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Treatment for Oral Mucositis—Current Options and an Update of Small Molecules Under Development

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Opinion statement

Despite its history as one of the most impactful toxicities associated with cytotoxic cancer therapy, oral mucositis (OM) remains an unmet clinical need which affects hundreds of thousands of patients. Descriptions of its complex pathogenesis have provided mechanistic targets which are being exploited to develop an effective therapeutic intervention. Favorable results of recently completed clinical trials in which agents focused on interrupting the early stages of the mucositis biological cascade were assessed provide reason for optimism, not only for oral mucositis but also for halo indications which share its pathobiogenesis.

Introduction

Oral mucositis (OM) remains a significant side effect of cytotoxic anti-cancer chemotherapy and radiotherapy. Of the 1.8 million patients who will be diagnosed with malignancies this year in the USA, almost half will suffer some degree of mucositis. For a lucky minority, OM manifestations will be limited and easily controlled transient mouth pain. But for many, mucositis will be of such severity as to cause major diet modifications and weight loss, necessitate opioid analgesics, require supplemental nutrition, and disrupt optimal cancer therapy [1]. For patients whose chemotherapy regimens (CT) are myelosuppressive, mucositis poses the additional threat of bacteremia and sepsis as it creates systemic portal of entry for microorganisms [2]. Patients with OM are

more likely to have negative treatment outcomes, poorer quality of lives, and incur more costs than patients who do not develop the condition [3].

OM has a predictable clinical trajectory that is determined by cancer regimen [4]. CT-associated OM becomes clinically apparent about 4 days after infusion when manifestations of mucosal atrophy, primarily sensitivity and erythema are noted. The tissue continues to deteriorate, and ulceration occurs a few days later, peaking at 2 weeks and persisting for 1–2 weeks after which it typically resolves spontaneously. It is the ulcerative phase that is most painful and associated with poor health outcomes. In contrast, OM associated with radiation regimens (RT) used to treat head and neck cancer (HNC) has a slower onset in response to the cumulative effects of daily fractions of 2 Gy (ref). While patients complain of burning mouth after a week of treatment, ulceration and more severe, opioid-requiring pain usually develops around week 4 and may extend over subsequent weeks, ultimately healing 4–6 weeks after the completion of RT (usually patients undergo 7 weeks of RT).

Even with aggressive cancer regimens, patients are at equal risk of developing OM. Germ line genomics are thought to be especially important in predisposing patients to OM, although epigenetics, the microbiome and metabolomics may also contribute [5•].

Current management practices for oral mucositis

To date, OM management has focused on symptom control using topical or systemic analgesics and the application of barrier agents to cover injured mucosa as a salve or ointment might cover irritated skin [6]. Such devices have been available for years and are most effective during early phases of OM when symptoms are most mild. Examples of these agents are GelClair, MuGard, and sucralfate suspension [6]. Magic mouthwash, a generic term to describe a class of institutionally developed rinses which include a coating agent such as kaopectate or milk of magnesia as a base. A variety of additives (usually based on institutional folklore) complete the suspension and include options like lidocaine, anti-fungals, topical steroids or antibiotics the utility of these formulations is marginal [7, 8].

Tooth remineralizing solutions such as Caphosol have been aggressively marketed as mucositis interventions. Results of clinical trials in different patient populations (stem cell transplant recipients and patients being treated with chemoradiation [CRT] for HNC) failed to confirm their value [9, 10].

Cryotherapy has been advocated as an OM intervention for certain CT regimens, including conditioning regimens prior to stem cell transplant [11]. Typically delivered as ice chips held in patients' mouths during infusion, it is believed that cold-induced vasoconstriction limits tissue levels of stomatotoxic agents and thereby reduces mucosal damage (ref). An ice chip-alterative cold delivery device has been developed, is commercially available and being studied in an ongoing clinical trial (A Trial Testing Chemo Mouthpiece Device and Best Supportive Care Against Best Supportive Care Only for Symptoms of Oral Mucositis in Patients Receiving Chemotherapy; NCT04595838).

