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A 66 Patient Multi-Institution Phase IV Post-Authorization Surveillance of ProThelial™ (High Potency Polymerized Cross-linked Sucralfate) - Single Agent Efficacy for the Prevention and Rapid Reversal of Chemo-radiation Induced Oral, Esophageal and Intestinal Mucositis

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Background: Standard potency sucralfate is not recommended by most clinical guidelines for prevention or treatment of oral and intestinal mucositis. However, its polymerized cross-linked (thereby high potency) formulation (HPPCLS) was cleared by the FDA for management of oral mucositis and has been associated with complete prevention and rapid reversal of oral, esophageal and intestinal mucositis. Statistically significant high quality evidence from a 66 patient multi-institution phase IV non-controlled observation study is reported here.

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Patients and Methods: In February 2014, as part of the Phase IV post-approval surveillance of HPPCLS, a non-interventional mucositis registry was established. The primary aim of the registry was the surveillance of patients' tolerance of HPPCLS. A secondary aim was the observation of the prescribing pattern of oncologists using HPPCLS to manage chemo-radiation induced mucositis.
Inclusion Criteria: Any cancer treatment patient who developed or was anticipated to develop oral mucositis and was prescribed HPPCLS.
Exclusion Criteria: Allergies or prior adverse reactions to sucralfate.
Conduct of Study: Patients identified by oncology clinical staff with mucositis or anticipated to develop mucositis, were prescribed a 75 ml single week-supply of HPPCLS as needed.
Results: Thirty-nine oncologists from 32 institutions prescribed HPPCLS to 66 patients. No adverse reactions were reported. Five patients were lost to follow-up and 61 patients reported outcomes. Eight patients experienced successful prevention of mucositis averting placement of gastrostomy tube and the remaining 53 patients with WHO-Grade 1-3 mucositis involving the mouth, esophagus, small bowel & colon experienced reversal in 2-3 days. Though cleared for oral use only, 48 of 61 patients were instructed by oncologists to swallow HPPCLS following swish-and-gargle.
Statistical Analysis: Quantitative Glasziou rate-ratio treatment effect beyond 10 (37-82 for HPPCLS) supported efficacy ($p \leq 0.05$).
Conclusion: HPPCLS paste may offer oncologists a single-agent approach to manage chemo-radiation induced mucositis. To wit a protocol is offered for practical use.

Keywords: Polymerized sucralfate; cross-linked sucralfate; mucositis; chemo-radiation mucositis.

Key message: *Oral, esophageal and intestinal mucositis due to chemo-radiation may be completely prevented and rapidly reversed using high potency polymerized cross-linked sucralfate. This unprecedented outcome should substantially reduce the problematic consequences of mucositis-morbidity, unplanned treatment interruptions, patient mortality and increased cost of care*.

1. INTRODUCTION

Mucositis is an inflammation of the oral, esophageal and gastrointestinal mucosa occurring when the tissue dose of chemo-radiation overwhelms innate systems tasked with maintaining membrane integrity and tissue homeostasis [1]. The occurrence of mucositis in the oropharynx, esophagus, small bowel and colon, if severe enough, can lead to regional organ dysfunction, namely – (a) the inability to eat, drink and swallow due to pain and ulceration in the upper alimentary canal, (b) chemo-induced nausea, vomiting and cramping in the small bowel [2], and (c) diarrhea and febrile bacteremia from the colon due to mucositis-associated enhanced permeability of epithelial tight junctions [3-5]. Indeed, the consequences of chemo-radiation induced mucositis are pervasive. Besides obvious morbidity to the patient, there are increased costs and resource utilization required to overcome the setback and improve the patient's health status sufficiently well enough to endure the next dose or cycle of chemoradiation. Failing this, subsequent unplanned treatment interruptions compromise maintenance of the "kill dose" intensity required for optimal survival and cancer remission [6].

Though mucositis is pervasive and its clinical effects assorted and distinct, there is consensus that the mechanism underlying it is identical throughout the GI tract [7]. While the five-phase model for mucositis [8] provides a general outline of its mechanisms, the inflammatory process is likely more iterative. Principally the secretion of pro-inflammatory cytokines, first initiated by damaged and endangered epithelial cells [9,10], then facilitated and amplified by local immune cells (lymphocytes, monocytes, macrophages, dendritic cells, neutrophils) [11] drive the pathophysiology in all three sectors of the GI tract (upper, middle and distal).

Mucositis is the collateral damage arising from optimal dosing of cancer treatment using radiotherapy and myeloablative or myelosuppressive chemotherapy (whether targeted or non- targeted). Regardless of the antineoplastic treatment used, the mucosal response to injury is predictable and for the most part identical. The pathobiology of mucositis, initially described as a four stage process [12,13] was later expanded to a five stage model [14] involving (1) Initial chemo-radiation injury, then (2) Reactive upregulation and cytokine message

generation in response to injury, leading to (3) Increased signaling and amplified cytokine upregulation, followed by (4) Ulceration and inflammation. The final and fifth (5) Stage is that of healing.

Prior to injury, mucosal homeostasis exists as a 'spring-loaded process' comprised primarily of genetically controlled yin-yang actions of pro-inflammatory and anti-inflammatory cytokines [15]. This 'process' contains points of control likely mediated by TGF (transforming growth factor) signaling that is [16-18] genetically tethered and distributed in a manner to provide measured responses commensurate to the magnitude of injury.

