How We Do It

Novel 2-3 day Simultaneous Reversal of Oral and Alimentary Mucositis using Polymerized Cross Linked Sucralfate

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ABSTRACT

The quest to optimize cancer treatments and to extend cancer survival is consistently thwarted by an unavoidable but expected consequence – mucositis of the oral and gastrointestinal tract. Prior to market approval our Translational Medicine Research Center clinically tested polymerized cross-linked sucralfate (PCLS) on a cancer treatment patient who underwent 6 weeks chemo-radiation for squamous cell carcinoma of head and neck (SCCHN). This late-breaking Phase 4 observational experience from our Center discusses the post-approval use of PCLS in 2 patients: one with advanced oroesophageal mucositis from radiation and cetuximab for SCCHN and another patient with oral, esophageal, small and large bowel mucositis caused by Folfirinox (5- fluorouracil, folinic acid, irinotecan and oxaliplatin) for inoperable metastatic pancreatic adenocarcinoma. Standard potency sucralfate is not recommended in the mucositis management guidelines of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). This higher potency sucralfate, PCLS, used in these patients exhibited an unprecedented simultaneously and rapid (2-3 day) reversal of oroesophageal mucositis and alimentary mucositis. These results raise the novel proposition of single-agent management of both oral and alimentary mucositis caused by radiation, classic and newer bioengineered oncolytics. If validated, PCLS should energize discussions regarding mucositis clinical guidelines. The experience of these patients has been accepted for presentation in the upcoming 2014 International Symposium of the MASCC/ISOO. Distinctions between standard potency sucralfate and PCLS are reviewed and modes of action explanations are offered.

KEYWORDS:

Sucralfate, Mucositis, MASCC/ISOO , Cetuximab, Folinic acid, 5-fluorouracil, Irinotecan, Oxaliplatin

INTRODUCTION

There is near universal disappointment in mucositis treatments to date. Most treatments palliate symptoms or lessen signs but none eliminate patient-reported experiences of mucositis. None is associated with the complete regression of ulcerations and mucositis symptoms, particularly its pain. None is associated with restoration of gastrointestinal function, and self-alimentation. “Mucositis is a critically toxic thing we do to patients, and we have not done much about it the past 50 years” an observation made by Dr Patrick Stiff in 2006, then professor of oncology at Loyola University Medical Center. 1 Despite the introduction of FDA-cleared coating agents and FDA approval of palifermin, oral and gastrointestinal mucositis are remain longstanding disruptive side effects of cancer treatment patients. Affecting upwards of 400,000 annually 2. mucositis occurs in patients undergoing treatment for cancer requiring combination chemo-radiation, cancer occurring in the head and neck or cancers requiring bone marrow transplantation (BMT). It remains a major challenge for patients’ compliance to optimal cancer treatment as its morbidity leads to reduction, postponement or cancellation of treatment. Largely palliative and ineffectual for many patients, mucositis treatments rarely help suffering patients to avoid dehydration, and often requires ER visits and/or hospitalization. Upon review of published reasons as to why cancer treatment patients require ER treatment 3, 4, 5 it becomes obvious that oral and gastrointestinal mucositis was the lead cause of visits to the ER. Of the 91,561 patients studied in one investigation5, 3,525 complained of nausea and vomiting, 3,146 had dehydration and 4,972 complained of malaise and fatigue for total of 12.7% of all cancer treatment patients requiring ER care. The next nearest cause of ER visits was abdominal pain at 4.7%. Poorly managed mucositis creates a substantial economic burden in cancer care 6. For example, patients receiving an average of 6 cycles of chemotherapy for solid tumors or lymphoma, generate additional hard costs of $2,384 per cycle for oral mucositis and $5,239 per cycle for oral and alimentary mucositis. The overall increased costs of poorly managed mucositis range from $14,304 to $31,434; this is on top of baseline hospitalization costs of $23,358. Therefore patients hospitalized with oral mucositis cost $37,662 while patients with both oral and alimentary mucositis cost $54,792.

