loss, location of the primary tumor, and large primary tumor (thus, a large high-dose radiation target). Other factors include the availability of caregiver support and patient com-

pliance with supportive care recommendations. Patients should be encouraged to continue to swallow at least liquids throughout their course of RT, even if they have a feeding tube.³ Swallowing exercises managed by a swallowing therapist during and after radiation will probably lead to better long-term swallowing outcomes. Minimizing RT dose and dose inhomogeneity to the uninvolved tongue base, pharyngeal walls, and laryngeal structures may also decrease the risk for long-term dysphagia.^{33,34} Radiation treatment planning must be done with great care and must be highly individualized to minimize the risk of underdosing tumor targets (see intensity-modulated radiation therapy [IMRT] later).

Managing Copious Mouth/Throat Secretions and Associated Nausea

Viscid, copious oral/oropharyngeal/hypopharyngeal mucus is a major problem for many patients with high-grade mucositis. For some, it may be their most bothersome symptom. The mucus causes queasiness and gagging and contributes to difficulty in maintaining adequate hydration and nutrition. We have found the following approaches to be helpful. Regular rinsing with salt and soda solution will help in the early phases of secretion management. Guaifenesin may also help liquefy early-phase secretions but may not be helpful because secretions thicken in later phases.

Later-phase or larger-volume mucus may respond to combination narcotics and anticholinergic drying agents found in selected cough preparations (Hycodan, Endo Pharmaceuticals, Chadds Ford, PA, and Tussinex, UCB, Inc, Smyrna, GA). If the patient is already on narcotics, the antihistamine component may be added. Scopolamine (via a transdermal patch) may also be an effective drying agent to reduce the volume of secretions. The elevation of the head of the patient's bed 30° is important to reduce edema and protect the airway. A cool mist vaporizer may help with lubrication and mobilization. Lorazepam may help block the cycle of repeated gagging and associated nausea. Lastly, a portable suction machine is useful in some patients, especially in the postoperative setting, who may not be able to gargle effectively.

RT Conformality: IMRT

IMRT involves the use of multiple intensity-modulated radiation beams that converge to create a dose cloud of radiation that tightly conforms to the intended target with sharp dose penumbra or falloff in adjacent areas often containing critical functional dose-limiting tissues. Careful IMRT planning may be used to limit the mucosal volumes exposed, limit “hot-spots,” and limit dose to functionally important structures, such as the larynx, the pharyngeal walls and cervical constrictors, and the cervical esophagus. Peak rates of high-grade mucositis may not differ between 2-dimensional, 3-dimensional, and IMRT, but IMRT has the potential to limit the total

volumes of mucosa involved with high-grade mucositis, thus reducing overall short- and long-term morbidity.³⁵

Amifostine

Amifostine (WR-2721) is FDA approved to decrease the rates and severity of both acute and chronic xerostomia.³⁶ The impact of amifostine on HN mucositis when used at traditional xerostomia prevention doses is less clear. We do not believe that the standard xerostomia doses have reliable direct antimucositis activity. Because salivary mucins protect the mucosal surface and saliva is antimicrobial and contains mucosal growth factors, the salivary preservation afforded by amifostine may have an indirect effect on mucositis. MASCC and NCCN guidelines do not make any recommendation for or against the use of amifostine for mucositis prevention during head and neck RT.

Investigational Approaches

N-acetyl Cysteine

RK-0202 is a combination of the thiol antioxidant N-acetyl cysteine and a proprietary vehicle for transmucosal delivery. A randomized phase II trial reported that RK-0202 reduced oral mucositis incidence as compared with placebo control,³⁷ thus justifying a phase III trial to confirm efficacy. One fundamental concern for any product that must contact the mucosa to be effective is lack of coverage of the more supraglottic, pharyngeal, including hypopharyngeal, and cervical esophageal mucosa.

Glutamine

Topical and systemic glutamine preparations have been studied for mucositis with inconsistent results. A more recent investigation (Safaris, MG Pharma, Minn., MN) used a proprietary transmucosal delivery system that enhances glutamine absorption. A prospective placebo-controlled phase III patients with breast cancer treated with anthracycline-based chemotherapy showed a 22% reduction in high-grade mucositis. The FDA issued an approvable letter in October 2006 for "oral mucositis" and asked for an additional phase III trial before full approval evaluation. There are currently no published HN RT data to support the use of this agent.

Growth Factors

A recent RTOG double-blind placebo-controlled phase III trial reported that subcutaneous granulocyte-macrophage colony stimulating factor (GM-CSF) failed to reduce oral mucositis.³⁸ The results of early-phase trials with the topical application of GM-CSF were encouraging,^{39,40} but a prospective randomized trial was negative.⁴¹

In addition to mixed efficacy data, safety issues have been raised with growth factors. One randomized chemoradiation trial⁴² included a secondary randomization for granulocyte colony stimulating factor (G-CSF). The G-CSF arm was closed early because of poorer survival. Similarly, the Henke trial investigated the effect of erythropoietin in anemic pa-

tients undergoing HN RT.^{43,44} This trial and another RTOG trial were closed early because of poor survival in patients receiving erythropoietin during RT and for the risk for thrombosis-related toxicity. G- and GM-CSF and erythropoietin are not recommended for use during RT for HN cancer, and this experience suggests that we proceed with caution and vigilance when using growth factors.