There are points of control within any inflammatory process [19] and if they are distributed along the GI tract, then a single-agent anti-mucositis intervention capable of targeting them within the respective mucosa would be ideal [20]. Until recently, none such interventions have existed. Theoretically cytoprotectants may be viewed as an option, however, few, if any, have shown substantial clinical promise [21-22] including standard sucralfate.

Given its efficacy for acid-independent management of GERD [23-25] and duodenal ulceration [26,27], standard sucralfate had long been favored by oncologists for the management of chemo-radiation induced mucositis [28-31] .

However the respective efficacies observed in peptic mucosal disease has yet to transfer to cancer treatment patients with mucositis, one study finding standard sucralfate to be no more effective than soda mouthwash [32]. Consistent with such findings, the Multinational Association of Supportive Care in Cancer (MASCC) has recommended against the use of standard sucralfate (suspension or pill) for oral or intestinal mucositis from 2006 to date [33-35], supporting its use only as an enema to manage radiation proctitis with bleeding. All other guidelines have followed suit opposing the use of standard sucralfate in the management of chemoradiation-induced mucositis. While standard sucralfate appears ineffective for this use, none of the other MASCC supported interventions, have any substantial impact on oral, esophageal or colonic mucositis though indeed each intervention has been found to be better than placebo. Consequently, the spectrum of negative consequences from mucositis persists nearly unabated.

In notable contrast high potency polymerized sucralfate (HPPCLS) has shown significant efficacy in both prevention and reversal of mucositis, regardless of its anatomical location within the gastrointestinal (GI) tract, its cause or the presence of continued chemo-radiation [36-38].

Patient reported duration of oral mucositis varies with cancer treatment modality and dosing required to achieve disease remission or cure. Stem cell transplant (SCT) patients undergoing myeloablative conditioning endure 46-60 days of oral mucositis before returning to baseline [39, 40]. Besides this, SCT patients may experience 10-12 days of intestinal mucositis which is generally associated with febrile bacteremia [4]. Patients receiving four to six cycles of chemotherapy must potentially endure 68-102 days of oral mucositis, 17 days per cycle, [41] often accompanied by mucositis related nausea and vomiting [42] or mucositis-related diarrhea [43-46]. Patients undergoing radiation with or without chemotherapy tolerate 70-84 days of mouth-throat soreness [47,48] regardless of the guideline-supported intervention prescribed. Nearly without exception, most anti-mucositis interventions have only fractional effects, thus the negative impact of mucositis persists. Emotionally, patients dread the experience [49,50] and medical office staff is overstretched, by an estimate of one study, 9 hours per mucositis patient per month [51].

In August 2013, the FDA cleared HPPCLS paste containing 10% sucralfate as a Class I medical device for the management of oral mucositis. A mucositis registry was established in February 2014 to capture the respective clinical experience of oncologists and patients. Outcomes of the first 32 consecutive patients of this registry reported earlier [36-38] supported the notion that a single agent anti-mucositis protocol may be plausible. The current report includes an additional 34 patients whose outcomes further support the concept of a single-agent approach to mucositis management.

2. MATERIALS AND METHODS

2.1 Material: Anti-Mucositis Agent Used

2.1.1 High potency polymerized cross-linked sucralfate (ProThelial™)

There is a chemical distinction between HPPCLS and standard sucralfate which is explained in

Table 1. In HPPCLS, sucralfate is both polymerized and cross-linked. Polymerization by weak multi-dentate carboxylic acids lead to sucralfate-sucralfate aggregation into sheets, while cross-linkage of sheets is mediated by multivalent cations present in a distinct ratio to the carboxylic acid. The resultant sucralfate supra-structure is an amalgamation of sucralfate that disallows simple hydration by water and facilitates a layered accumulation of sucralfate that is more slowly hydrated (removed) from the mucosal lining than standard sucralfate. Cross-linking electronegative sheets of polymerized sucralfate in a 'pancake' fashion leads to an orderly, compounded layering of sucralfate on the mucosal lining, a process known as (pi) ∏-stacking [52,53]. Parallel pi-stacking of sucralfate disallows free dispersal of single molecules of sucralfate free dispersal by water hydration which with the associated consequence of random positioning of hydrated sucralfate molecules across the mucosal lining. In HPPCLS, sucralfate layers preferentially as 'sheets' stacked upon each other which this increases the surface concentration of sucralfate upon the mucosal lining.

2.1.2 Potency

The entire clinical effect of sucralfate is inextricably linked to its surface concentration on the mucosal lining. Therefore the potency of sucralfate correlates to the respective surface concentration achieved per administration. Hollander et al. [54] demonstrated that the higher the surface concentration of sucralfate on the gastric lining, the greater are the related physiological effects on the mucosa (e.g., epithelial regeneration, glandular mucus expression, protective prostaglandin secretion).

2.1.3 High potency versus standard potency

Three hours following dose administration of HPPCLS (ProThelial™), sucralfate maintains a mucosal surface concentration that is 800% greater than standard potency sucralfate on normal lining and 2,400% greater on ulcerated lining [55,56]. Table 2 shows the comparative mucosal surface concentration of a 10% solution of standard sucralfate and HPPCLS. HPPCLS has enhanced sucralfate concentration, likely due to enhanced mucoadherence. Thus (not surprisingly), there should be enhanced mucosal effects in accordance to Hollander's principal observation [57].