Studies assessing low level laser therapy (photobiomodulation) to control OM have produced a substantial body of literature comprised mostly of investigator-initiated, single institution trials. Variations in technique and energy parameters have been problematic and results are not uniform [12, 13]. Inconsistent reports relative to PBM's effect on tumor response raise unanswered questions regarding its impact on long term effects, not dissimilar to concerns

associated with palifermin [14]. A multicenter trial of 69 patients is currently beginning (NCT 03972527; Prospective, multicenter, randomized, double-blind, placebo-controlled, adaptive sample size, two-treatment parallel, pivotal clinical study).

Past strategies and interventions—lessons learned

A role for the oral microbiome's role in mucositis pathogenesis has been speculated following the observation that cancer therapy results in an alteration in the oral flora's composition [15]. The finding that the oral bacterial load increased subsequent to the development of OM-associated ulceration lead to speculation that secondary colonization might be important in extending the duration or increasing the intensity of existing mucositis [4].

In response to a hypothesis reduction in oral bacteria load would favorably impact OM, a number of clinical trials were conducted in the early 2000s. In a double-blind, randomized, placebo-controlled international study, iseganan was evaluated in patients receiving aggressive myeloablative, stomatotoxic chemotherapy. Iseganan is a structured analog of porcine-derived protegrin and broad-spectrum antibiotic having extended salivary antimicrobial activity and good mucosal adherence. The trial randomized 323 patients [16]. A 5 times daily swish and swallow dosing regimen beginning on the day of infusion and continuing for 21–28 days resulted in a trend ($p < 0.067$) toward a reduced incidence of ulcerative mucositis (using CTCv2 criteria). While iseganan did not modify OM development, its effect was observed during the later stages of mucositis when secondary colonization would be expected to be most impactful.

Randomized studies of antimicrobial strategies have produced less favorable results in patients being treated with RT for HNC. In one of the largest mucositis clinical trials ever completed ($n = 545$ patients), iseganan was assessed in HNC patients being treated with RT. Iseganan, administered in the same swish and swallow formulation noted above, failed to impact the severity or incidence of mucositis [17].

Other anti-microbials have also been ineffective in the same patient group. A 1994 randomized trial ($n = 52$ patients) found that topical application of chlorhexidine worsened the course of OM [18]. Two other unsuccessful studies evaluated 4 antimicrobial troches. A lozenge comprised of bacitracin, clotrimazole, and gentamicin failed to impact time to onset or extent of mucositis in a two-arm, randomized study of 137 patients receiving radiotherapy for a range of HNCs [19]. A differently formulated lozenge (polymyxin, tobramycin, amphotericin) failed to prevent the development of severe mucositis in a similar group of patients [20].

The disparity in outcomes of microbial manipulation observed between patients receiving CT those receiving RT for HNC points to OM's multifactorial nature and the fact that OM's pathoetiology is impacted by the patient's systemic state. Before the biological complexity of mucositis was realized, it was believed to be simply the unavoidable consequence of non-specific epithelial basal stem cell destruction caused by the cytotoxic effects of CT or RT [4]. Early mechanistic approaches to OM intervention were based on countering direct non-specific basal cell destruction, for which growth factors such as

keratinocyte growth factor-1 (KGF1; palifermin, Kepivance) and fibroblast growth factor-20 (Velafermin) were representative examples.

Palifermin is the only drug or biological approved as a mucositis intervention in the USA. While its use is restricted to OM prevention in patients with hematologic malignancies receiving conditioning regimens in preparation for hematopoietic stem cell transplant, it has also shown to be efficacious in patients being treated with CRT for HNC [21–23]. It was hypothesized that palifermin's ability to stimulate keratinocyte proliferation would result in mucosal hyperplasia, thereby increasing tissue tolerance to subsequent challenge, minimize atrophy and thus reduce the likelihood of ulcer development at best, or at least reduce its duration [24]. The major challenge with the approach was the concern that the proliferation noted in normal tissue would be replicated in KGF1-receptor-bearing tumor cells and negatively impact their behavior. Critically, any mucositis intervention cannot risk impugning anti-cancer therapies or negatively impact tumor behavior.

