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COMMENTARY

Commentary Regarding Mucositis during Cancer Therapy

Duration of Mucositis: Far Longer than 2 to 4 Weeks and May Be Avoidable Altogether

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Précis:

The impression oral mucositis is a brief consequence of chemoradiation is misguided. Patient-reported clinically significant oral mucositis may last 46 to 102 days depending on the cancer treatment, and may possibly be avoided with polymerized cross-linked sucralfate.

Keywords: *Mucositis; Chemoradiation; Sucralfate; Polymerized Sucralfate.*

Commentary Regarding Mucositis during Cancer Therapy

The oft-repeated refrain that "mucositis is self-limited when uncomplicated by infection and typically heals within 2 to 4 weeks after cessation of cytotoxic chemotherapy" or radiation [1]**,** is an inexact statement that can be unintentionally disarming**.** It gives the impression that the duration of mucositis is short therefore tolerable particularly if there is no infection. Again, when referenced in material intended for patients **[2]**, this statement is repackaged as follows: "In patients getting chemotherapy, mucositis will heal by itself when there is no infection. Healing usually takes 2 - 4 weeks."

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To be fair, the reference continues: "Mucositis caused by radiation therapy usually lasts 6 - 8 weeks", which is closer to the reality, but is still far short of the 10-14 weeks required for the mucosa and mouth throat soreness to return to baseline [3, 4] . The impression that mucositis is a short-lived event is inaccurate, can be misleading and therefore detracts from appropriate clinical vigilance necessary to manage it.

Another impression given by these statements is that mucositis persisting beyond "2 to 4 weeks" is likely due to local infection which in turn should be suspected as the main driver of the mucositis process and not the cancer therapy itself. This impression likely underlies the observation of why many patients with persisting mucositis are prescribed an anti-fungal, anti-viral or antibiotic agent. However, because there is no clear evidence that antimicrobials shorten the course or lessen the severity of oral mucositis, their use is not recommended in mucositis guidelines [5]. Clearly, cancer therapy itself is the main driver of clinical mucositis.

The concept that mucositis is likely an ephemeral, self-limited process that is over in "2 to 4 weeks" serves to 'disconnect' the clinician prescribing chemo-radiation from

the patient experiencing mucositis. Indeed, Fromme et al [6] disclosed that physician reporting on adverse reactions to chemotherapy lacked both sensitivity and specificity being incongruent with patient-reported experiences. Trotti et al [7] reviewed 33 studies examining 6,181 patients with mucositis. Only 13 reported all grades of mucositis, 9 reported grades 3-4 only and only 1 reported on the quality of life**.** Though the most severe forms of mucositis - Grades 3,4- are likely to be reported, dose reductions and unplanned treatment interruptions occur more frequently with less severe mucositis (23% with Grades 1, 2) than with severe mucositis (21% with Grades 3,4) [8]. These disconnects remain as hidden biases that can compromise the appropriate management of mucositis. Unfortunately, the lack of clinically effective mucositis interventions bury these disconnects from view and rendering them irrelevant. Yet an unforeseen effect of these 'buried" disconnects is that the advent of effective mucositis interventions will be challenged, as some clinicians may possibly be lulled into a position of indifference.

Ulcerations, erythema and the pain of mucositis patients receiving daily radiation are more likely to be noticed by the clinical staff as compared to patients receiving chemotherapy who can escape notice of the clinical staff, as they often would have navigated through the worst of their mucositis experience by the beginning of their next cycle of chemotherapy. The mouth and throat soreness of chemotherapy-induced mucositis intensifies with successive cycles, with amplification by one report, as much as 44% [9]. Recurrent bouts of mucositis double the likelihood of dose reduction and unplanned treatment interruptions [8] which directly and negatively impacts tumor kill and thereby survival. Therefore, recognition of patient-reported duration of clinical mucositis is an essential element for clinicians to sense of urgency in addressing mucositis when it occurs.

Patient-reported duration of mucositis is scattered throughout the literature and generally is addressed as an ancillary point of discussion. It is difficult to find a single reference detailing patient-reported duration of clinical mucositis in context of the multiple treatment scenarios.