2.2 Methods: Registry Study Design – Phase IV Post-Authorization

2.2.1 Rationale of phase IV study

Conducting a post-authorization surveillance of therapy is required by regulatory authorities to proactively monitor unanticipated adverse events, patients' acceptance of therapy and treatment outcomes.

2.2.2 Objective of phase IV study

Beyond the compilation of unanticipated adverse reactions to HPPCLS, a chief objective was to observe the prescription pattern of practitioner use. Though authorized as a Class I medical device to be applied, swished, gargled and then expectorated, the FDA insisted that the prescribing information informed clinicians that HPPCLS was safe to swallow up to 4 grams daily for 56 consecutive days. Physicians have a 30 year history of prescribing sucralfate (1982-2012) and are comfortable with its use for mucosal disease beyond the oral cavity. Therefore it was important to record their use of HPPCLS in practice, namely just how many physicians would instruct patients to swallow the oral preparation.

2.2.3 The mucositis registry as study tool

A formal mucositis registry was established to capture unanticipated adverse reactions to HPPCLS, record the physicians' method of use in a practice setting, and the subsequent outcomes resulting from their specific manner of use. The registry was populated consecutively by patients identified by practitioners for immediate access to HPPCLS. The immediacy was determined solely by the practitioner who had the intent to either prevent or reverse mucositis. The first patients were enrolled in February 2014, six months following FDA market authorization.

2.3 Conduct of the Study

2.3.1 Ethical approval

This Phase IV surveillance study was observational involving no element of intervention requiring review by an ethics committee. Observations were made within established clinical settings involving the routine management of mucositis with the informed consent of all participants involved. Patient acceptance of HPPCLS in terms of taste and the occurrence of adverse events was an additional

non-interventional aspect of this study. Observations were collected in a manner that did not individualize participation so as to invoke risks of harm or stigma to any involved.

2.3.2 Oncologist selection

Clinicians (oncologists, mid-level practitioners and oncology nurse specialists) voluntarily responded to national outreach efforts by specialty pharmacies that provided information regarding HPPCLS. Immediate access to HPPCLS was provided through a physician-assigned patient sample program.

2.3.3 Patient selection

Patients who had mucositis or were vulnerable to develop mucositis were identified by clinicians aware of the availability of HPPCLS. These patients were then selected by prescribing clinicians. Physician-assigned samples of HPPCLS were provided at no cost to patients or insurers for the management of their mucositis.

2.3.4 Inclusion criteria

Any patient identified by a clinician as on to receive HPPCLS was enrolled into the registry. Cancer type, stage or treatment were not a limitation to patient enrollment. All patients who received a physician-assigned sample were requested to be placed on the mucositis registry.

2.3.5 Exclusion criteria

Patients were excluded if they had any previously known adverse reaction (e.g. allergy) to sucralfate.

2.3.6 Physician named samples

All patients were prescribed a 75 mL one week physician-prescribed sample of HPPCLS and received respective patient instruction sheets accordingly. Patients were maintained weekly on assigned samples at the request of the clinician; purchase of HPPCLS was not required. Depending on the severity of mucositis or management goal (treatment versus prevention) each patient-administered dose ranged from 2.5 ml to 10.0 ml of paste as assigned.

2.3.7 Instruction for use

Patients were instructed to use their tongue to apply dose to all surfaces inside mouth, then gargle for 10 seconds, hold in their mouth for 15 seconds and then expectorate or swallow if so instructed by their clinicians. If tongue application was difficult, then cotton tipped swabs were used to apply HPPCLS onto all oral surfaces, followed by gargling. Patients were informed by clinicians that HPPCLS was safe to swallow, in adults (age 12 and older) 1 gram four times daily for up to 56 continuous days.

2.3.8 Assessing grade of mucositis

Grade and functions related to difficulty with eating, drinking, swallowing, nausea vomiting and diarrhea were identified by the clinical staff prescribing HPPCLS and confirmed through follow up phone calls by registry attendants. The functional patient-reported scale of the World Health Organization (WHO) [58] was used to determine the grade of oral mucositis. As indicated in Table 3, the severity of mucositis-related alimentary toxicity was assessed using

Table 1. Comparing standard sucralfate to polymerized cross-linked sucralfate

Standard potency sucralfate	High potency sucralfate	
Single molecular sucralfate	**Polymerized sucralfate**	**Cross-linked sucralfate**
● Individual, hydrated molecules	●Sheets of sucralfate hydrogen bonded	● Sheets are cross-linked
● Singular sucralfate molecules mostly in aqueous suspension	●By Multi-dentate chelators (EDTA, oxalate, malate, citrate)	● Cross-linking via bivalent, trivalent cations (Fe, Mg, Ca,)
● Minimal amount of mucosal coating is achieved	● As Sheets of sucralfate there is less singular hydrated sucralfate in solution and more sucralfate is available for layering.	● Pi-stacking of sucralfate sheets Fastens them into a multilayered structure
	● More complete mucosal coating	● 3 hours following dosing there is 7 fold greater coating on normal lining and a 23 fold greater coating on ulcerated lining

Table 2. Surface sucralfate concentration on acid injured & normal GI mucosa three hour post-dose

GI TRACT mucosa	10% sucralfate as HPPLCS	10% standard sucralfate suspension	Increase concentration of HPPCLS on the mucosa
Acid injured GI mucosa	82.81 µg per sq cm	3.56 µg per sq cm	23 fold increase
Normal non-injured GI mucosa	22.01 µg per sq cm	3.12 µg per sq cm	7 fold increase
Pharynx erosions	126.24 µg per sq cm	5.26 µg per sq cm	24 fold increase
Distal esophageal erosions	93.28 µg per sq cm	4.24 µg per sq cm	22 fold increase
Gastric mucosal erosions	82.81 µg per sq cm	3.56 µg per sq cm	23 fold increase
Colonic mucosal erosions	94.34 µg per sq cm	3.87 µg per sq cm	24 fold increase

grading scales developed by both the WHO and the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group (EORTC/RTOG) [59] grading scale (Table 3).