Since palifermin's early development in the 1990s, much has been learned about mucositis pathogenesis. We now understand that direct non-specific toxicity of epithelial basal cells is not the major biological driver of OM, rather, injury precipitated by a CT- or RT- induced biological cascade which terminates with the release of a range of damaging mediators [4, 25]. In fact, palifermin's stimulation of epithelial stem cell proliferation is but a small component of its diverse biological potential as it initiates a range of actions which are consistent with tissue protection based on known pathways associated with mucositis [26]. Especially relevant to its observed OM efficacy are its effects on the oxidative stress response, the innate immune response, and pro-inflammatory cytokines. KGF1 increases Nrf2 activity, effects TLR4 and impacts pro-inflammatory cytokine levels. Each of these actions, as discussed below, has been used as the basis for drugs currently under development for OM.

Current mechanistic targets for mucositis being investigated for oral mucositis (Table 1)

Biological targets most likely to impact the OM's course and severity of are those which occur early in its pathogenesis. Thus, one must consider pathways during the initiation and/or amplification phase as being particularly vulnerable [4, 27•, 28]. Indeed, agents which focus on downstream OM mediators are often too little and too late to block or reverse the snowballing tissue destroying cascade that characterizes OM development. This is especially true in the case of radiation-associated mucositis where the biological challenge is ongoing with each radiation fraction.

The significant unmet clinical need for a mucositis intervention in a growing patient pool has stimulated the quest for a successful treatment. Further catalyzing the commercial enthusiasm for OM are its estimated current and growing market size (over one billion USD; [29]), and the recognition by regulatory agencies of its as impact on patients' quality of life and ability to tolerate optimum cancer treatment. Consequently, many agents in development have obtained fast-track and/or breakthrough status. Additionally, OM's shared pathobiology with a myriad of other regimen-related toxicities (i.e., radiation-

Table 1. Small molecules under development. The table notes the company developing each agent, the NCT identifier (ClinicalTrials.gov) for those agents tested in the USA, the principal biological target, and study phase. Those trials that have been completed and reported are annotated as (C), those ongoing as (A). EU indicates the study is being performed only in Europe

Sponsor	NCT identifier	Molecule description/target	Phase
Galera	NCT02508389	Superoxide dismutase mimetic	2b (C)
Galera	NCT03689712	Superoxide dismutase mimetic	3 (A)
Galera	NCT04529850	Superoxide dismutase mimetic	2 (A; EU)
Prothex	NCT03515538	Nrf2	2a (C)
Soligenix	NCT03237325	Innate immune response	3 (A) analysis pending
Soligenix	NCT02013050	Innate immune response	2a (C)
Enzychem	NCT03200340	Innate immune response	2 (A)
Innovation	NCT02324335	Defensin mimetic	2 (C)
IZUN	NCT1400620	NF-κB	2 (C)
Onxeo/Monopar	NCT01385748	NF-κB	2 (C)
Supportive Therapeutics	N/A	Nrf2	1b (A)

induced dermatitis and proctitis, fibrosis, and pneumonitis) suggests that a drug that is effective in preventing or attenuating mucositis will likely be efficacious for other indications.

Common features of drugs under development and considerations for assessment

While several exploratory, investigator-initiated, one-center studies are ongoing, the following discussion focuses on small molecules in clinical development by the pharmaceutical industry.

By far, the most common indication being evaluated in clinical trials is OM associated with standard concomitant chemoradiation (CRT) regimens used to treat mouth, oropharyngeal and nasopharyngeal cancers. The uniformity in OM incidence and trajectory associated with CRT provides investigators assurance in power calculations and a threshold for results with clinical meaningfulness. Severe forms of OM occur in 60%–70% of CRT-treated patients. Since treatment requires daily weekday hospital visits clinical trial compliance is enhanced. Additionally, the severity of symptoms, OM's impact of quality of life and nutrition, and health resource use are measurable endpoints. One of the challenges in this patient population, especially for studies in which incidence is the primary efficacy endpoint, is the extended cancer treatment period (typically 7 weeks). For study drug formulations which are administered topically or by mouth, patient oral or swallowing discomfort (especially in placebo-recipients) and chemotherapy-induced nausea risk contributing to study discontinuation. Conversely, the necessity of IV infusions among patients who receive parental formulations presents a different set of challenges. In the current clinical trial

environment, formulations delivered by all routes are being successfully evaluated.

