DEBATE ARTICLE

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# Polymerized Cross-linked Sucralfate Paste Should Acquire a Recommendation for Use in the MASCC/ISOO Mucositis Guidelines through the Adaptation of a New Category of Level of Evidence


## Abstract

The level of evidence categories used for guideline recommendations of the MASCC/ISOO (Multi-national Association of Support in Cancer Care and International Society of Oral Oncology) should be expanded to include as Level IA evidence case reports that show Glasziou treatment effects, that is treatment effects with rate ratios beyond 1,100%. This category expansion of evidence can be used by the Panel on guidelines to elevate obscure, but versatile interventions to mainstream attention, thereby exposing practitioners to novel therapeutic tools that alter the course of disease and perhaps save lives.

This article probes the pros and cons of this point decidedly in favor of establishing a Level IA evidence category for mucositis interventions. This position is made due to the published case reports of polymerized cross-linked sucralfate and repeated demonstrations of rapid, complete and simultaneous reversal of oral and alimentary mucositis within 2 to 3 days.


## Introduction

In 2013 the MASCC/ISOO panel [1] published a practice guideline update. The article chronicles the storied history of the Panel's effort to promulgate practical guidelines that would be useful for the practitioners to manage both oral and gastrointestinal mucositis. The article discussed efforts to conduct systemic reviews on interventions given a status of "recommendation for" by the Panel. As mentioned in the articles abstract, the stated goal of the Panel is "to produce clinical practice guidelines for the management of mucositis using the best available evidence".

## Criteria Used to Evaluate Literature

The Panel used suggestions from Hadorn et al. [2] to direct its analysis of published research and adopted the criteria outlined by Somerfield et al [3] to assign levels of evidence on published investigations. The Table outlines the criterion used to assign levels to the evidence gathered from published articles.

| Table 1. Levels Of Evidence Used by MASCC/ISOO Panel on Mucositis Guidelines | | |
|---|---|---|
| | I | Evidence obtained from meta-analysis of multiple, well-designed, controlled studies; randomized trials with low false-positive and false-negative errors (high power) |
| | II | Evidence obtained from at least one well-designed experimental study; randomized trials with high false-positive and /or false-negative errors (low power) |
| | III | Evidence obtained from well-designed, quasi-experimental studies, such as nonrandomized, controlled single-group, pretest-posttest comparison, cohort, time or matched case-control series |
| | IV | Evidence obtained from well-designed, non-experimental studies, such as comparative and correlational descriptive and case studies |
| | V | Evidence obtained from case reports and clinical examples |

The vast majority of interventions give rise to treatment effects that are only 20-50 bases basis points better than placebo that is between 1 to 2 fold better than placebo. That magnitude of treatment effect, 200% - 300% beyond placebo, can be overpowered by biases arising from methodology. Since historically there are few interventions associated with this magnitude of treatment effect beyond this, well-designed RCT are inevitably required to assess efficacy and the above stratification of level of evidence makes sense.

## Exclusion of Evidence with Glasziou Treatment Effects

The categorization of evidence outlined in Table 1 is complete in the space of treatment effects that are tens of percentage point increases better than placebo. There is however a magnitude of treatment effect well beyond placebo, which, if surpassed, substantiates the efficacy of an intervention as being statistically beyond the reach of bias. As described by Glasziou et al, [4] if the rate of response of a medical condition to an intervention is less than one-tenth the rate of response the condition has to placebo (known as the rate ratio), then RCTs are unnecessary to authenticate that intervention's novel treatment effect. That is with a rate ratio of 10 or above, the efficacy of novel intervention is assured. Only safety remains to be determined regarding that prospective intervention. Table 1 excludes from its ranking evidence that arises from case reports exhibiting high-powered treatment effects, that is treatment effects that statistically outstrip the influence of bias from study design or random chance. Glasziou treatment effects (so termed by author), described by Glasziou et al [4] are those wherein the rate of treatment response of a novel intervention is less than 10% of that using placebo or using an alternative intervention.

**High Potency Polymerized Cross-linked Sucralfate**

Standard potency non-polymerized sucralfate is not recommended by MASCC/ISOO for the treatment or prevention of mucositis, oral or alimentary [5]  High-potency polymerized sucralfate, associated with rapid reversal of both oral and alimentary mucositis in patients is not the same entity. High-potency PCLS is standard sucralfate polymerized into 'sucralfate sheets' by calcium chelated malate resulting in a preferentially ordered layering of sucralfate on the mucosa, achieving and maintaining elevated concentrations of sucralfate long after the initial dose. Three hours following administration, PCLS maintains a 7-fold (or 800%) greater surface concentration of sucralfate on normal lining and a 23-fold (or 2,400%) greater concentration on inflamed, ulcerated mucosa [6] Polymerized cross-linked sucralfate is associated with 28-day, 83% healing of erosions in a random clinical GERD trial [7] and a 7-day, 80% healing of GERD erosions [8].