Bone marrow transplant patients with oral mucositis incurred additional hospitalization costs of $42,749 per patient on average. 7 The advent of palifermin, has helped lower the incidence of Grade 4 mucositis from 62% with placebo to 20% and overall Grade 3/4 mucositis from 98% with placebo to 63%, reducing cumulative analgesic dose to less than half. However it has a limited indication to decrease the incidence and duration of severe oral mucositis in BMT patients and a hosts of side effects attended by many intravenous therapies. It has never reversed any grade of oral mucositis and is not recommended for alimentary mucositis.

Besides the financial costs of ineffectually treated mucositis, patients and their support groups to feel powerless 9 when forced to endure mucositis. Oncologists well aware of the dilemma are clinically limited by the therapeutic options that range from unapproved magic mouthwash to FDA-cleared or approved agents that either too narrowly focused or have proven unlikely to materially affect the clinical impact of mucositis.

Insurers extend formulary coverage for mucositis remedies that coat the mucosa, but largely fail to alter the clinical scenario of dehydration, pain and debilitation that often lead to unwanted dose reductions or unscheduled interruptions in cancer therapy. Costs of poorly managed mucositis are high and unavoidably are passed on to insurers which in turn are passed those costs to all subscribers.

Our Center was the first to report the use of “high potency sucralfate” (otherwise known as polymerized cross-linked sucralfate, PCLS) being associated with the prevention and reversal of both oral and alimentary mucositis in a Stage 4b head and neck cancer. 10 This early Phase 4 (post-FDA clearance) report discussed 2 additional cancer treatment patients with oral and alimentary mucositis who also had similar unexpected and dramatic effects using PCLS and will be presented in the 2014 Symposium of the MASCC/ISOO.

This article will also discuss the therapeutic distinctions between standard potency sucralfate and high potency PCLS and it will review mode of action explanations on how physical mucosal interactions of PCLS translate into clinical effects for oral and alimentary mucositis.

Materials and Methods

This Phase 4 post-approval interventional study reports on 2 patients with advanced-stage carcinoma: one patient undergoing concurrent chemoradiation, while the other patient was treated with a quadri-combo chemotherapy regimen known as Folfirinox (5- fluorouracil, folinic acid, irinotecan, oxaliplatin). Both treatments are associated with high Grade 3 to Grade 4 toxicity, with patients developing severe oral and gastrointestinal mucositis, often reduced to feeding tube alimentation. The settings for these observations were academic oncology institutions. The patient with stage 4 SCCHN was treated by a radiation oncologist in the Midwestern university affiliated Swedish Covenant Hospital, while the other patient's stage 4 pancreatic cancer was treated by a medical oncologist in Vanderbilt-Ingram Cancer Center. Both patients were enrolled in the compassionate use PCLS Assigned Sample program sponsored by Mueller Medical International and administrated by the Translational Medicine Research Center.

High-Potency Polymerized Cross-Linked Sucralfate

The active ingredient of ProThelial™ (Mueller Medical International LLC, Foster, RI USA) is high potency, polymerized cross-linked form of sucralfate (HPS), a product associated with 800-2400 percent residual surface concentration of sucralfate, three hours following administration. 11 Additionally, HPS has been associated with 28-day, 83% healing of erosions in a random clinical GERD trial 12 and a 7-day, 80% healing of GERD erosions.13 This marked enhancement of surface concentration of sucralfate underpins it physical and device mode of action, its ability to achieve clinical effects through its engagement with the mucosa.

Manner of Use

PCLS is FDA cleared as a medical device to be used orally and then expectorated. However, in the patients reported in this study, alternative to the package insert, the physicians instructed patients to swish and swallow. Prescribing information asserts the safety of swallowing PCLS, though not promoted. The FDA-cleared quantity of sucralfate per dose of PCLS is 250mg to 500mg used three times daily for the first day, followed by the same amount used twice daily. The customary FDA-approved dosing of ingested standard-potency sucraflate is 1,000 mg swallowed four times daily.

