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Review

Oral mucositis in head and neck cancer: Evidence-based management and review of clinical trial data

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ABSTRACT

Oral Mucositis (OM) continues to be an oncologic challenge in the context of antineoplastic therapy for head and neck cancer (HNC) treatment. It is a dose-limiting toxicity of chemotherapy and radiation treatment and negatively impacts quality of life and cancer treatment efficacy. Significant effort in the field of OM has been made to help alleviate its symptoms and its subsequent clinical and economic impact. Despite these advances, the treatment of oral mucositis remains difficult and focuses on palliative measures. There are, however, many promising new biological targets currently undergoing investigation to ameliorate or help prevent the toxicity of OM in HNC. Some of these targets undergoing investigation in phase 2 and 3 clinical trials are further highlighted along with the pathobiology of OM, clinical course, prevention, and management measures.

Introduction

Mucositis is damage that occurs to the mucosal lining of the upper and lower gastrointestinal tract, which is often a complication and toxicity of both chemotherapy and radiation therapy for cancer treatment. This damage can occur throughout the gastrointestinal tract; however, this review will focus on oral mucositis (OM) as a result of anti-neoplastic treatment of solid tumors of the head and neck, comprising the anatomic regions of the oropharynx, oral cavity, nasopharynx, larynx, hypopharynx, and salivary glands.

Despite advancements in the study of OM, it nonetheless remains a significant challenge in the treatment of head and neck cancers (HNC). There is currently no approved therapy for mucositis in this context, despite its clinical impact. Clinically, sequelae of OM include significant pain, dysphagia, dehydration, dysgeusia, anorexia, significant weight loss, and increased susceptibility to secondary and systemic infections. As a result, it is not a surprise that OM also is associated with increased resource use and can have a significant economic impact. Depending on the severity, OM is correlated with an incremental cost of at least $1700–$6000 per patient (estimates in 2006 US dollars) [1]. One study found that the estimated median cost for HNC cancer treatment with CRT exceeds $39,000 for patients with mucositis in comparison to those without mucositis with costs of approximately $21,000 (in 2005 US dollars). These costs were driven by more frequent and lengthy inpatient hospitalizations for supportive and alimentary care, procedures and tests, and analgesic management [2]. Most importantly, the severity of OM can influence dose reductions, interruptions of cancer therapy, and compromise treatment efficacy and outcomes.

There are many promising biologically-based therapeutic agents that are under clinical development for the management of oral mucositis. This review will further discuss the clinical course of OM, its pathobiology, preventative measures to combat OM, and symptomatic control during HNC treatment. Evidence-based clinical data is also discussed in respect to promising new biological targets to combat OM.

Definition, epidemiology, and clinical course

Several scales are available to characterize or grade the extent of OM. The Radiation Therapy Oncology Group (RTOG) grading is a scale of I through IV. Grade I OM includes mucositis causing mild pain and not requiring analgesics. Grade II is typified by the development of patchy mucositis or those requiring analgesics. Grade III OM marks the beginning of confluent mucositis or pain that requires narcotic analgesics. Grade IV is characterized by ulcers, necrosis, or bleeding [3,4]. The World Health Organization (WHO) OM scale is often used in clinical practice and measures both clinician-based observations (erythema, ulceration) and functional symptoms (ability to eat). It is a grade 0 (no changes) through 4 (mucositis to the extent that alimentation is not possible) scale [4]. The National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, most recent version

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4.03), is often used in clinical trials to document the side effects caused by anti-neoplastic therapies [4–6]. This scale grades OM severity from a scale of 1 to 5 and is based on pain severity and functional alteration (ability to eat) with a grade 1 indicating mild or no symptoms, grade 2 is typified by moderate pain or ulcer not interfering with oral intake, grade 3 by severe pain interfering with oral intake, grade 4 by life-threatening symptoms, and grade 5 indicating death [6]. Additionally, another scale, the OM Daily Questionnaire (OMDQ), was created to for daily patient reporting of symptoms and is often used in more modern studies [7].