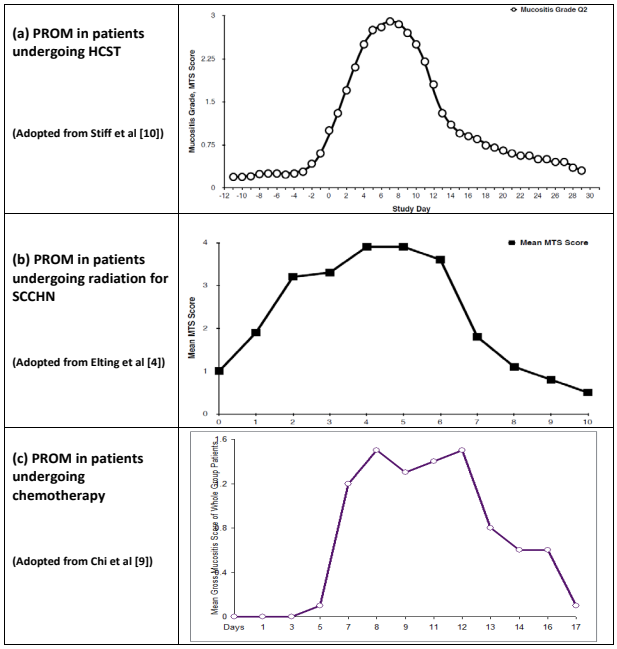
In practice, there are three clinical treatment scenarios of significance that are associated with the development of mucositis: (a) myeloablative conditioning in hematopoietic stem-cell transplant (HSCT), (b) multicycle chemotherapy and (c) radiation therapy with or without chemotherapy. Treatment-specific illustrations of the duration of patient-reported oral mucositis (PROM) are shown in Table 1.

First, for HSCT patients (Table 1a) typically receiving single myeloablative doses of chemotherapy and irradiation, the painful mouth throat soreness affecting eating and drinking begins on day 2, with erosions and ulcerations appearing day 5-7 of oral mucositis. The peak mouth-throat soreness spans an additional 2-3 days before slowly declining over the following 18 days, [10] with an extrapolated return to baseline by day 46. Kushner et al [11] reported that patient-reported return to baseline for this cohort may take up to 60 days following myeloablative therapy. Nearly 100% of these patients experience grade 3 to 4 oral mucositis.

Secondly, patients receiving the standard 6 to 7 week (42-49 days) radiation treatment for head and neck cancer can experience multiple grades of mucositis over 70 day period (Table 1b) [3,4]. With combined chemo-radiation, clinical mucositis will persist up to 84 days, and on occasion beyond [4]. Two years following chemo-radiation, a prior episode of mucositis-related inflammation contributes to chronically persistent difficulty in swallowing (confirmed by video fluoroscopy) that negatively impacts the patient-reported quality of life [12].

Lastly, and perhaps the most complicated patient group, is that of patients receiving single doses of multiple chemotherapeutic agents in 4 to 6 cycles. In this patient group mucositis experience varies based on the time of exposure to, and the type of agent used. In a triple regimen of cisplatin, fluorouracil and leucovorin administered over a four-day continuous infusion, the resultant episode of mucositis persisted over a period of 17 to 21 days per cycle (Table 1c) [9]. This is likely the minimal time duration of mucositis. Of course, when cycles are given weekly (as with certain regimens) the period of mucositis can be extended. Generally, chemotherapy is administered in 4 to 6 cycles, with the majority of cycles repeating every 14 to 21 days, and a minority of cycles repeated every 7 or 28 days [13]. Regardless, as mentioned earlier, the intensity of mucositis ulceration and patient-reported pain amplifies with successive cycles [9].

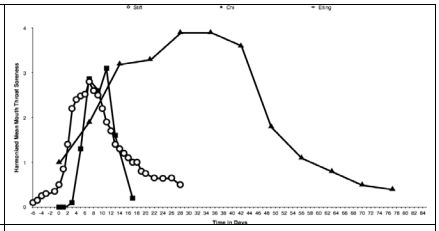
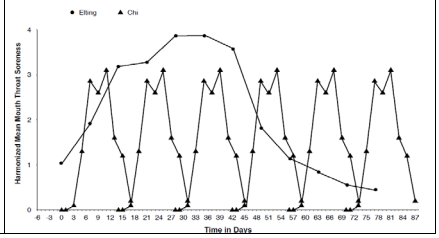
Table 1.
Duration of Patient Reported Oral Mucositis (PROM)



Harmonizing data points in terms of a mean mucositis score (for the y-axis) over a period of 84 days (as the x-axis) provides a perspective on the duration (Table 2) of clinical (symptomatic) mucositis. Table 2a compiles all three scenarios offering a contrast of the experience of mucositis in terms of time. For patients receiving multiple cycles of chemotherapy (Table 2b), recurrent episodes of ever-worsening mucositis can be daunting.