Key factors in assessing and comparing trial outcomes

Historically, one of the challenges in assessing and comparing clinical trial outcomes was the lack of a standardized measurement of mucositis severity. Many grading scales are available [30]. The most common (WHO, CTCAE, and RTOG) were originally developed as measures of adverse events. While WHO OM grading criteria have remained consistent since its inception, CTCAE and RTOG scales have undergone periodic changes thereby hindering comparisons of study outcomes. Currently, the WHO scale is the gold standard and is most common in drug development trials. Clinician assessment is a critical component of the WHO scale. Hence, assuring that individuals charged with this responsibility receive uniform and effective training with competency measurements is required to optimize inter-observer and inter-site outcome consistency [31, 32].

Inclusion criteria for trials typically include a requirement for pathologically confirmed diagnoses of squamous cell carcinoma of the oral cavity (OC) and oropharynx (OPC). Depending on the trial, tumors of the nasopharynx and hypopharynx may be allowed. Most important is the need to assure that studied patients receive equivalent radiation doses to anatomic sites at risk for OM. This objective is typically met by mandating that a minimum number of at-risk sites are in the radiation field which is planned to receive a cumulative dose of at least 50 Gy to 55 Gy, and further assured by independent review of the radiation plan.

In agreement with treatment guidelines, the overwhelming number of patients who receive RT for HNC receive concomitant chemotherapy as a radiosensitizer in which cisplatin is the agent of choice, administered as weekly infusions of 40 mg/m^2 or tri-weekly high-dose infusions of 80–100 mg/m^2 [33]. The low-dose regimen is the newer of the two, and its use was motivated but its lower rate of toxic events, particularly cisplatin-associated renal toxicity. The impact of treatment regimen on tumor response is mixed and may be dependent on whether the primary tumor site is in the OC or OPC.

Whereas the prevalence of OC in the USA is declining, HPV-related OPC is on the rise. The OPC cohort, especially non-smokers, has a high response rate to CRT [34]. OC and OPC smokers do less well. Data suggest that for OC, the tri-weekly high-dose regimen may be superior, whereas for OPC, tumor outcomes between the two regimens are equivalent [35, 36]. There may be some variability in mucositis risk between the two regimens, although that is unclear. Typically, OM clinical trials allow both treatment regimens; typically, these are stratified in the randomization and analyses. As reported in a large phase 2 trial, OPC was markedly more common than OC and the low-dose regimen was used in almost two-thirds of cases [37•].

Small molecules targeting oxidative stress

Oxidative stress induced by radiation and/or chemotherapy is a primary initiating event in both direct DNA damage and the more critical indirect pathways

in the pathobiological cascade leading to mucosal injury. Two pharmacological strategies to attenuate ROS impact are being evaluated, supplementation of physiological antioxidant defense mechanisms and stimulation of transcription factors which induce naturally occurring ROS control.

Superoxide dismutase mimetic: avasopasem manganese

Oxidative stress is a constant threat to cell survival and health. Among the intrinsic mechanisms effectively mitigating this challenge, the superoxide dismutases (SODs) play a compelling role in maintaining oxidative homeostasis [38]. However, in the context of regimen-related toxicities, particularly those associated with fractionated radiation schemes, the accumulating excessive and repeated generation of superoxides overwhelms the ability of naturally occurring anti-oxidative SOD enzymes to sufficiently control the challenge. Consequently, superoxides are is a critical driver of cancer regimen-related tissue damage.

One clinical strategy to alleviate this problem is the provision of SOD supplementation, an approach that was attempted using naturally occurring SODs over two decades ago [39]. However, characteristics of naturally occurring dismutases limited their utility and efficacy. In response, SOD mimetics were developed which, in addition, to having superior qualities are at least as active than as naturally occurring enzymes.

An early pre-clinical study [40] suggested the efficacy of one such mimetic. An analog, avasopasem manganese, has since been developed for OM mitigation by Galera Therapeutics.

In a 223-patient, double-blind, randomized, placebo-controlled phase 2b clinical trial in patients with (locally advanced) nonmetastatic squamous cell carcinoma of the head and neck receiving concurrent radiotherapy (NCT02508389 available at clinicaltrials.gov), avasopasem (GC4419), 90 mg/day, significantly reduced the duration of severe oral mucositis (SOM) by 92%, compared to placebo, including a reduction in median SOM duration from 19 to 1.5 days. The incidence of SOM and the incidence of Grade 4 OM were also significantly reduced (by 34% and 47%, respectively) in patients treated with avasopasem. No significant safety signals were observed, demonstrating avasopasem is well-tolerated when added to a standard radiotherapy regimen [37•]. The drug is now in a phase 3 trial (NCT03689712) in the United States North America and a phase 2 open-label study in Europe (NCT04529850), both for reduction of SOM, and a phase 2, US open-label study for reduction of chemoradiotherapy esophagitis (NCT04225026).