Mucositis Cancer Treatment Patients

Case 1. Squamous Cell Carcinoma of Head and Neck – On Cetuximab & Radiation

A 49 yo male under the care of a radiation oncologist of Midwestern University affiliated teaching hospital in Chicago for advanced stage 4 squamous cell carcinoma of the tonsil, was treated with combined chemo-radiation. By the end of the second week of treatment, he developed substantially grade 3 oral mucositis. The cancer treatment regimen leading to oroesophageal mucositis included cetuximab, an epidermal growth factor receptor antagonist, used in combination with locoregional radiation. In an FDA reviewed trial of 424 patients, SCCHN patients (squamous cell carcinoma of head and neck), cetuximab plus radiation extended cancer survival from 29 months using radiation alone to 49 months. However, the addition of cetuximab to radiation increases incidence of alimentary mucositis (nausea 49% vs 37%, emesis 29% vs 23%, diarrhea 19% vs 13%), of delayed-onset radiation oral mucositis (48% vs 39%) and delayed onset esophageal mucositis (44% vs 35%). The grade 3 mucositis in this patient caused by the combination of cetuximab and radiation was reversed in 3 days using PCLS (500mg polymerized cross-linked sucralfate). Eliminated was pain at rest and upon swallowing, the use of narcotic analgesic for pain, nausa, cramping and loose stools. Self-alimentation was continued during cancer treatment. The patient tolerated PCLS well and reported no adverse reaction.

Case 2. Pancreatic Adenocarcinoma on FolFirinox

A 48 yo male under the care of a medical oncologist at the Vanderbilt Ingram Cancer Center for metastatic Stage 4 pancreatic carcinoma was treated with Folfirinox alone. Between week 2-3, the patient developed Grade 4 oroesophageal mucositis, unable to tolerate solids and liquids, he was entirely dependent on tube feeding. Pancreatic adenocarcinoma is the fourth leading cause of cancer-related death with nearly 37,000 deaths as of 2010. The overwhelming majority, above 90%, of these patients are inoperable at presentation, making systemic chemotherapy the primary form of treatment. Gemcitabine, which at one time replaced fluorouracil, has itself been replaced by Folfirinox, which is a chemotherapy combination of 5-fluorouracil, folinic acid, irinotecan and oxaliplatin. Folfirinox extended patient survival from 6.8 to 11.1 months. Not surprisingly, it is attended by high grade 3/4 hematologic toxicities with grade 3/4 oral and alimentary mucositis. This patient was feeding-tube dependent by week 2 and was placed on PCLS by the oncologist. Being instructed by the physician to swish and swallow PCLS, (500mg polymerized cross-linked sucralfate tid on day 1 then bid thereafter), the patient experienced (a) complete reversal of oral ulcerations in 3 days, (b) ability to swallow without pain in 3 days (c) simultaneous reversal of nausea, vomiting and diarrhea and (c) restoration of ability to eat a regular diet relying on complete oral alimentation.

Discussion

Since the approval of palifermin in 2004, no approved mucositis intervention has reduced the incidence and/or duration of oral mucositis and no approved intervention has been associated with reversal of mucositis. Polymerized cross-linked sucralfate (PCLS) appears to have these and several other associated effects.

Rate of Response – the Glasziou Effect

The completed clinical effects of PCLS occurred within 2 -3 days; no mucositis interventions have been associated with this rapidity of response. These clinical effects include the complete reversal of signs and symptoms of mucositis. Glasziou et al 15 described a statistically significant treatment effect that is beyond the influence of bias commonly controlled for and minimized by randomized clinical trial. Referred to (by the author as) the Glasziou effect when the rate of response to an intervention is less than one tenth that anticipated effected by placebo or intervention then that response is classified as dramatic and statistically distinct from chance. Most episodes of mucositis last 2-3 weeks after completion of a 4-6 week course of cancer treatment regardless of the mucositis intervention.16, 17 Thus compared to the 6-9 weeks (42-63 days) duration of mucositis will persists (despite the mucositis intervention used), a 2-3 day-completed treatment response of PCLS represent a rate of reaction for this intervention that ranges from 3.17% to 7.14% of the rate possible with other interventions.