Fibroblast growth factor-7 is an epithelial specific growth factor. The recombinant human form is called keratinocyte growth factor (palifermin). Palifermin reduced the incidence and duration of severe oral mucositis in a phase III trial including patients with hematologic malignancies undergoing total-body irradiation with high-dose chemotherapy and peripheral blood stem cell support.⁴⁵ This led to its approval by the US FDA for that specific indication.

A recently reported randomized phase II study evaluated palifermin weekly for 10 doses in patients with locally advanced HNC receiving once-daily or twice-daily RT with concurrent cisplatin/5-fluorouracil chemotherapy.⁴⁶ Mucositis, dysphagia, and xerostomia were reduced during hyperfractionated radiotherapy (n = 40) but not during standard radiation therapy (n = 59) and not for the combined group. The drug was well tolerated and did not adversely affect survival. It was hypothesized that a lack of consistent activity in this trial was because of the use of a suboptimal dose schedule (ie, weekly 60 $\mu\text{g}/\text{kg}$ palifermin). This led to dose-finding studies that confirmed that the dose of 60 $\mu\text{g}/\text{kg}$, when administered as a single dose, was suboptimal in inducing epithelial cell proliferation as measured by Ki67 staining, but this surrogate endpoint was achieved with higher doses. This led to 2 phase III industry-sponsored trials evaluating palifermin at these higher doses during RT for HN cancer. These recently closed and preliminary results should be reported soon. The evaluation of acute (toxicity) and long-term safety (tumor protection/promotion) for growth factors in mucositis prevention will be required before use outside of clinical trials can be recommended.

Low-Level Laser Therapy

Low-level laser therapy (LLLT) or "soft laser" has been investigated during RT for head and neck cancer and in the transplant setting. It is thought to have analgesic, antiinflammatory, and wound healing effects and no known clinical toxicity. The optimal details of the technology including the type of light source, wavelength, and dose schedule are not yet worked out, and its use requires training and certification. There have been several positive randomized studies supporting the use of LLLT in the transplant setting.^{47,48} MASCC guidelines suggest LLLT use in the transplant setting but do not offer any specific recommendation during RT for HNC for which there are less available data.

Targeting Infection

It is important that patients be monitored closely for signs of oral/pharyngeal infection that may commonly include candidiasis, bacterial, or herpes simplex. A rapid increase in pain,

acute exacerbation, or prolonged post-RT mucositis may signify infection. Patients with such suspicion should undergo culture and sensitivity evaluation and empiric and/or evidence-based antimicrobial therapy.

Antimicrobial and antiseptic agents have also been evaluated for their value to prevent mucositis. The use of oral antiseptics has not been fruitful. Chlorhexidine has been shown to be ineffective or even detrimental to HN RT patients, so it is not recommended.⁴⁹

Systemic and topical formulations of antimicrobial agents have been evaluated for mucositis. A combination of topical polymyxin B, tobramycin, and amphotericin B has been studied most extensively. Symonds et al⁴⁸ randomized head and neck RT patients to receive polymyxin B, tobramycin, and amphotericin B pastilles. The primary endpoint of a reduced incidence of very thick pseudomembrane formation was not met, but some secondary endpoints appeared to be improved.⁵⁰ A large phase III prospective randomized trial tested the topical broad-spectrum antimicrobial isegagan, but this was also negative.⁵¹ These collective data do not currently support the use of prophylactic antiseptic or antimicrobial agents to reduce or prevent mucositis during HN RT.

Targeting Inflammation

Steroidal and nonsteroidal antiinflammatory agents have been the focus of many preclinical and clinical research efforts for mucositis prevention. Disappointingly, betamethasone, prednisolone, and antiinflammatory prostaglandins E1 (misoprostol) and E2 (Prostin, Pfizer, NY, NY) did not reduce HN RIM or chemotherapy stomatitis in clinical trials.⁵²⁻⁵⁶

Benzydamine is a topical nonsteroidal agent that is currently available in Canada and the European Union as different preparations. Benzydamine has anti-inflammatory, analgesic/anesthetic, and antimicrobial effects that have been shown in clinical trials.⁵⁷ The more recently published phase III trial evaluated the primary endpoint of the efficacy of benzydamine to reduce mucositis at 50 Gy.⁵⁷ This endpoint was reported positive, but there were no efficacy data beyond that limited dose and no difference in pain on swallowing. Currently, MASCC guidelines do recommend, although NCCN guidelines do not recommend, the use of benzydamine for the prevention of RIM in patients with HN cancer receiving moderate-dose radiation therapy. The lack of consensus reflects the fact that most patients are treated to doses ≥ 60 Gy and that most of the assessed benefit of the drug at 50 Gy was no longer evident at doses >60 Gy. Moreover, patients receiving accelerated RT on that trial did not benefit even up to the 50-Gy assessment point. A large phase III randomized benzydamine versus placebo trial in the United States was closed early because an interim analysis concluded that continuation would be futile.

Conclusion

RIM is the most significant and dose-limiting acute toxicity during radiation or chemoradiation for HNC and is associ-

ated with both short- and long-term functional consequences. Multiple strategies to reduce the burden of mucositis have been reviewed. There are currently no approved agents or strategies that reliably prevent RIM, although several agents are under investigation. The current recommendations for mucositis are directed at limiting its extent and/or severity by appropriate treatment selection, attention to RT planning details, and the use of supportive and palliative care including basic oral care, aggressive use of analgesics, the use of feeding tubes in selected cases, and swallowing exercises and therapy.

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