2.3.9 Outcomes collection

Outcomes data were collected by registry attendants through calls made to clinical practices and to patients. All information was collected within four to seven days of patients' initial use of HPPCLS. Staff and patients were specifically asked regarding the timing of clearance of symptoms and signs of mucositis if any, with a focus on the presence or absence of symptoms or signs on day 1, day 2, day 3 and day 4.

3. RESULTS

3.1 Registry Characteristics and Outcomes

3.1.1 Registry characteristics

The Mucositis Registry was populated from February 10 through December 30, 2014 and included 66 sequentially enrolled patients.

3.1.2 Registry clinicians and institutions

There were 39 oncologists from 32 different oncology institutions across the US who prescribed HPPCLS to 58 patients with mucositis and to 8 patients in whom clinicians intended to prevent mucositis (oral and esophageal) so as to avert placement of gastrostomy feeding tube.

3.1.3 Registry institutions

There were 32 participating institutions across 14 states in the US including Connecticut, Florida, Georgia, Illinois, Kansas, Massachusetts, Maine, Michigan, New York, Pennsylvania, Rhode Island, Tennessee, Texas and Washington State. The type of oncology practices included National Cancer Institute (NCI) designated facilities (*n* = 4), National Cancer Center Network (NCCN) practices (*n*=2), hospital-based institutions (*n* = 20) and community-based practices (n = 6).

3.1.4 Registry patients

There were 66 consecutive patients from the registry included in this report: 48 males (age 46 to 92) and 18 females (age range 14 to 84). Five patients were lost to follow up leaving 61 patients represented in the respective outcomes for this report. All patients had either undergone or were to undergo chemotherapy, radiation or combined chemo-radiation for cancer treatment. No adverse reactions were encountered and HPPCLS was well tolerated which met the main objective of this surveillance study. Of the 61 patients completing follow up, 53 were prescribed HPPCLS for treatment while 8 were prescribed HPPCLS for prevention.

3.1.5 Types of cancers in registry

There were 13 different types of cancers occurring at 10 different organ systems -Head and neck, esophagus, lung, pancreas, colon, bladder, ovary, lymphoma, sarcoma, and skin. The type of cancers under treatment in the registry included unspecified squamous cell carcinoma (SCC) of the head and neck (n=18), SCC of the tonsil (n=10), SCC of the tongue (n=12), SCC of the oral cavity (n=7), SCC of the larynx (n=6), esophageal cancer (n=2), pancreatic cancer (n=2), colon cancer (n=2), lung cancer (n=2), bladder cancer (n=1), ovarian cancer (n=1), soft tissue sarcoma (n=1), lymphoma (n=1) and metastatic melanoma (n=1).

3.1.6 Types of cancer treatment in registry

There were three modalities of treatment represented in the registry – targeted immuno-antineoplastic agents (*n*=5), non-targeted traditional antineoplastic agents (*n*= 8) and radiotherapy (*n*=2). Individual treatments causing oral, esophageal, small and large bowel mucositis included ipilimumab, novilumab, cetuximab, bevacizumab, pazapanib, folinic acid, 5FU, irinotecan, oxaliplatin, carboplatin, cisplatin, paclitaxel, gemcitabine, IMRT (intensity-modulated radiotherapy), non-IMRT.

3.1.7 Baseline grades of mucositis

The WHO scale for oral mucositis and the EORTC/RTOG and WHO Scale for GI Toxicity were used (Table 3). Of the 61 patients to report outcomes, 8 patients that were prescribed HPPCLS to prevent oral and esophageal mucositis were assigned a baseline mucositis Grade of 0. For the remaining 53 patients to report outcomes the baseline type and grades of mucositis (Table 4) were as follows: Only 11 had solely oral mucositis, the remaining 41 had a combination of oral mucositis and esophageal, small bowel (nausea, cramping, periumbilical pain) or colonic (diarrhea) mucositis. Of those with solely oral mucositis, 2 had Grade 1, 7 had Grade 2 and 2 had Grade 3 at baseline. Baseline grades of oral mucositis among all 53 patients were as follows 8 had Grade 1, 28 had Grade 2, 17 had Grade 3 and none had Grade 4. Forty one patients with oral mucositis also had mucositis involving esophagus, small bowel and colon. Of these 41 patients having oral mucositis in combination with mucositis elsewhere (anatomically) there were 20 patients with Grade 2 esophageal mucositis, 10 patients with Grade 2 small bowel mucositis and 11 with Grade 2-3 colonic mucositis.

3.1.8 Baseline anti-mucositis interventions used by clinicians

Historically the 24 of the 39 practitioners of this registry had managed mucositis with mouth rinses (FDA approved ones and magic mouthwash), antacids, oral hygiene, generic sucralfate suspension and cryotherapy. The remaining practitioners had no treatment preferences. All were not satisfied, as persisting mucositis altered their ability to maintain optimal dosing.

