Oropharyngeal Mucositis in Cancer Therapy

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To begin with, let me acknowledge that Drs. Epstein and Schubert are experienced doctors of dental medicine who have been involved in the evaluation and therapy of cytotoxic therapy–related mucositis for a long time. I fully agree with them that cytotoxic therapy–associated mucositis is a major clinical problem and that there is a dearth of good studies that address ways to alleviate the condition. Drs. Epstein and Schubert do an excellent job describing the incidence, causative factors, and etiology of cytotoxic therapy–related oral mucositis, and they are to be congratulated for this. Nonetheless, I view a few points differently, as discussed below.

Mucositis Grading

First, I disagree with the authors' opinion on the grading of oropharyngeal mucositis as illustrated by their statement that "when mucositis is being assessed as part of a clinical trial, a tissue-derived score based on a validated scale such as the Oral Mucositis Assessment Scale or Oral Mucositis Index should be used." There are good data to demonstrate the congruence of several different mucositis grading scales, regardless of whether these grading scales are based primarily on visualization of the oral mucosa by an expert or on patient-reported symptoms.[1] Indeed, one of the two treatments recommended by Drs. Epstein and Schubert—oral cryotherapy for the prevention of bolus fluorouracil (5-FU)-resultant oral mucositis—was studied by looking at symptom-related mucositis scores in two clinical trials conducted by independent groups of investigators.[2,3] This contention that symptom-based mucositis scoring is appropriate in clinical trials was recently confirmed in a trial of keratinocyte growth factor (KGF) to alleviate cytotoxic therapy-related mucositis. Investigators reported that patient-derived symptoms correlated well with oral inspections of the oral mucosa.[4,5] These data, and the recognition that patient-described mucositis-related symptoms are probably much more clinically important than are the size of particular lesions in their mouths, support the conclusion that symptom-derived mucositis scores are quite appropriate, both in clinical practice and in clinical research. Keratinocyte Growth Factor

Drs. Epstein and Schubert reference a recently conducted phase I clinical trial of KGF, noting that "fewer patients developed ulcerated mucositis (43% vs 67%, P = .06)." Although this statement is true, the authors do not note that, in this same clinical trial, substantially increased dermatologic toxicities were seen in the patients receiving KGF, compared to placebo.[4] Therefore, the reduction in mucositis was traded for substantial increases in dermatologic toxicity. In order for KGF to be clinically useful in this situation, a better therapeutic window will be necessary.[5] In addition, they discuss another KGF trial in patients receiving high-dose chemotherapy and total-body irradiation, for whom statistically significant reductions in mucositis were noted. The reference to this trial is currently only available as an abstract from this year's meeting of the American Society of Clinical Oncology. A full report of this promising-sounding clinical trial is necessary before we can more fully understand the potential risks and benefits of KGF in this situation. Thus, based on the available published references the authors provide, I view KGF as a potentially promising new therapy for the prevention of mucositis, as opposed to something that should be used presently in clinical practice. Hopefully, further positive results will become available in the near future to demonstrate that KGF has therapeutic efficacy. Benzydamine