By far the longest periods of mucositis experienced are in patients receiving combined chemo-radiation where symptoms can persist beyond 80 days, while the shortest period is among patients receiving myeloablative therapy for HSCT with symptoms that extrapolate out to 46 days. Of the 400,000 patients [14] developing oral mucositis annually, approximately 55,000, or 14%, are patients with head and neck cancer many of them requiring combined chemo-radiation [15]. An additional 6,300, [16] or 1.6% of all oral mucositis patients underwent HCST. The remaining 84.4% largely consists of patients receiving multiple cycles of chemotherapy who develop mucositis on successive cycles [9].

Table 2.
Composite of Patient Reported Oral Mucositis (PROM)

(a) Composite graph of PROM with harmonized mean mucositis score **(Adopted from Stiff et al [10], Elting et al [4] and Chi et al [9]) .**	
(b) Composite graph of PROM with harmonized mean mucositis score following 42 days radiation and 6 cycles of chemotherapy repeated every 14 days **(Adopted from Elting et al [4] and Chi et al [9])**	

Thus, the actual duration of mucositis (Table 3) is as long as 46 to 60 days in HSCT patients, more than 84 days in patients receiving combined chemo-radiation and, in the vast majority of patients receiving four to six cycles of chemotherapy, there can be 68 to 102 days of clinical mucositis to endure.

Table 3.
Duration in days of Clinically Significant Oral Mucositis

Therapy	Days of Mucositis	Percent Patients Affected	Reference
Myeloablative Therapy HSCT	46-60 days	1.6%	Stiff et al. [10] Kushner et al. [11]
Radiation +/- Chemotherapy	> 70-84 days	13.8%	Elting et al [3,4,8]
Multiple Cycle Chemotherapy	68 -102 days	84.6%	Chi et al. [10]

Considered in this perspective, mucositis is an excessive burden borne throughout treatment for those who develop it, severely impacting their ability to swallow, eat and drink. This limitation directly causes weight loss, dehydration, ER visits, hospitalizations and increased cost of care [3, 4].

Based on the clinical outcomes of a post-market mucositis registry involving a recently FDA cleared therapeutic intervention, mucositis may possibly be avoidable altogether [17]. A sucralfate-based medical device, described as polymerized cross-linked sucralfate, differentiates itself from other interventions by an association with mucositis prevention and rapid reversal in patients undergoing chemo-radiation [18, 19]. In a post-market mucositis registry, 27 patients were successfully treated, experiencing rapid reversal of oral mucositis in 2-3 days. Six patients were successfully prevented from developing mucositis averting surgical insertions of prophylactic gastrostomy feeding tubes [20]. The observational data from the medical device registry demonstrated a positive Glasziou treatment effect [21], an effect wherein efficacy is secured by the sheer magnitude of the intervention's treatment response. In chemo-radiation mucositis, a time of 2-3 days to achieve a mucositis-free state, compared to a customary time of 70-84 days for placebo or the natural course of the disease, establishes a positive Glasziou treatment effect. The rate of symptom/sign improvement associated with an intervention exceeds 1,000 times that expected from placebo or any other intervention. The confounding biases generally controlled in randomized (non-observational) trial, are not of sufficient strength to alter the treatment effect that is 1,000 times greater than placebo [21].

Conclusion

In the supportive care of cancer treatment patients, the duration of mucositis should not be a trivial point. Rather, if one takes into account the real-world timing of common cancer treatment scenarios, then the duration of mucositis experienced by patients should be a clear point of regard by oncologists. It should be appreciated that patients undergoing HSCT will experience mucositis for 46 to 60 days, patients receiving radiation for head and neck cancer will likely suffer mucositis for more than 80 days, and those receiving four to six cycles of chemotherapy will endure 68 to 102 days of mucositis cumulatively throughout their treatment. Notwithstanding other sequelae of mucositis (e.g., systemic infections, dose reductions, increased costs, altered survival), this fact alone - the actual duration of mucositis - begs the use of interventions that could possibly ease the added burden on a disease process (cancer) largely viewed as life-threatening in most patients.

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