3.1.9 Tube-feed dependent patients

There were two patients with pre-existing gastrostomy tubes. One patient with Grade 1 oral mucositis (burning-mouth syndrome) had been gastrostomy feeding tube dependent for 3 weeks due to Grade 2 mucositis development (esophageal, small bowel and colonic) while receiving 8 weeks of treatment on folfirinox (folinic acid, 5FU, irinotecan, oxaliplatin). Following surgery to debulk tumor growth, a second gastrostomy tube patient with Grade 1 oral mucositis had been on tube feed for 1 week while undergoing simultaneous chemotherapy (carboplatin, paclitaxel) and radiation for Stage IVb head and neck cancer of the tonsils.

3.1.10 Mucositis prevention patients (feeding tube anticipated)

Eight patients without mucositis were prescribed HPPCLS because treating oncologists anticipated them to develop mucositis severe enough so as to require a prophylactic gastrostomy feeding tube. These included 6 males (ages 78-92) and 2 females (ages 74, 84) who were assigned baseline grade 0 mucositis, pretreatment.

3.2 Registry Outcomes

3.2.1 Clinician practice outcomes

There were 39 oncologists from 32 different oncology institutions across 14 states US who prescribed HPPCLS to 58 patients with existing mucositis (5 of whom were lost to follow up) and to 8 patients in whom clinicians anticipated the development of oral and esophageal mucositis. In the latter intent-to-prevent group of patients, clinicians sought to avert placement of gastrostomy feeding tube. Forty-eight of the 61 patients reporting outcomes (or 78.7%) were instructed to swallow HPPCLS (an off-label procedure) rather than expectorate following tongue application and gargling.

3.2.2 Patient outcomes

Thirty-two of the 66 patients had been reported previously [38]. An additional 34 patients were consecutively added to the registry.

3.2.3 Adverse events/palatability

As with the previously reported 32 patients the additional 34 patients reported no adverse

reaction to HPPCLS. Though well tolerated, a few (*n* = 4, 6.6%) complained of taste and fewer still (n=2, 3.3%) complained of chalkiness.

3.2.4 Oral mucositis outcome

There were 11 patients with only oral mucositis (OM), two with Grade 1, seven with Grade 2 and two with Grade 3. All 11 patients experience elimination of OM in 2- 3 days.

3.2.5 Esophageal mucositis outcome

There were 20 patients with grade 2 esophageal mucositis. All patients experience elimination of painful swallowing as well as tolerance of liquid and solids within 2-3 days. Some patients had been on antacids and proton pump inhibitors with no appreciably patient-reported effect.

Table 3. EORTCRTOG & WHO toxicity criteria acute chemo-radiation morbidity

	Oral & GI toxicity scale				
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
WHO oral mucosal toxicity grade	None	Painless ulcers, erythema or mild soreness with swallowing liquid, hard & soft solids	Painful erythema, edema, or ulcers but can eat only soft solids & liquids	Painful erythema, edema, or ulcers and cannot eat solids, barely drink liquids	Alimentation is not possible; Dependence on IV & Feeding-Tube
EORTCRTOG esophagus toxicity grade	None	Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing	Unable to take solid food normally; Swallowing semi-solid food; Dilation may be indicated	Severe fibrosis; Able to swallow only liquids; May have pain on swallowing Dilation required	Necrosis/Perforation Fistula
EORTCRTOG small bowel toxicity grade	None	Mild diarrhea; Mild cramping; Bowel movement 5 times daily	Moderate diarrhea and colic; Bowel movement >5 times daily;	Obstruction or bleeding, requiring surgery	Necrosis/Perforation Fistula
EORTCRTOG colorectal toxicity grade	None	Increased frequency or change in quality of bowel habits not requiring medication, rectal discomfort not requiring analgesics; Slight rectal discharge or bleeding	Diarrhea requiring parasympatholytic drugs, mucous discharge not necessitating sanitary pads, rectal or abdominal pain requiring analgesics; Excessive rectal mucus or intermittent bleeding	Diarrhea requiring parenteral support, severe mucous or bloody discharge necessitating sanitary pads/abdominal distension (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; gastrointestinal bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
WHO colorectal toxicity grade	None	Increase of 2–3 stools per d over pretreatment	Increase of 4– 6 stools per d, or nocturnal stools, or moderate cramping	Increase of 7–9 stools per d, or incontinence, or severe cramping	Increase of >10 stools per d or grossly bloody diarrhea, or need for parenteral support

EORTC/RTOG is the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group; WHO is the World Health Organization

Table 4. Baseline types (Location) and grades mucositis

Location mucositis	Grade	Number patients	Grade system
Oral mucositis	Grade 1	8	WHO
	Grade 2	28	WHO
	Grade 3	17	WHO
	Grade 4	0	WHO
Esophageal mucositis	Grade 2	20	WHO/EORTC-RTOG
Small bowel mucositis	Grade 2-3	10	WHO/EORTC-RTOG
Colonic mucositis	Grade 2-3	11	WHO/EORTC-RTOG

WHO – World Health Organization; EORTC-RTOG - European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group

3.2.6 Small bowel mucositis outcome

There were 10 patients with Grade 2 small bowel enteritis who had symptoms of nausea, vomiting, peri-umbilical crampy discomfort. All 10 patients experienced complete symptom reversal within 2-3 days. Patients had been maintained anti-emetics with no significant patient-reported effect.