Drs. Epstein and Schubert propose the use of benzydamine as an analgesic based on two referenced clinical trials for which they were coauthors,[6,7] stating, "If available, benzydamine should be recommended for prophylactic use in patients receiving radiation therapy." They note that benzydamine is available in Europe and Canada but is not available in the United States, where it is currently being studied in pivotal phase III trials. Based on the available data, I side with the Food
and Drug Administration conclusion that there is not currently enough proof to recommend that benzydamine be used in clinical practice. The first of the two studies cited by Drs. Epstein and Schubert to support their recommendation is a small trial that was published in 1989.[6] This trial enrolled 43 patients. However, 6 patients randomly assigned to the placebo group were removed from the analysis because they reportedly did not comply with the protocol, leaving only 25 evaluable patients. In looking at patient symptoms during radiation therapy in this trial, the investigators found no statistically significant differences between the placebo and benzydamine groups. There was, however, some evidence of decreased oral mucositis-as visualized by the investigators-in the benzydamine group. The second referenced trial, the results of which were published in 2001,[7] was considerably larger, involving 172 patients. As the main outcome variable of this study, oral mucositis scores were based on physical examination, looking for erythema, pseudomembrane production, and ulceration. Utilizing this methodology, the investigators noted approximately a 30% reduction of mucositis in the benzydamine group, compared to the placebo group ($P = .006$). In addition, statistically significant reductions in the use of analgesics were reported in patients receiving benzydamine vs placebo. There were, however, no statistically significant differences between the two study groups for the following outcomes: mouth pain, throat pain, pain during meals, weight loss, suspension of radiation therapy because of oral mucositis complications, or the use of nasogastric or percutaneous endoscopic gastrostomy tube feedings. In addition, it was noted that adverse events were seen in 87% of the benzydamine subjects and 91% of the placebo subjects in this trial. The investigators comment that 58% of these toxicities were felt to have been "attributed to the expected local pharmacologic actions of the study drug and vehicle on inflamed mucous membranes (ie, oropharyngeal burning, numbness/tingling, taste loss, and taste alteration)."[7] Another thing to note regarding the above two trials is that a potentially toxic placebo was used for comparison with the active therapy groups. The placebo ingredients, similar to the active agent, "included approximately 10% alcohol by volume, methanol, peppermint oil, clove oil, and other flavoring agents."[7] It can easily be hypothesized that this alcohol-based preparation actually caused increased mucositis and increased toxic symptoms in the study participants. This hypothesis is supported by another trial, which looked at a chlorhexidine mouthwash vs placebo.[8] In this trial, for which an inert placebo (no alcohol in a bland placebo preparation) was used, the patients receiving chlorhexidine had substantially increased toxicity and a trend for increased mucositis scores compared to the placebo group. Thus, it can be argued that further information is necessary before we can recommend benzydamine as a prophylactic therapy for patients receiving radiation treatments. Hopefully, such information will be forthcoming soon.

**Chlorhexidine**

Drs. Epstein and Schubert appropriately note that chlorhexidine should not be routinely used for radiation-induced mucositis based on clinical trial results. In their recommendations, however, they note that "chlorhexidine can be considered for use in cancer patients to help reduce plaque levels and thus reduce risk of gingivitis and caries." Given the irritation of the alcohol and flavoring agents in chlorhexidine, it would be better to avoid chlorhexidine altogether in patients at risk for mucositis.

**Miscellaneous Topical Approaches**

Drs. Epstein and Schubert note that coating agents such as milk of magnesia, Amphojel, and Kaopectate "clearly can have palliative effects that may improve patient comfort." Nonetheless, I am unaware of any published clinical trial data to confirm such a statement. Given the large number of negative clinical trials that have evaluated purportedly helpful agents,[9-16] it must be noted that these agents may well not help decrease mucositis, might actually increase mucosal injury,[16] and might cause toxicity.[11,12,15] In the same vein, the authors nicely discuss the limitations of sucralfate, based on clinical trial results, but then go on to state that "sucralfate primarily appears to be able to help decrease oropharyngeal pain." This seems to be a statement based on anecdotal experience unsupported by clinical trial data. Results of phase III clinical trials show that sucralfate does not decrease oral mucositis from 5-FU therapy,[12] esophagitis from radiation therapy,[11] or proctitis from radiation therapy.[15] Indeed, in each of these studies, sucralfate caused more toxicity than did the placebo. Accordingly, not only is sucralfate not recommended, its use is contraindicated during cancer therapy as a means of reducing mucosal toxicity.

**Conclusions**

In conclusion, I agree with Drs. Epstein and Schubert regarding the magnitude of the clinical problem associated with cytotoxic therapy-associated mucositis, for which patients are certainly in need of effective therapies. Stronger evidence of efficacy without major toxicity is needed, however, before agents such as benzydamine, chlorhexidine, or sucralfate can be recommended for use in clinical practice. This is particularly true of agents such as sucralfate and chlorhexidine, for which the balance of evidence suggests not only a lack of efficacy, but also a harmful effect from treatment.
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