Nrf-2 modulators: RRx-001 and ST-617

In contrast to Galera's approach, two companies have recently completed early clinical trials of drugs which target the transcription factor Nrf2. Nrf2 is a robust controller of an array of genes, including those involved in the physiologic response to oxidative stress [41]. Specifically, Nrf2 stimulation activates genes associated with the production of anti-oxidative enzymes.

In a small phase 2a trial of Prothex's RRx-001, a dinitroazetide (NCT03515538) was evaluated in patients receiving concomitant chemoradiation for cancers of the mouth or oropharynx, at 12 US sites [42]. The trial was open label and compared three different dosing schedules of study drug (n = 11–13/group) against a standard-of-care control arm (n = 10). In all arms, the first dose was administered 2 weeks prior to the first radiation dose. Rx-001 was

delivered by IV infusion after mixing with patients' blood. Overwhelming study patients were being treated for OPCs (71%). Although the cohort sizes were small, efficacy trends favored RRx-001-treated patients vs. placebo controls. Median duration of SOM from the start to the last day of radiation (through 70 Gy) was reduced in the test arms (5 days, 13 days, 9 days) compared to the placebo cohort (duration 23 days). Rx001 also increased time to onset of SOM from a median of 26 days in the placebo arm to 33 to 38 days in the active arm (pooled 36 days). Of the 3 treatment schedules tested, the one in which RRx-001 was delivered only prior to CRT favorably affected incidence of most severe forms (grade 4) mucositis. Whereas 30% of patients in the placebo cohort developed grade 4 mucositis (unable to eat or drink anything), none of the patients in the pre-treatment only arm was so impacted. Consequently, gastrostomy use in the pre-treatment only population was reduced compared to placebo patients (60% vs. 33%). Further clinical trials are planned.

Using a rinse/swallow formulation, Supportive Therapeutics evaluated the safety, pharmacokinetics, pharmacodynamics and efficacy of their small molecule Nrf2 activator, ST-617, in an ongoing small, multi-national phase 1b dose-finding study (phase 1B, international, open-label trial to evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of ST-617 for the attenuation of Oral Mucositis in patients receiving Chemoradiation for Head and Neck Cancer) in which patients were treated with three doses of ST-617 [43]. As of October 2020, a total of 16 patients receiving concomitant chemoradiation for OC and OPC were enrolled in 3 dosing arms, 50 mg (n = 7), 100 mg (n = 6), and 150 mg (n = 3; ongoing) at study sites (n = 7) in South Africa and Australia. Based on recently reported results (ESMO; ASTRO), it appeared that ST-617 was safe and well-tolerated. Analyses of tissue (oral mucosa) and blood demonstrated that ST-617 successfully reduced ROS and RNS in a dose-dependent manner. Promisingly, compared to historical controls, patients receiving the 50 mg and 100 mg doses of ST-617 demonstrated attenuation of SOM. Results of the 150 mg cohort are pending. A phase 2 trial is planned.

Small molecules targeting the innate immune response

The innate immune response is a key element in the initiation phase of oral mucositis. Two small molecules are in development for which the innate immune response is specifically targeted.

Dusquetide

Dusquetide, a small molecule under development by Soligenix, Inc., modulates the innate immune response by binding to p62 (SQSTM1) thereby impacting innate immune activation by DAMPS, PAMPS, and CRAMPS [44•] and is in late clinical development. It is administered as a 4-min IV infusion, twice weekly, beginning 3 days after the first radiation dose and continuing for 2 weeks following the last dose of radiation therapy. Results of a multicenter phase 2a study [44•] in which 108 patients were randomized to 3 efficacy cohorts (PL, 1.5 mg/kg, 6.0 mg/kg) demonstrated a 50% reduction in SOM duration in patients receiving the lower dose (1.5 mg) (9 days; placebo 18 days; n = 38).