3.2.7 Colonic mucositis outcome

There were 11 patients with Grade 2-3 colonic mucositis with diarrhea and subumbilical cramps. All 11 patients experience resolution of diarrhea and cramps within 2-4 days on HPPCLS. Patients had been maintained on anti-diarrheal without any significant patient-reported effect.

3.2.8 Tube feed dependent outcome

There were 2 patients who were feeding tube dependent prior to prescribing HPPCLS. Within 2-3 days of HPPCLS treatment, each patient no longer required tube feed supplements but were able to self-aliment.

3.2.9 Prevent mucositis/avert tube outcome

There were 8 patients, mostly elderly, 6 men age 78-92 and 2 women, ages 74 and 82 who were to undergo chemoradiation for SCCHN and were to require prophylactic placement of feeding tube for anticipated Grade 3 oral/esophageal mucositis. These patients started HPPCLS the day of therapy. None developed mucositis throughout chemoradiation treatment.

Table 5 summarizes outcomes reported by 61 patients.

3.3 Statistical Analysis

3.3.1 Statistical measure of efficacy

As reported elsewhere [60], patient-reported duration of oral mucositis once established during chemo-radiation will predictably persists for 46 - 60 days in SCT patients [39,40], 70-84 days for SCCHN patients [47,48] and up to 102 cumulative days for patients receiving 6 cycles of chemotherapy (17 days per cycle) [41]. Table 6 illustrates the baseline of patient-reported duration of oral mucositis. The expected duration of patient-reported oral mucositis should last from 46 to 102 days depending on the cancer treatment therapy used.In this study, patient-reported Grade 2, 3 oral mucositis reversed in 2 – 3 days in all treated with HPPCLS. This magnitude of treatment effect occurred repeatedly (53 occurrences) in different treatment scenarios.

Similar magnitudes of effects were observed in 20 patients with esophageal mucositis, in 10 patients with small bowel mucositis and in 11 patients with colonic mucositis. Most other interventions will predictably fail to reverse oral mucositis in the above 53 instances. This time-to-event (reversal of oral mucositis) demonstrated a positive Glasziou treatment effect [61] that is statistically significant ($p \leq 0.05$).

3.3.2 Confounding bias, treatment effect size

In well adequately powered controlled trials, only a fraction of cancer treatment patients will predictably experience a significant magnitude of treatment effect using most anti-mucositis interventions. The inflammatory reaction to anti-cancer agents overpower most interventions. In this uncontrolled low powered observational study, the high magnitude of the treatment effect for HPPCLS consistently resulted in the elimination of related mucositis at an unprecedented rate.

3.3.3 Rate ratio of the glasziou treatment effect

The rate ratio resulting from comparing the time-to-event (patient-reported healing) values

generated by HPPCLS with the time-to-event values of the natural course of disease was 68, far greater than the threshold of 10 required for a positive Glasziou treatment effect [61]. The clinical outcome from HPPCLS demonstrates a quantifiable effect that is statistically beyond that expected for the natural course of patient-reported mucositis. In all treatment cases represented in the registry, the rate of complete response of oral mucositis (pain, erosion, and function restoration) to HPPCLS was 2-3 days, or 2.5 days. Comparing this time-to-event number to those expected for the natural course of chemo-radiation induced oral mucositis - 46, 60, 84 or 102 days the rate ratio can be calculated respectively. As explained by Glasziou et al. [61] the rate ratio in this situation would be calculated as follows:

> Rate for HPPCLS ÷ [0.5 ÷ days for mucositis to resolve naturally] = Rate Ratio [1 ÷ 2.5 days] ÷ [0.5 ÷ 46, 60, 84 or 102 days] = 36.7, 48.2, 67.8 or 81.6

The magnitude of the clinical response to HPPCLS compared to the natural course of mucositis generated rate ratios beyond '10', the number required to secure assumption of efficacy beyond confounding biases.

3.3.4 Quality of evidence

Because the magnitude of the treatment effect for most other mucositis interventions is similar to that of a placebo (and in a minority of cases can be similar to effect of no treatment), randomized controlled and blinded studies are considered Level I quality of evidence while non-randomized, uncontrolled observational studies with no blinding (such as in this report) are considered Level IV/V quality [62,63]. This is accurate because the magnitude of treatment effect for most interventions are within 30-50 base points better than placebo [64] and every treatment effect contains its own placebo effect contributing to its efficacy. This may be referred to as the 'common range of outcomes'. In the infrequent occurrence where the magnitude of treatment effect for an intervention is 10 times (or greater) than this 'common range of outcomes', it is highly unlikely that confounding factors influenced its outcome. Guyatt et al. [62] asserted that "the larger the magnitude of effect, the stronger becomes the evidence" and that "the presence of a dose-response gradient" or a "very large effect suggests a rating of high quality evidence" Glasziou et al. [61] determine that the magnitude qualifying as "large" is a rate ratio of 10 or greater. HPPCLS was associated with rate ratios of 37 to 82. Additionally the fact that higher doses of HPPCLS were required for more severe grades of mucositis support a dose-response gradient. In this respect Guyatt et al. [62] make the case supported by author in the past [65], that the Level I quality of evidence for clinical guidelines should accommodate evidence rising from interventions with large, dose-gradient treatment effects, and in our view with rate ratios equaling or exceeding 10.