The incidence of OM varies considerably in the published literature and is likely underreported given heterogeneity of reporting and scoring criteria. OM occurs in up to 40% of cancer patients that receive chemotherapy and is near ubiquitous in the treatment of head and neck cancers receiving concurrent chemoradiotherapy [8]. The severity of OM is also highly variable; it depends on both treatment modalities used (radiation cumulative dose, volume and region treated, fractionation, the use of concurrent or induction cytotoxic therapy) as well as patient-related risk factors (gender, age, lifestyle, poor dental health, comorbidities, oral microbiome, epigenetic and genetic susceptibilities) [5,9–12]. Nonetheless, the prevalence of severe or life threatening OM has been reported in up to 66–85% in patients treated for HNC with antineoplastic therapies [1,7].

The clinical manifestations of mucositis begin as painful erythema and inflammation of the affected mucosa, which can then lead to ulceration propagated by the daily mechanical insult of radiation treatment. The kinetics of OM follow a well-documented course during the treatment of HNC [5,7,9]. Radiation therapy is fractionated with small doses delivered daily to a cumulative dose of 60–70 Gray (Gy) over the course of 6–7 weeks. The first symptoms of OM typically begin to appear at cumulative doses of 10–15 Gy (weeks 1–2) of radiotherapy. These symptoms worsen in severity throughout the subsequent days to weeks. Deep, and at times, confluent ulcers in the mucosa of the tongue, gingiva, and palate can develop by 30 Gy of cumulative dose (week 3). Pain intensifies rapidly and these symptoms can last for weeks and are difficult to manage. Furthermore, ulcerations are prone to secondary infection, and especially in immunocompromised patients, this can lead to life-threatening systemic infections. Ultimately, healing in most patients occurs approximately 2–4 weeks after completion of therapy [5,7,9]. Concurrent regimens with cytotoxic systemic therapy (cisplatin, carboplatin, 5-FU) or with targeted therapy (cetuximab) are correlated with severe OM [10,12].

OM can have considerable morbidity, especially with worsening severity of symptoms [12]. Clinically, sequelae of OM include significant pain, dysphagia, dehydration, dysgeusia, anorexia, significant weight loss, electrolyte imbalances, and increased susceptibility to secondary and systemic infections. The severity of OM has been associated with compromised swallowing function, resulting in a higher incidence of feeding tube placement for nutritional support [13,14]. The severity and duration of OM can cause chronic and permanent damage to the mucosa long-term. Additionally, these symptoms can influence treatment efficacy by causing dose reductions in chemotherapy and interruption of radiation therapy [13]. In turn, dose modifications have been associated with increased cancer recurrence and decreased survival rate [14,15].

Pathobiology

Historically, OM was thought to be a result of direct epithelial injury from chemotherapy or radiation. Epithelial cells of the oral mucosa have a fast turnover rate of 7–14 days, which helps explain their susceptibility to apoptosis from cytotoxic therapy and the onset of OM approximately 1–2 weeks after treatment initiation with either chemotherapy or radiation [9,11]. However, in more recent years, research has shown the pathogenesis of oral mucositis likely to be more complex involving many overlapping steps. Sonis has proposed a multi-step biological model for chemotherapy and radiotherapy-induced oral mucositis [16].

This model begins with an initiation phase, followed by upregulation and activation, signal amplification, ulceration, and ultimately a healing phase [5,8,16–18]. The initiation phase is characterized by clonogenic cell death and production of reactive oxygen species (ROS), which ultimately results in DNA damage and apoptosis, and also activation of the innate immune response. The innate immune system responds to CRT-induced damage-associated molecular patterns (DAMPs), which helps to initiate the inflammatory cascade. In the second phase, this leads to expression of transcription factors, such as nuclear factor kappa B (NF-kB) and subsequent production of a pro-inflammatory cascade. There are many feedback mechanisms that cause signal amplification and perpetuation of the inflammation and immune response (ceramide pathways, caspase pathways, matrix metalloproteinase pathways) ultimately leading to mucosal thinning and the ulceration phase. During this phase, there can be compromise of the mucosa causing microbial colonization and susceptibility to infection, bacteremia, and possibly sepsis. Ulcers continue to send DAMP signals and likely pathogen-associated molecular pattern (PAMP) signals due to infection, which can further perpetuate and exacerbate the immune response. Once treatment culminates, the healing phase begins with increased extracellular matrix signaling, re-epithelialization, and repair of the affected mucosa [5,8,16–18].