**Manner of Use**

PCLS (ProThelial™, Mueller Medical International LLC, Foster RI, USA) is FDA cleared as a medical device to be used orally and then expectorated. However, contrary to the package insert, oncologists instructing patients to swish and swallow PCLS have reported patient experiences of resolution of both oral and alimentary mucositis. As required by regulation, the prescribing information asserts the safety of swallowing PCLS, though not promoting it. 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 standard-potency sucraflate is 1,000 mg swallowed four times daily.

**Treatment Response of PCLS in Case Reports vs Panel Supported Interventions**

It takes 2-3 weeks following a 4-6 week therapy of oncologics before there is a patient-reported or clinician-confirmed reversal of mucositis [9].  Therefore, the earliest that mucositis can be reversed by any one intervention is 6 weeks; and the longest that mucositis would persist in a cancer treatment patient using any one mucositis intervention suggested by the Panel is approximately 9 weeks. This assumes that the causative oncologic therapy lasts between 4-6 weeks.  Two different studies on mucositis reported similar results, one documented 70 days [9] before function returns to baseline and the other reported 60 days [10].

In the 5 cases presented in this report, the rate of complete response of oral mucositis (pain, erosion, & function restoration) and/or gastrointestinal mucositis to PCLS  was 2-3 days [11]. Comparing this unprecedented treatment effect of 2-3 days for PCLS to the standard 60-70 days for placebo or other interventions, the resulting rate ratio would range from 20 to 35. Stated another way, the rate of completed treatment response for PCLS is 2.85% to 5.0% of the rate required by the nearest mucositis intervention recommended for use by the Panel.

**An alternative criterion**

Table 2 is a suggested new level of evidence to be considered by the MASCC/ISOO panel for mucositis guidelines.

| Table 2, Suggested New Levels Of Evidence for MASCC/ISOO Panel on Mucositis Guidelines | | |
|---|---|---|
| | IA | Evidence obtained from reports demonstrating rate ratio equal to or more than 10 |
| | I B | Evidence obtained from meta-analysis of multiple, well-designed, controlled studies; randomized trials with low false-positive and false-negative errors (high power) |
| | II | Evidence obtained from at least one well-designed experimental study; randomized trials with high false-positive and/or false-negative errors (low power) |
| | III | Evidence obtained from well-designed, quasi-experimental studies, such as nonrandomized, controlled single-group, pretest-posttest comparison, cohort, time or matched case-control series |
| | IV | Evidence obtained from well-designed, non-experimental studies, such as comparative and correlational descriptive and case studies |
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Historically, interventions that generate treatment effects that exemplify IA level evidence include insulin for diabetics, neostigmine for myasthenia gravis or penicillin for infections. The latter involved the study of 10 patients, wherein 5 were given penicillin intravenously, one orally and four topically [12]. More recent case-report data that alter guidelines of clinical practice include the use of 2-chlordeoxyadenosine for remission of hairy-cell leukemia [13], the use of imatinib in the treatment of chronic myeloid leukemia [14] and the use of combination chemotherapy to treat advanced Hodgkin's disease [15]. Indeed, there are case reports that demonstrate rate ratios beyond the power of 10 and the evidence criterion used to base clinical guidelines should accommodate such occurrences that occur in medical research. Provided known or demonstrated safety of an intervention, this type of accommodation will provide meaningful interventions to the community of practitioners sooner than otherwise possible.

**Cons in Support of Status Quo**

Of course the identification of such interventions does not excuse them from the assessment by RCT especially those that involved active controls wherein comparisons between competing interventions are carried out.

**Other Reasons To Support Discussions to Recommend use of PCLS**

Table 3 shows the known published patient experience using PCLS.

Table 3. Patients on Polymerized Cross Linked Sucralfate Status-Post Market Clearance

| Patient | Age Gender | Institution University | Cancer | Oncology Treatment | Oral Mucositis | Gastrointestinal Mucositis | Reversal of Ulceration | Reversal of Painful Swallowing | Reversal of Nausea, Cramps | Reversal of Diarrhea |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 43yoM | Brown University Boston University | SCCHN | Radiation + Carboplatin + Paclitacel | Grade 2 | Grade 2 | 2 days | 2 days | 1 day | 1 day |
| 2 | 49yoM | Midwestern | SCCHN | Radiation+ Cetuximab | Grade 3 | Grade 2 | 2 days | 3 days | 1 days | 1 day |
| 3 | 48yoM | Vanderbilt Ingram CaCtr | Pancreatic Carcinoma | Folfirinox | Grade 4 | Grade 3 | 3 days | 3 days | 2 days | 2 days |
| 4 | 48yoF | UConn Yale | Metastatic Melanoma | Ipilimumab Nivolumab | Grade 3 | Grade 4 | 2 days | 2 days | 2 days | 2 days |
| 5 | 63yoF | Vanderbilt Ingram CaCtr | Metastatic Colon Ca | Folfox | Grade 3 | Grade 4 | 2 days | 1 day | 2 days | 2 days |