In contrast to data reported in Galera's phase 2 study in which SOM was unaffected by the choice of cisplatin regimen, the phase 2 dusquetide results found that both the duration and incidence of SOM was greater in patients for whom their chemoradiation regimen included high-dose cisplatin (80 mg/kg-100 mg/kg) compared to those who received weekly low-dose cisplatin.

Enrollment was recently completed for a phase 3 trial of dusquetide (A Pivotal, Double-Blind, Randomized, Placebo-Controlled, Multinational Study of SGX942 (Dusquetide) for the Treatment of Oral Mucositis in Patients Being Treated With Concomitant Chemoradiation for the Treatment of Squamous Cell Carcinoma of the Head and Neck) (NCT03237325) which enrolled 268 patients at 53 study sites in the USA and Europe. Patients in the active arm received the best informed by the phase 2. Unique to the phase 3 study design was the limitation of enrollment to patients whose concomitant chemotherapy was restricted to tri-weekly, high-dose cisplatin (80–100 mg/kg), which contrasts with other trials which also include low-dose weekly cisplatin regimens. Duration of severe oral mucositis, rather than incidence, is the primary efficacy endpoint. Topline results are expected in late 2020.

EC-18

EC-18 is a synthesized monoacetyldiglyceride based on a naturally occurring molecule that is common in seed oils, milk fat and an extract isolated from the antlers of silk deer. The naturally occurring compound has a long history as a component of oriental medicines. EC-18 has been reported to have a range of biological activities [45], many of which are consistent with potential targets for radiation- and chemotherapy-induced tissue injury, particularly its mitigation of activation of the innate immune response. EC-18 is being developed by Enzychem for multiple indications, including OM.

EC-18 is amid a 2-stage, phase 2 multi-institutional, randomized, placebo-controlled study at 20 sites in the USA (NCT03200340). One hundred four patients being treated with concomitant chemoradiation (cisplatin) for cancers of the OC, OPC nasopharynx and hypopharynx are being enrolled. The first stage of the study (completed) consisted of a dose-ranging comparison for safety and toleration in which three doses of EC-18 ($n = 6$ per arm) were evaluated against an equally sized placebo cohort. The drug was administered in a capsule formulation in which total daily doses of 500 mg, 1000 mg, and 2000 mg were administered twice daily. In the absence of safety concerns, the 2000 mg dose was determined to be optimal for the efficacy component of the trial ($n = 86$) and is currently the dose being assessed in the ongoing trial. Enrollment is expected to be completed in Q1 of 2021.

Small molecules targeting NF-κB and pro-inflammatory cytokine production

Brilacidin

Brilacidin is a fully synthetic defensin mimetic which regulates immune responsiveness and inflammation through its modulation of the cAMP pathway and subsequent inhibition of PDE4 and PDE3 to mitigate pro-inflammatory responses and activate anti-inflammatory activity [46, 47]. A topical rinse formulation is under development by Innovation Pharmaceuticals.

A small, US-centric, multi-institutional phase 2 trial was completed in patients receiving CRT for cancers of the mouth and oropharynx (Phase 2 Study to Evaluate the Efficacy & Safety of Brilacidin Oral Rinse Administered Daily for 7 Weeks in Attenuating Oral Mucositis in Patients With Head & Neck Cancer Receiving Chemoradiation; NCT02324335) in which patients rinsed with test solution three times per day for the duration of their cancer therapy. Results were reported in ClinicalTrials.gov.

Sixty-one patients were randomized; 46 in the modified intent-to-treat population were evaluated for efficacy (at least one dose of study drug and having been treated with a cumulative radiation dose of 55 Gy). The primary study efficacy endpoint was the incidence of SOM (WHO grades 3 or 4). Of patients in the placebo arm ($n = 25$), 60% ($n = 15$) developed SOM vs. 42.9% ($n = 9$) of patients who received brilacidin. Interestingly, the drug was more active in patients who received high-dose cisplatin every 3 weeks, than in patients being treated with weekly low-dose infusions. A subset analysis in this small group of patients suggested more activity than was observed overall: incidence in the placebo cohort ($n = 14$) was higher 71.4% than was noted in the 8 patients who received active drug (25%; $n = 2$).

A phase 3 study is planned.