OM preventive measures

Given its effect on quality of life, efficacy of cancer treatment, and its economic burden, a plethora of interventions have been studied in order to best prevent and manage OM. The most effective ways to minimize OM are to attempt limiting the volume of mucosa that is treated within the high dose radiation field. However, this is not always feasible without compromising treatment of the cancer. The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) has published clinical practice guidelines for mucositis prevention secondary to cancer therapy [19]. The MASCC/ISOO guidelines report the benefits of a standardized oral care protocol including brushing with a soft toothbrush, flossing, and the use of non-medicated rinses (saline or sodium bicarbonate rinses) to maintain healthy oral hygiene during treatment. The data for oral care were not strong enough to support a full recommendation; however, given the positive benefits, a meticulous oral care regimen is suggested [19].

In addition to meticulous oral hygiene, there are several promising biologically-based therapeutic agents under clinical development in the management and preventions of OM. These are highlighted in the subsequent text. A full list of ongoing and completed phase II and III clinical trials are detailed in Table 1 and Table 2, respectively (clinicaltrials.gov).

Palifermin

Palifermin, IV recombinant human keratinocyte growth factor-1, is thought to proliferate epithelial cell proliferation and restoration to combat OM. It remains the only United States Food and Drug Administration (FDA) approved drug for OM prevention and has been approved for use only in hematologic malignancies in patients undergoing total body irradiation and high-dose chemotherapy for autologous stem-cell transplantation [20]. In respect to OM in HNC, palifermin was studied in two different trials. The first trial, a randomized, placebo-controlled, double-blind study of patients with locally advanced HNC receiving definitive chemoradiotherapy (70 Gy in 35 fractions with concurrent cisplatin 100 mg/m^2 every 3 weeks), showed a lower incidence of severe mucositis (WHO grade 3 or 4) with the use of palifermin (54% *v* 69% in placebo; $P = .041$). However, opioid analgesic use, average mouth and throat soreness scores, and CRT

Table 1
Active or recruiting phase 2 and 3 clinical trials investigating oral mucositis in head and neck cancers (clinicaltrials.gov).

NCT Number	Agent	Mechanism	Phase	Country
NCT02868151	Oral Vitamin C	Antioxidant	Phase 2/3	India
NCT03237325	Dusquetide/SGX942	Immunomodulatory/Innate defense regulator	Phase 3	USA
NCT03387774	Ulinastatin	Anti-inflammatory/serine protease inhibitor	Phase 3	China
NCT03515538	RRx-001 infusion	Antioxidant	Phase 2	USA
NCT03234465	AG013 oral rinse/Lactococcus Lactis	Mucosal protectant	Phase 2	USA
NCT03720340	Recombinant Human Interleukin-11	Anti-inflammatory	Phase 3	China
NCT03689712	GC4419 infusion	Antioxidant/superoxide dismutase mimetic	Phase 3	USA
NCT01772706	Low Level Laser Therapy	Unknown/anti-inflammatory, wound healing	Phase 3	France
NCT02682992	Low Level Laser Therapy	Unknown/anti-inflammatory, wound healing	Phase 2	USA
NCT02508389	GC4419 infusion	Antioxidant/superoxide dismutase mimetic	Phase 2	USA
NCT03461354	MucoLox	Mucosal protectant	Phase 2	USA
NCT02123511	Acetylcysteine	Antioxidant	Phase 2	USA

compliance were not different between treatment arms [21]. A multicenter, double-blind, randomized, placebo-controlled trial in 186 patients with stages II to IVB HNC evaluated the use of palifermin for OM during adjuvant CRT, also [22]. Patients in this trial received a conventionally-fractionated cumulative dose of 60 or 66 Gy after a complete or incomplete resection, and those with an incomplete resection received concurrent cisplatin (100 mg/m^2) every three weeks. The use of palifermin during postoperative CRT reduced the incidence of severe OM (51% *v* 67% placebo, P = .027). Furthermore, weekly palifermin decreased the median duration of severe OM (4.5 v 22 days; P = .037) and prolonged the median time to develop severe OM (45 *v* 32 days; P = .022). Palifermin remains extremely, expensive, however, with costs estimated up to $30,000 for administration during lymphoma stem cell transplant treatment [23]. Also, there are concerns that this class of drug can potentiate tumor growth and mitigate cancer treatment efficacy.