Other Unique Clinical Effects of PCLS

Besides its rapidity, PCLS has other unique clinical effects. Second to the rapid rate of clinical effect, there are the observation that PCLS affect simultaneously both OM and GIM restoring function. Thirdly, the treatment effect of PCLS appears wider in scope than any other mucositis intervention to date. It eliminates pain (lessen dependence on narcotic analgesia), restores normal oral mucosa, and restores upper GI function with swallowing and the ability to tolerate solids and liquids. This outcome alone permits the patient to maintain their nutritional status without supplementation while undergoing cancer treatment. Additionally, in these patients, PCLS minimized nausea and small intestinal cramping and it eliminated frequent loose movements in patients suffering from chemotherapy-induced diarrhea. Fourth, in these patients was useful for the management of mucositis caused by radiation, cetuximab, 5-fluorouracil, folinic acid, irinotecan and oxaliplatin. Fifth, PCLS was well-tolerated by each patient with no patient-reported side effects, sucralfate, (the active ingredient of PCLS), having an acceptable safety profile. Sixth, the use of PCLS is not intrusive, or disruptive; it is a singular agent with an acceptable means of administration, dosed at a twice daily frequency. Table 1 itemizes the characteristics of PCLS.

Table 1. About PCLS (Polymerized Cross-Linked Sucralfate

- FDA Cleared Medical Device for Management of Oral Mucositis
- Polymerized Cross-linked Sucralfate (Enhanced Potency Reduced Dosing)
- Prevention of Oral Mucositis
- Reversal of Oral Mucositis
- Rapid 2-3 Day Onset of Clinical Effect

Non-Package Insert Clinical Effects

- Prevention of Alimentary (Gastrointestinal) Mucositis
- Reversal of Alimentary (Gastrointestinal) Mucositis
- Potential as a Single Agent Approach to Managing Oral & Alimentary Mucositis
  Physician discovered but non-promoted non-package insert feature

Why PCLS Work for Mucositis but Standard Potency Sucralfate Does Not

The clinical actions of PCLS are not entirely unexpected. Early literature that examining the effect on the gastric mucosa of undissolved fragments of sucralfate have identified many of the mucosal reactions presumed involved in the clinical effects. Those effects- enhanced mucus/bicarbonate production, cellular regeneration, and secretion of prostaglandins - were dose-dependent, that is, determined by the concentration of sucralfate on the lining.

Standard Potency vs High Potency Sucralfate In Managing Mucositis

Standard potency non-polymerized sucralfate is not recommended by MASCC/ISOO for the treatment or prevention of mucositis, oral or alimentary. 18 High-potency polymerized sucralfate, associated with rapid reversal of both oral and alimentary mucositis in patients is not the same. High-potency polymerized cross-linked sucralfate is standard sucralfate polymerized into 'sucralfate sheets' by calcium chelated malate resulting in a preferentially ordered layering of sucralfate upon the mucosa, achieving and maintaining elevated concentrations of sucralfate long after the initial dose. Three hours following administration, PCLS maintains a 7-fold greater surface concentration of sucralfate on normal lining and a 23-fold greater concentration on inflamed, ulcerated mucosa 11. In August 2013, the FDA cleared the use of PCLS, as a medical device for the management of oral mucositis.

Rapid Healing By Standard-Potency Sucralfate Occur at High Mucosal Doses

Early sucralfate investigations 19, 20 showed that undissolved (thus high-dose concentration) sucralfate adherent to the human gastric mucosa caused rapid mucosal changes within 10-60 minutes. 21 These changes included the release of mucus and bicarbonate as well as vacuolization and exfoliation of superficial enterocytes being replaced by newly regenerated cells. Laboratory animals given high doses of standard-potency sucralfate (3-20 times the standard 14 mg/kg dose) were observed to resist gastric injury, rapidly heal mucosal injuries 22 and showed increased secretion of luminal prostaglandins, mucus and bicarbonate. 19 These mucosal changes were shown to be linked to the local expression of growth factor receptors 23, 24 and the secretion of epidermal growth factor .25, 26. Later research identified that sucralfate-mediated mucosal changes are growth factor dependent. 27. Independently Itoh et al and Konturek et al concluded that sucralfate accelerates growth-factor mediated mucosal healing.28, 29

Rapid Healing By High-Potency PCLS Given At Low Mucosal Doses

High-potency sucralfate is the active ingredient of PCLS™. At standard 14 mg/kg doses, high-potency sucralfate causes a 7-23 fold hyper-concentration of sucralfate on mucosal lining. In a placebo-controlled, double blinded multi-center trial involving 60 patients 12 , there was a 28-day 87.7% healing rate of GERD erosions (compared to placebo's 37.7%) in patients using high-potency sucralfate at 1.5 gram twice daily. This represented a 2.34-fold or 334% improvement in healing over placebo. Esophageal erosions in both treatment groups were exposed to untreated gastric acid, making the results observed with high-potency sucralfate that much more remarkable.