3.3.5 Relative risk

The theoretical expectation of any mucositis intervention has been well established in the practical experience of clinicians. The therapeutic effects of palifermin, mouth rinses and other guideline-supported options while better than placebo, have not been associated with rate ratios beyond 1. Patient-reported duration of Grade, 1, 2, and 3 oral mucositis during cancer treatment persisted in more than 60% of patients treated with palifermin in controlled trials [65], and in more than 75% of patients treated with multiple MASCC supported interventions [66]. Although these patients received myeloablative doses of chemotherapy, it is highly unlikely (though possible) that associated cases of

Table 5. Observed outcomes of prescribing HPPCLS for oral, pharyngeal, esophageal and intestinal mucositis

Management intent	Anatomical location	No. of patients	Response time	Response type
Prevent mucositis	Oral/Pharyngeal esophageal	8	Immediate	Complete prevention
Treat/Reverse mucositis	Oral/ Pharyngeal	53	2-3 days	Complete elimination
Treat/Reverse mucositis	Esophageal	20	2-3 days	Complete elimination
Treat/Reverse mucositis	Small Bowel	10	2-3 days	Complete elimination
Treat/Reverse mucositis	Colon	11	2-4 days	Complete elimination

Table 6. Composite of patient reported oral mucositis (PROM)

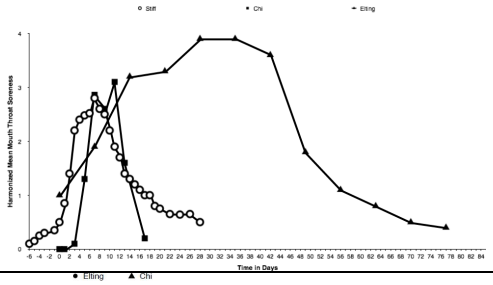
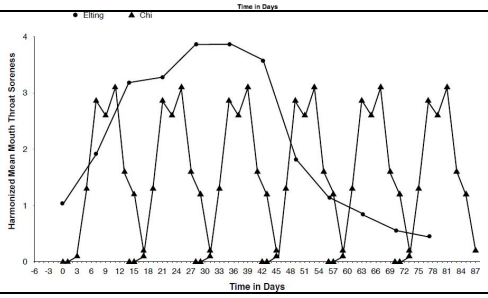
(a) Composite graph of harmonized mean mucositis score over time **(**Adopted from Stiff et al. [39], Elting et al. [4] and Chi et al. [41])	
(b) Composite graph of harmonized mean mucositis score following 42 days radiation and 6 cycles of chemotherapy repeated every 14 days (Adopted from Elting et al. [47,48] and Chi et al. [41])	

Table 7. Proposed single agent protocol using ProThelial™ for chemo-radiation induced mucositis

Management goal	Cancer therapy	Loading dosing	Maintenance dosing through 1 week post- cancer therapy
Treatment grade 1,2	Chemo-radiation	2.5 ml to 5 ml TID x 1 day [250 – 500 mg]	2.5 ml to 5 ml BID [250 – 500 mg]
Treatment grade 3,4	Chemo-radiation	10 ml TID x 2 days [1000 mg]	5-10 ml BID [500 – 100 mg]
Prevention grade 1,2	Chemo-radiation	2.5 ml to 5 ml TID x 1 day [250 – 500 mg]	2.5 ml to 5 ml BID [250 – 500 mg]
Prevention grade 3,4	Chemo-radiation	10 ml TID x 2 days [1000 mg]	10 ml TID [1000 mg]

Prevention regimen start first day of cancer treatment; BID is twice daily; TID is three times daily

Grade 1, 2 and 3 oral mucositis are physiologically distinct from those caused by non-myeloablative doses of chemotherapy, such that a therapeutic intervention effective for Grade 1-3 oral mucositis due to non-myeloablative doses of chemotherapy would be completely ineffective for Grade 1-3 oral mucosits caused by myeloablative doses of chemotherapy. Physiologically, Grade 1-3 oral mucositis should be indistinguishable on the basis of the mucositogenic agent causing the injury.

Based on this consideration, the relative risk of some patients remaining unresponsive to an anti-mucositis treatment could be calculated. In the trials reported by Spielberger et al. [66] and Bhatt et al. [67], the proportion of patients remaining unaffected by applied respective interventions is 0.63 and 0.75 respectively. In all 53 consecutive patients wherein the intent was to reverse and in the 8 consecutive patients wherein the intent was prevention there were no patients unaffected by HPPCLS. Since over a 10 month period of time, 53 and 8 consecutively enrolled patients treated by 39 different oncologists, failed to be non-responsive, it seems reasonable to assume that, should the study continue without end 0.05 patients [61] may be found to be unaffected by the use of HPPCLS.

The relative risk would then be 0.63 and 0.75 divided by 0.05 or 12.6 and 15 respectively. According to Guyatt et al. and Oxman [61,62] if the relative risk ratio is greater than 2, then there is a strong evidence of association, and if greater than 5 then there is “very strong evidence of association”. In other words, despite the uncontrolled low powered design of this

observational study, the magnitude of the treatment effect observed with HPPCLS supports probable efficacy.