Dusquetide

Dusquetide (SGX942) is an Innate Defense Regulator (IDR) that binds to the protein p62 and is able to modulate the innate immune response to PAMPs and DAMPs. Dusquetide was hypothesized to help prevent OM by decreasing the proinflammatory response and signal amplification of the innate immune system, which is implicated in the pathogenesis of OM. Dusquetide administration reduced the duration of OM by approximately 50% in both mice and hamster animal models [24]. These results were further validated in a randomized phase 2a clinical trial in which locally advanced HNC patients received between 55 Gy and 72 Gy radiation with concurrent cisplatin (either weekly 30–40 mg/m^2 or 80–100 mg/m^2 every three weeks). Patients that received 1.5 mg/kg of dusquetide had a 50% reduction in the median duration of severe OM in comparison to placebo administration (18 *v* 9 days). Interestingly, treatment with this novel IDR also reduced non-fungal infections [24]. These results were substantiated with longer follow up of 12 months, and dusquetide administration was also possibly correlated with accelerated tumor resolution. Further studies with larger numbers, however, are needed to substantiate a possible anti-tumor ancillary effect with dusquetide [25]. These are currently underway.

GC4419

GC4419 is a manganese-based low molecular weight molecule that mimics the activity of superoxide dismutase (SOD) enzymes. Implicated in the pathogenesis of OM is the excessive formation of ROS (initiation phase), and as such, a selective SOD mimetic as a way of counteracting superoxide *in vivo* is an attractive drug target. In a Phase 1b/2a multicenter trial of GC4419, a maximum tolerated dose was not reached and only two dose-limiting toxicities, grade 3 gastroenteritis and vomiting with hyponatremia at the highest dose of the drug, were observed [26]. GC4419 was administered to patients undergoing definitive CRT with concurrent cisplatin for oral cavity and oropharyngeal cancers by a 60 min daily IV infusion prior to each radiation treatment. Severe OM occurred through 60 Gy of treatment in 4 of 14 patients (29%) with median duration of only 2.5 days and a median time to onset of > 50 days [26]. A Phase 2b trial is currently in progress to further elucidate the role of GC4419 with longer follow up (clinicaltrials.gov identifier: NCT02508389).

Clonidine Lauriad

Clonidine Lauriad is a mucoadhesive buccal tablet that reduces NF-κB activation and diminishes the downstream activation of proinflammatory cytokines. In a multicenter phase 2 study, clonidine Lauriad

Table 2
Completed phase 2 and phase 3 clinical trials investigating oral mucositis in head and neck cancers (clinicaltrials.gov).

NCT Number	Agent	Mechanism	Phase	Country
NCT02630004	Melatonin Oral Gel 3%	Antioxidant	Phase 1/2	Spain
NCT02430298	Oral Melatonin capsule/suspension	Antioxidant	Phase 2	Thailand
NCT02397486	Pentoxifylline & Vitamin E	Antioxidant	Phase 2	Egypt
NCT02324335	Brilacidin oral rinse	Anti-microbial/Defensin mimetic	Phase 2	USA
NCT02303197	Oral Chining decoction	Herbal, Anti-inflammatory	Phase 3	China
NCT02085460	Rebamipide liquid	Anti-inflammatory/Anti-oxidant	Phase 2	Japan
NCT02013050	Dusquetide/SGX942	Innate defense regulator	Phase 2	USA
NCT01941992	Samital extract	Herbal, antioxidant, anti-inflammatory	Phase 2	Italy
NCT01439724	Low Level Laser Therapy	Unknown/anti-inflammatory, wound healing	Phase 3	Brazil
NCT01400620	IZN-6N4 oral rinse	Herbal, anti-inflammatory	Phase 2	USA
NCT01385748	Clonidine Lauriad	Anti-inflammatory	Phase 2	USA
NCT01149642	Oral dietary supplement	Immunomodulatory	Phase 3	France
NCT00756951	SCV-07 infusion	Immunomodulatory	Phase 2	USA
NCT00289003	Soluble Beta-1,3/1,6-Glucan	Immunomodulatory	Phase 2	Germany/UK
NCT00101582	Palifermin	Epithelial cell proliferation	Phase 3	USA/Canada/EU