Similarly, in a randomized 7-day, four-arm trial involving 41 patients with erosive GERD 13 , the rate of healing for patients using high-potency sucralfate was 80%. The 7-day healing rates for acid therapy groups were considerably

lower: omeprazole (20 mg bid) was 30% and for ranitidine (150 mg bid) and antacid groups healing was 0%. Apparently the topical coating of high-potency sucralfate affects a mucosa-centric mechanism for healing that appears indifferent to gastric pH or acid exposure. Comparing the 7-day healing rate of high-potency sucralfate to that of omeprazole, there was a 2.67 or 367% improvement similar to that seen when high-potency sucralfate is compared to placebo, where there was a 2.34 fold or 334% improvement.

Device Mechanism Of Action for PCLS– Expedited Healing

High-potency sucralfate in polymerized sucralfate malate paste has a device mechanism of action as follows. It is assumed that the more efficient layering of polymerized sucralfate paste produces adherent restrictive microenvironment across the mucosal lining which advantages the activation of growth factor receptors by growth factor. Restrictive micro-environs generated by cross-linked layers of polymerized sucralfate "crowds" free-moving growth factor, limiting its random movements to "pockets" that overlie growth factor receptors. Spatially limiting the movement of growth factor to the vicinity of its receptor heightens the chances of receptor site activation. This device action leads to expedited healing.

Device Mechanism Of Action for PCLS – Reversing Mucosa-Based Pain, Nausea, Vomiting & Diarrhea

The surface "pockets" of restrictive micro-environs created by PCLS's unique layering probably affect the flux of ions across mucosal receptors responsible for pain, nausea, vomiting and neuro-secretory diarrhea. These specialized mucosal receptors triggered by chemo-radiation maintain their state of activation by means of gated-ion fluxes across surface membranes that face the lumen of the gut. It is probable that the same restrictive micro-environs that crowd growth factors to the vicinity of their receptors also affect the surrounding space available to membranes for ion-flux and exchange. Spatial limitation of the immediate surface environment surrounding ion-gated receptors along the GI tract impact the receptor's ability to perpetuate the ion fluxes required to keep the receptor "turned on" or stimulated. Physically restrictive micro-environs surrounding membranes of stimulated receptors exhaust the ions immediately available to it. This limits the ability of the receptor to stay "on". The result is the quiescence of the membrane and the reduction of receptor-associated pain, nausea (thereby vomiting) and neurosecretory diarrhea, all of which are triggered by chemoradiation therapy.

Conclusions

Polymerized cross-linked sucralfate appears to be a cutting edge therapy that may provide a novel approach to the management of both oral and gastrointestinal mucositis. The possibility that for some patients mucositis certain to occur could be entirely eliminated changes cancer treatment by lessening the likelihood of dose delays, reductions or cessation. For medical compliance is possible, treatment optimization is probable and added costs of care brought on by mucositis is reduced if not likely eliminated. The low dosing of sucralfate (250-500mg 2-3 times daily) providing rapid reversal of ulcerations and other gastrointestinal signs such as diarrhea, nausea and cramps bespeaks the technological advance that PCLS affords to the practice of oncology. Given the typical rapid and complete treatment effect associated with PCLS randomized clinical trials may be necessary only to quantify rather than verify efficacy and to identify for further study those patients who fail to respond to PCLS. The MASCC/ISOO should concern itself to discuss the relevance and implication of these results as well as advise the audience of practitioners regarding guideline positions on PCLS. Obviously, beyond our Translational Medicine Research experience, more observational studies should be conducted to gain experience and confidence in this new therapy especially within the many and varied cancer treatment scenarios that patient must endure.

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