There are several other reasons supporting the Panels discussion of the use of PCLS in patients with oral and alimentary mucositis. First, PCLS is fast, affecting complete reversal of signs and symptoms of mucositis within 2- 3days. Second, PCLS appears useful simultaneously for both OM and GIM. Third, the treatment effect of PCLS appears wider in scope than any other mucositis intervention to date. It eliminates pain, restores normal oral mucosa, and restores upper GI function with swallowing and the ability to tolerate solids and liquids. This feature alone permits the patients to self-maintain their nutritional status 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, PCLS seems useful for the management of mucositis caused by a diverse group of oncologic agents each having differing mechanisms of action. Cancer therapy included radiation, 5-fluorouracil, folinic acid, irinotecan, oxaliplatin, paclitaxel, carboplatin, cetuximab, ipilimumab and nivolumab. Fifth, PCLS was well-tolerated by all with no patient-reported side effects. Of course, sucralfate, the active ingredient of PCLS, has an acceptable safety profile. Sixth, PCLS is a singular agent with an acceptable means of administration, dosed at a frequency that is not cumbersome.

**Conclusions**

Inclusion of the Glasziou treatment effect as a high level criterion for evidence of efficacy will legitimize discussions by the Working Committee regarding this novel mucositis intervention. To date there has been no FDA approved or cleared mucositis treatment associated with the simultaneously reversal of both oral and alimentary mucositis and that within 2-3 days. High potency PCLS has that distinction and its dramatic treatment effect is a stark difference from standard potency sucralfate that is not recommended by the Committee on mucositis guidelines. Perhaps it is appropriate for the Committee to now seize upon the observation of a positive Glasziou treatment effect of PCLS as the basis for discussing its place in the clinical mucositis guidelines.

**REFERENCES**

1.Bowen JM, Elad S, Huthcins RD, Lalla RV.  Methodology for the MASCC/ISOO mucositis clinical practice guidelines update. Support Care Cance (2013) 21:21: 303-308 [doi 10.1007/s00520-012-1592-7.

2. Hadorn DC, Backer D, Hodges JS, Hicks N (1996). Rating the quality of evidence for clinical practice guidelines. J Clin Epidemiol 49(7): 749-754.

3. Sommerfield M, Padberg J, Pfiser D, Bennett C, Recht A, Smith T, Weeks J, Winn R, Durant J. (2000) ASCO clinical practice guidelines: process, progress, pitfalls, and prospects. Classic Papers and Current Comments 4(4):881-886

4.Glasziou P, Chalmers I, Rawlins M, McCullouch P. When are randomized trials unnecessary? Picking signal from noise. BMJ Feb (2007) 334:349-351

5.Rubenstein et al (2004) Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer [Suppl 1] 100(9): 2026-2046.

6.Kashimura K, Ozawa K. Sucralfate Preparations. US Patent 5,968,906. Oct 19, 1999.

7. Mian Mashhud Ahmad MD et al (2004) High potency sucralfate treatment of Erosive GERD, NERD & Co-morbid IBS, a randomized, double blinded placebo-controlled trial.  Clinical trial data on file at Mueller Medical. Abstract accepted for presentation at DDW 2014 of American Gastroenterological Association .

8. Mian Mashhud Ahmad MD et al (2005) Accelerated mucosal healing using high potency sucralfate. A seven day randomized comparison to omeprazole, ranitidine and antacids in erosive GERD. Clinical trial data on file at Mueller Medical. Abstract accepted for presentation at DDW 2014 of American Gastroenterological Association.

9. Elting LS, Keefe DM, Sonis ST, Garden AS, Spijkervet FKL, Barasch A, Tishler RB, Canty TP, Kudrimoti MK, Vera-Llonch M, Patient-reported measurements of oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy. Cancer 2008 113(10):2704-2713; Lalla RV, Sonis ST, Peterson DE. Management of oral mucositis in patients with cancer.  Dent Clin North Am 2008; 52(1):61-viii.

10. Kushner JA, Lawrence HP, Shoval I, Kiss TL,  Devins GM, Lee L, Tenenbaum HC (2008) Development and validation of a patient-reported oral mucositis symptom (PROMS) scale (Fig 3, 4). J Can Dent Assoc 74 (1): 59, 59a-59i.

11. McCullough RW. Reasons why the MASCC/ISOO should commence guideline discussions on High Potency Polymerized Cross-linked Sucralfate (ProThelial™):  Rapid (2-3 day) Complete Reversal of Oral and Gastrointestinal

Mucositis using a Single FDA-Cleared Agent in Cancer Patient in Different Treatments. J Supp CancerCare (submitted April 2014).

12. Abraham EP, Chain E, Fletcher CM, Gardner AD, Heatley NG, Jennings MA: Further observation on penicillin. Lancet 1941 2:177-88.

13. Piro LD, Carrer CJ, Carson DA, Beutleer E: Lasting remission in hairy-cell leukemia induced by a single infusion of 2-chlordeoxyadensine. N Engl JMed 1990 322:1117-112.

14. Kantarjian H, Hematologic and cytogenetic responses to imatinib mesylate in chronic myeloid leukemia. N Engl J Med 2002; 346:545-52.

15. deVitra VT, Serpick A, Carbone PP. Combination chemotherapy in the treatment of advanced Hodgkin’s disease. Ann Intern Med 1970; 73:881.