was applied to the gum 1–3 days prior to radiation and continued once daily throughout the course of CRT [27]. Severe OM (WHO grade 3 or 4) developed in 45.3% of patients in the clonidine MBT group and in 60% of patients in the placebo group (P = .064). The median radiation dose of developing severe OM was 60 Gy for the clonidine group and 48 Gy for the placebo group (HR = 0.754 [0.484;1.175]; P = .211) [27]. Though the primary endpoint in this study did not reach significance, further studies are necessary to understand the full impact of clonidine in helping prevent OM.

Benzydamine

Benzydamine is a nonsteroidal anti-inflammatory drug that inhibits proinflammatory cytokines including TNF-a. In a double-blind trial, 145 patients receiving cumulative radiation doses of up to 50 Gy were randomly assigned to benzydamine 0.15% oral rinse 4–8 times daily or placebo [28]. The use of benzydamine oral wash reduced erythema and ulceration by 30% (P = .006) and also significantly delayed the use of systemic analgesics (P = .05). Benzydamine was not effective in the context of accelerated radiation doses (2.2 Gy/day), however [28]. Similarly, in another double-blind trial evaluating the use of benzydamine for the prevention of radiation-induced OM in the treatment of HNC, found a positive benefit [29]. The frequency of severe mucositis (≥ grade 3) was found to be 43.6% in the benzydamine group and 78.6% in the placebo group (P = .001) and severe mucositis was 2.6 times more likely in the placebo group [29]. As a result, the MASCC/ISOO guidelines recommend the use of benzydamine in patients receiving moderate-dose radiation therapy (up to 50 Gy) without concurrent chemotherapy [19]. Other studies also note a benefit with benzydamine wash with higher doses of radiation of > 50 Gy, as well [30]. These studies support the use of benzydamine prophylactically, however, it remains unclear if benzydamine is beneficial in the CRT setting in the treatment of HNC.

Low-level laser therapy

Low-level laser therapy (LLLT) is a local application of a monochromatic, narrow-band, light source. Though the mechanism of LLLT is largely unknown, studies in animal models suggest that LLLT promotes wound healing and has an anti-inflammatory effect [31,32]. Additionally, several trials have observed that pretreatment with laser therapy help prevent and also lessen the severity of OM. In a triple-blinded trial, 221 patients undergoing a definitive CRT to 66 Gy with concurrent cisplatin (every 3 weeks) for oropharyngeal or oral cavity cancers were assigned to either daily laser or sham treatment [33]. LLLT (HeNe, λ = 632.8 nm) was delivered daily to six oral cavity sites (excluding cancer site) prior to radiation for 45 days. LLLT decreased the incidence of grade 3 or 4 mucositis at the end of CRT (23% v 69%). Laser therapy also decreased average pain scores, analgesic usage, and the need for total parenteral nutrition (TPN) [33]. A systematic review with meta-analysis of the effect of LLLT on OM caused by cancer therapies also reported that LLLT significantly reduces the relative risk of developing OM, and also reduces pain and duration [34]. The MASCC/ISOO guidelines, thus, recommend LLLT use for the prevention of OM in the setting of hematopoietic stem cell conditioning regimens, and LLLT is suggested for use in the prevention of OM in patients receiving HNC without concomitant chemotherapy [19]. Regarding safety, the possible impact on tumor cells is unknown since results from in vitro studies showed conflicting effects of low-level laser on malignant cells. Therefore, vigilance is warranted, and it is recommended not to directly treat the tumor area [35].