3.3.6 Significance of prevention outcomes

Eight elderly patients all with SCCHN and intended to receive prophylactic placement of gastrostomy tubes experienced complete prevention using HPPCLS, averting required placement of feeding tubes. While this number, *n* = 8, is low, the magnitude of the HPPCLS treatment effect elevate these outcomes into significance. Similar to the category of treatment effect observed with physostigmine administered to patients with myasthenia gravis, if the outcome is repeated more than once, the outcome is medically significant, based on the known plausible mechanism of action. It is highly unlikely that the administration of any intervention could repeatedly prevent oral, pharyngeal and esophageal mucositis in multiple patients at high risk of developing it.

4. DISCUSSION

Current therapeutic choices for clinicians to effectively manage mucositis effectively are sparse, though the guidelines for mucositis management, are plentiful [34,35,68-70]. Options currently authorized by regulators (mouth rinses, palifermin, low level laser treatment etc) and those supported off-label by guidelines have similar fractional impact on the overall incidence of mucositis or on its course once established. Best efforts in choice of interventions still leave the vast majority of mucositis patients to struggle with its morbidity and payers to shoulder the cost of clinical endeavors to prolong survival and promote a meaningful quality of life. Despite the number of agents available to date, few have found broad use in mucositis management. For example, none of the MASCC supported interventions can be used to both treat and prevent mucositis [34,35]. Furthermore, none are recommended for simultaneous management of mucositis in multiple anatomical locations (i.e., upper, middle and distal GI tract).

The current study has shown the use of HPPCLS to be associated with complete prevention of oral, pharyngeal and esophageal mucositis in eight patients from several different clinical practices. It has also shown that mucositis occurring in different anatomical locations can be managed simultaneously with HPPCLS. Furthermore, patients previously committed to gastrostomy tube feeding to supplement their diet were restored to normal alimentation using HPPCLS.

Still there are several limitations to the study. The data are taken from a self-reported registry that was not designed to investigate efficacy. The study was uncontrolled and designed, as most post-authorization studies are, to capture reportable adverse events, patients' acceptance of the intervention and to observe physicians use of HPPCLS in a real world setting. The outcomes were recorded from 32 different oncology institutions involving 39 different oncologists using the same prescribing information and can be regarded as an extended case series covering treatment outcomes over a period of ten months. By weakness of design, the data were subject to selection bias being derived from a voluntary registry without randomization and placebo or active-controls. Patient selection was determined by physicians based on outreach information provided by specialty pharmacies. On one hand, the lack of diversity of cancer patients, 53 out of 66 (80%) being those with SCCHN, narrowed the field of application. On the other hand, those undergoing radiotherapy for HNC tend to be most vulnerable in developing oral, pharyngeal and esophageal mucositis [71] during cancer treatment.

Despite these limitations, HPPCLS was associated with the following outcomes not seen with other interventions: (1) Repeated, rapid (2-3 day) and complete reversal of mucositis accompanied with restoration of GI function; (2) Simultaneous reversal of mucositis in multiple anatomical locations throughout the GI tract; and (3) Sustained mucosal integrity during continued chemoradiation, once mucositis was reversed by HPPCLS.

Finally, the general magnitude of effect for most other interventions and their comparators (placebo) are similar [64] and far less than that for HPPCLS. In fact, the natural course of disease (i.e., the time-to-healing event) for chemoradiation induced mucositis is within the magnitude of that for these other interventions and their comparators. Consequently, typical controls, blinding and randomization are required to differentiate respective treatment effects from confounding biases. In contrast, the rate ratios for HPPCLS are far beyond the threshold of 10 required to overcome confounding biases (a positive Glasziou treatment effect), and therefore significantly distinguishable from those ratios for other anti-mucositis interventions.

5. CONCLUSION

Mucositis guidelines [34,35] are useful. However, they are based on controlled trial data using interventions whose magnitude of clinical effect is highly vulnerable to interference by confounding bias. The magnitudes of treatment effects for respective interventions are generally indistinguishable from those of comparators and confounding [64].

Of interventions recommended or suggested by the MASCC guidelines, none have been associated (consistently or otherwise) with complete elimination or complete prevention of mucositis. Conversely, HPPCLS has been consistently and repeatedly associated with rapid and complete elimination, as well as complete prevention, of mucositis. This has been demonstrated by the real-world outcomes of multiple patients with wide variety of cancer and cancer treatments in this registry. Ten months into this registry, there has yet to be a patient who has not only benefited from HPPCLS, but more specifically has not experienced complete reversal or prevention. While it is indeed possible (and likely) that over time there will be patients who do not benefit from HPPCLS treatment, this has not been found to be the case at the writing of this report.

Table 7 is proposed as a starting point for a possible anti-mucositis protocol. It is based on the real world experience represented by data reported here. Of course further evaluation of HPPCLS is needed. However, alternative therapeutic options for mucositis patients currently available are inadequate. Palifermin has limited use, incompletely managing mucositis in BMT units. Similarly, FDA authorized rinses, are limited to attenuation of mucositis pain and fractional restorative effects. The problem of mucositis is financially expensive, clinically disruptive and emotional disheartening to patients undergoing treatment for cancer. For some patients, the occurrence of oral and gastrointestinal mucositis impacts survival. As a potential tool, HPPCLS should be examined by practitioners and challenged as key component of a single-agent anti-mucositis protocol.

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COMPETING INTERESTS

Author is an employee of Mueller Medical International LLC, owner of technology underpinning HPPCLS.

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