Validive

In addition to its action as an anti-hypertensive, clonidine's activity as an α-2 adrenergic receptor agonist modulates NF-κB function to attenuate pro-inflammatory cytokine production. Using clonidine as an active agent, BioAlliance/Onxeo developed a mucobuccal tablet (Validive) which had a longer dissolution time than had been previously described for their Lauriad technology. The tablet, when placed in a patient's mucobuccal fold enables high local and sustained levels of the drug.

A phase 2 (A Phase II, Multi-center, Randomised, Double-blind, Placebo-controlled Study Comparing the Efficacy and Safety of Clonidine Lauriad® 50 μg and 100 μg Mucoadhesive Buccal Tablet (MBT) Applied Once Daily to Those of Placebo in the Prevention and Treatment of Chemoradiation Therapy Induced Oral Mucositis in Patients With Head and Neck Cancer; NCT01385748) completed enrollment in late 2014 [48•]. One hundred eighty-three patients ($n = 183$) were randomized to one of three cohorts (placebo $n = 62$), low-dose clonidine ($n = 56$) or high-dose clonidine ($n = 65$). The study's primary efficacy endpoint was the incidence of SOM.

SOM incidence in the aggregate clonidine-treated cohorts was less (45%) than was reported in placebo-treated patients (60%; $p = 0.06$). Likewise, the threshold of cumulative radiation associated with SOM onset was higher in patients in the consolidated active arms (60 Gy) than in PL patients (48 Gy), and this was reflected in SOM time-to-onset (45 days vs. 36 days). Reversible hypotension was noted in 6.7% of patients in the active arms.

Validive was licensed to Monopar in 2019. Additional clinical trials are planned for late 2020.

IZN6N4

IZN6N4 is a polymolecular biologically active blend derived from *Sambucus nigra*, *Centella asiatica*, and *Echinacea purpurea* being developed for the

mitigation of SOM by Izun Pharmaceuticals [49]. The blend has immunomodulatory, antioxidant, anti-inflammatory and wound-healing activities, and has been successfully applied as an intervention of periodontal disease and diabetic foot ulcers.

A multi-national (USA, Israel) trial (Safety and Efficacy of IZN-6N4 Oral Rinse for the Prevention of Oral Mucositis in Patients With Head and Neck Cancer; NCT1400620) conducted at 12 centers enrolled 110 patients with HNC scheduled to receive standard CRT regimens. IZN6N4 or placebo was used as an expectorated rinse 3 times daily throughout the course of radiation. Results reported in late 2017 demonstrated that, compared to placebo controls, patients treated with IZN-6N4 had less mouth and throat pain and soreness and were more able to maintain their weights throughout the course of radiotherapy. Although not statistically significant, treatment with IZN-6N4 also reduced the incidence of severe SOM compared to placebo. Additional clinical studies are planned.

Summary and conclusions

OM remains a clinically significant toxicity of the most common forms of cancer therapy. It is particularly devastating in patients who are treated with chemoradiation regimens for HNC and with myeloablative forms of chemotherapy. Mucositis is among the most studied and biologically understood of regimen-related toxicities. Since the elements which drive its pathogenesis are shared with other forms of radiation and chemotherapy side effects, a successful intervention for OM will likely to pave the way for halo indications such as radiation-associated dermatitis, proctitis and pneumonitis, fibrosis and even chemotherapy-induced cognitive dysfunction and chemotherapy- and radiation-induced fatigue.

The recognition of the biological complexities which underlie mucositis and the understanding that many of the events perpetuated by radiation or chemotherapy are not the consequence of direct epithelial cell damage, but the result of secondary signaling events has provided a series of potential therapeutic targets. Of these, oxidative stress, the innate immune response, and pro-inflammatory cytokines have been the targets of choice. While the results of phase 2 trials have been a cause for optimism, it will probably be at least another year before definitive data are available.

Compliance with Ethical Standards

Conflict of Interest

Stephen T. Sonis is an employee of Biomodels LLC and Primary Endpoint Solutions, LLC; both companies assist industry (including companies described in this paper), government, and academics to study and enable drugs, biologicals, and devices to treat patients for a wide range of indications including oral mucositis. Dr. Sonis does not have equity in any of the companies with which he works, nor does he receive direct compensation from them. Dr.

Sonis is also a founder of Inform Genomics, Inc.; and is listed as an inventor on the following issued patents: 6458777, 6663850, 6713463, 6841578B2, 7297123, and 10,475539.

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