Natural agents

The use of natural herbal remedies in cancer treatment has gained force in the last few decades and has become an emerging research area. In the context of OM as a result of antineoplastic therapies in the treatment of HNC, there are a number of agents that have been studied and are currently under investigation. These include plant extracts, Manuka honey, Vitamin A, aloe vera, chamomile, glutamine, and many others [36]. The current data is conflicting in the treatment and prevention of OM with some of these agents, however. Further randomized, controlled, clinical trials are needed to further elucidate a possible role for natural agents in OM.

Symptomatic treatment

Symptomatically, OM is managed with optimization of dentition before treatment, maintenance of a meticulous oral hygiene during treatment, dietary modification, treatment of any secondary infections, and analgesics. OM management requires a multidisciplinary approach with staff dieticians, dentists, nursing, speech and swallow evaluations, and pain management physicians. As previously mentioned, an oral care regimen is endorsed by the MASCC/ISOO clinical guidelines [19]. No guidelines are provided for the individual use of mouth rinses, however evidence suggests against the use of chlorhexidine mouthwash for OM prevention in patients receiving radiation to the head and neck [19]. As a patient undergoes CRT with curative intent, supportive measures such as nutrition, hydration, and electrolyte support are requisite. The patient is at extreme risk for nutritional depletion, cachexia, dysphagia and odynophagia, and possibly refeeding syndrome [37].

Pain management is highly important and plays a crucial role in improving quality of life during HNC treatment. In the most recent MASCC/ISOO guidelines, patient-controlled analgesia with morphine is recommended only in the symptomatic treatment of OM in patients undergoing hematopoietic stem cell transplants [19]. Analgesia, however, is requisite at some point during the treatment of HNC and available options are anti-inflammatories, short and long-acting opioids, and transdermal fentanyl, with escalation depending on individual patient needs and frequent multi-disciplinary assessment [3,4,37].

Mouthwashes or mouth rinses are typically used in many clinical centers, either formulated with morphine, or “magic” or “miracle” mouthwashes formulated with a mixture of topical anesthetic (typically 2% lidocaine), antacid (magnesium aluminum hydroxide), and diphenhydramine. These “magic” mouthwash cocktails differ institutionally and can also incorporate steroids and anti-micotics. A newly published phase III trial of patients undergoing radiation for HNC showed that a mouthwash with diphenhydramine/lidocaine/antacid demonstrated a statistically significant decrease in pain associated with oral mucositis compared with placebo (Alliance A221304) in the 4 h after single dose administration. However, despite statistical significance, the predetermined effect size was deemed to be less than clinically important as defined by the authors [38]. Also, there was no difference in the use of supplementary analgesics after the 4 h between the “magic” mouthwash and placebo arms, suggesting that pain relief was short-lived. A pilot study of HNC patients treated with CRT of twenty-six patients, evaluated the use of a “magic” mouthwash formulation of viscous lidocaine/magnesium aluminum hydroxide/diphenhydramine in comparison to a 2% morphine mouthwash [39]. Patients randomized to both groups were instructed to use 15 ml of the oral rinse every three hours on an as needed basis, to orally swish the rinse for two minutes, and to expectorate afterward. The patients in the morphine group experienced a shorter duration of severe pain in comparison to the “magic” mouthwash, and this effect was significant after thirty minutes and lasted several days. The patients receiving morphine mouthwash also required less supplemental systemic analgesics than the “magic” mouthwash cohort [39]. The MASCC/ISOO panel suggests the usage of 2% morphine in patients undergoing CRT treatment for HNC [19]. Further studies are needed to fully compare morphine mouthwashes to “magic” mouthwash formulations in order

to be able to validate one's utility over the other.

Another mouthwash or rinse used for topical pain control of OM in HNC is doxepin. Doxepin is a traditional tricyclic antidepressant with analgesic and anesthetic properties when used topically. In a single-arm trial, a 5 ml solution of doxepin (5 mg/ml) oral rinse was shown to reduce the severity and frequency of OM in HNC patients [40]. These results were validated in a multicenter, randomized, double-blind, placebo-controlled trial with a crossover phase, which evaluated 155 patients undergoing radiotherapy to a planned minimum dose of 50 Gy for HNC (with or without concurrent chemotherapy) [41]. Patients were administered a single dose of doxepin (25 mg in 5 ml) or a placebo solution. Doxepin treatment significantly reduced pain secondary to OM. Doxepin also was associated with greater drowsiness and an unpleasant taste, but nonetheless, patients opted to continue treatment with doxepin [41]. The A221304 phase III trial compared OM pain reduction and adverse effects of doxepin mouthwash to a placebo and also a "magic" mouthwash to a placebo in HNC patients undergoing definitive RT (including parts of the oral cavity and oropharynx). Patients that received doxepin mouthwash had a statistically significant decrease in pain associated with oral mucositis compared with placebo (also seen in the "magic" mouthwash vs placebo cohort) [38]. However, the mean difference of pain reduction with doxepin use, though statistically significant, was not deemed a "clinically important difference" by the authors due to a predetermined effect size of pain reduction by the area under the curve of 3.5 points [38]. As seen in the "magic" mouthwash group, there was no difference in the need for analgesic use in patients that received doxepin, also suggesting that the pain relief was short-lived. Importantly, however, the use of doxepin mouthwash vs. placebo was associated with significantly worse drowsiness, unpleasant taste, and stinging or burning, which are important side effects to consider in patients already at risk for pain and dysgeusia from treatment [38]. Nonetheless, current MASCC/ISOO guidelines suggest the use of a 0.5% doxepin mouthwash to treat pain due to oral mucositis [19]. The benefit of doxepin, however, compared to opioids or "magic" mouthwash remains unknown, and its role awaits further investigation.

It is important to note that there are many other agents that have also been studied in the prevention and symptomatic management of OM in HNC that are beyond the scope of this review. These include the use of sucralfate, antimicrobial lozenges, iseganan antimicrobial mouthwash, misoprostol, granulocyte-colony stimulation factor (G-CSF), and pilocarpine in the treatment of OM secondary to HNC therapies. Evidence-based recommendations do not support use of these agents at this time [19].

Study design and assessment of mucositis

OM is difficult to objectively quantify with variability between clinician observers and in patient-reported outcomes. Because several scales to assess OM exist, it is often difficult to interpret the literature and clinical impact of OM, especially from study to study. The previously mentioned OM assessment scales include the RTOG, WHO, NCI-CTCAE, and OMDQ systems. The WHO scale has been used most extensively in studies with grades 3 or 4 as clinical endpoints of the efficacy of intervention (ulcers with erythema and inability to swallow food to mucositis resulting in inability of alimentation) [4]. The NCI-CTCAE v4.3 takes into account patient-reported variables (pain, dysphagia, alimentation), and thus incorporates changes in QOL for the patient and has been used in clinical trial design since 1998 [6]. Over time, it is difficult to compare outcomes when trials have used different scoring criteria, and even more difficult to ascertain what constitutes clinically significant or severe OM from different studies. Furthermore, the NCI-CTCAE and RTOG scoring criteria have undergone change and revision several times, further complicating accurate and clinically meaningful comparisons between studies using different assessment tools.

In addition to the quality of OM assessment and objective scoring, it is important to take into account the frequency of scoring in trials, which may more precisely reflect clinical efficacy. Less frequent evaluations of OM may severely underestimate its incidence and severity, and a twice to thrice weekly evaluation is suggested when a patient is undergoing concurrent CRT [42].

Conclusions

OM secondary to antineoplastic therapies in HNC continues to represent a significant oncological challenge. Management of OM has focused on palliation and symptom control, however poor pain control may be achieved even through the appropriate prescription of analgesics [7]. Thus, this further emphasizes the importance of developing treatment strategies that biologically target the pathobiology of OM in addition to symptom management. A number of these were discussed in the preceding text, and many more targeted agents are in the early stages of clinical evaluation. Some of these include brilacidin (clinicaltrials.gov, NCT02324335), a defensin mimetic with antimicrobrial properties, and RRx-001 (clinicaltrials.gov, NCT035115538), a likely chemoradioprotector that may mediate oxidative damage. Targeting immune response pathways in the pathobiology of OM holds promise of prophylaxis against the severity of symptoms and reduction of OM morbidity. Importantly, a reduction in OM morbidity may influence treatment tolerance, compliance, and quality of life. Future trial design will also incorporate more objective and perhaps more frequent monitoring of OM symptoms.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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