The Challenges of Oral Mucositis and Its Therapy

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In many regards, oral mucositis has long been an ignored toxicity in those patients who undergo anticancer therapies, including those who receive high-dose therapy with an autologous or allogeneic stem cell transplant. Until recently, this has been largely due to the lack of effective therapy to prevent or treat oral mucositis, other than topical rinses, anesthetics, or systemic opioids. The result is that limited investigations have been performed to characterize, accurately measure, or report this toxicity or its sequelae in settings where it is frequently encountered. In fact, a careful review of the literature reveals that mucositis is significantly underreported when measured as a toxicity, as opposed to an endpoint, of similar chemotherapy regimens.

At the same time, patients do report mucositis as a major adverse effect of chemotherapy or local radiotherapy. In the transplant setting, two independent surveys have identified mucositis as the worst toxicity reported by patients following either ablative chemotherapy or chemoradiotherapy regimens [1, 2]. Most transplant patients rate this toxicity as a 9 or 10 on a visual analog scale of 0–10 and report it as being worse than anticipated. What should be disturbing to those who try to palliate this toxicity is that only a minority of patients felt that symptom control was adequate, with approximately 20% actually reporting no control of symptoms at all. Objectively, the severity of mucositis appears to affect transplant outcome, with an increased number of febrile days and increased risk of infection. Parenteral nutrition use and costs are also higher for those patients with more severe mucositis [3].

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With the availability of effective agents such as palifermin for the prevention of mucositis, as outlined in the accompanying summaries, has come the realization that little is known about this toxicity, and even less on how to accurately assess the efficacy of new agents like palifermin that might have a favorable impact [4]. This lack of knowledge includes defining an optimal severity scale and appropriate endpoints for improvement after therapy, the timing of assessments, and some measure of quality of life. Although a variety of mucositis scales have been used over the years, their accuracy has never been thoroughly assessed. In addition, important variables have never been evaluated, such as intraobserver variability, accurately defining appropriate sites for measurement and the frequency of measurements needed to assess a response, and whether objective measurements of mucositis correlate with the symptoms reported by patients.

Measuring Mucositis Accurately

Perhaps the most important issue in mucositis research is defining the most appropriate endpoint. The obvious choice is a combination of symptom (namely, pain) relief, improved function (the ability to eat and drink), and an objective measurement of the mucosal damage caused by the inciting agent(s). This obviously requires a scale to measure mucositis that accurately reflects both symptomatic and objective severity. In addition, an ideal scale should be easy to learn and teach and not require lesion measurements, which become increasingly difficult as the mucositis becomes more extensive. Although symptomatic relief and restoration of function should be the goal of any agent developed for mucositis, improvement in symptoms may not occur despite an improvement in mucosal damage. The optimal scale actually appears to be the World Health Organization (WHO) scale, which, though simple to assign, takes into consideration both objective and subjective measures of mucositis, unlike the Oral Mucosal Assessment Scale, the Oral Assessment Guide (OAG), or the

Radiation Therapy Oncology Group (RTOG) scales, which are purely objective [5]. Nevertheless, in early studies, utilizing both types of scales would appear to be appropriate.

After choosing a scale, determination of an appropriate endpoint should follow. Like the assessment of neutropenia in patients treated with a hematopoietic growth factor, important endpoints include peak mucositis score (similar to the neutrophil nadir after chemotherapy), the incidence of "significant" mucositis (similar to the incidence of "severe" neutropenia [eg, an absolute neutrophil count < 500/μL]), or the duration of "significant" mucositis (similar to the duration of "severe" neutropenia). Since severity and the duration of the most severe stages of mucositis intuitively would be the most appropriate endpoints to measure, duration of the most severe grade(s) of mucositis would be an optimal candidate for a single endpoint. What should be firm is the definition of severe or "significant" mucositis. Most clinicians and researchers would agree that WHO grade 3 (ulcers and unable to eat solids) and grade 4 (ulcers and unable to take liquids or solids by mouth) toxicities meet this criteria. In addition, since severe mucositis is associated with bacteremia due to gram-positive streptococci, a measure of infection risk should also be considered.

Assessment of New Therapies for Mucositis

In the assessment of new agents, documentation of intraobserver variability needs to be minimized and would likely be best accomplished by training. Using two overlapping scales serves as a check of the accuracy of measurements. Although measurements of lesion size would likely be inaccurate, documentation of lesions in the most frequently observed sites—the lateral tongue, cheeks, lower lip, and floor of the mouth (ie, the sites most likely to be affected by trauma caused by teeth)—should be accurately assessed. Finally, the frequency of measurements needs to be determined in advance. In a typical patient receiving chemotherapy or a bone marrow transplant (BMT), mucositis develops about 7 days after the initiation of mucotoxic therapy, worsens over the next week, and then stabilizes at its most severe level for several days, whereupon it starts to improve, about 10–12 days after it began. Because of the rapid changes that occur in the mouth, it may be necessary to perform assessments daily in this setting. The same may not be true, however, for radiotherapy-induced lesions.

These scales have two major deficiencies. None truly measures the misery that patients with this treatment-related toxicity experience. In addition, assessments stop at the posterior pharynx. Not infrequently, significant pain does not completely overlap with objective measures of mucositis, especially in the BMT setting, where symptoms seem to precede the onset of actual mucositis. Unseen throat mucositis can be associated with significant pain and may be experienced for several days before the onset of oral mucositis, even in the face of adequate prophylaxis against local herpes simplex and candidal infections. Thus, any assessment of an agent that is active in mucositis must include a measure of pain and/or quality of life for it to be considered effective.

Palifermin: The First Truly Effective Agent

Palifermin, a member of the fibroblast growth factor family [6], is the first agent that specifically ameliorates the mucosal toxicity of high-dose chemotherapy and radiation therapy. It binds to its receptor on a variety of epithelial tissues, including skin keratinocytes and stratified squamous epithelium, gastrointestinal and oral epithelial cells, hepatocytes, and type II pneumocytes. In both animal and human models of mucositis, palifermin induces epithelial thickening of the non-keratinocyte layers of the oral mucosa; it has a similar activity in the digestive tract, primarily in the stomach and upper small bowel [7]. Given to normal volunteers, palifermin stimulates the proliferation of oral epithelial cells, as well as increases the percentage of cells that are actively dividing, as measured by an increase in mitotic figures and Ki-67 positivity. In murine models of mucositis, induced by treatment with 5-fluorouracil, methotrexate, and localized irradiation in combination with or alternatively with total body irradiation (TBI), palifermin increased survival by 55% [7]. It has now been tested in phase I–III clinical trials, and the issues of optimal scale, appropriate endpoints, timing of measurements, training of observers, and documentation of patient-reported symptoms have all been thoughtfully addressed as well.

INITIAL CLINICAL STUDIES

The initial phase I study of palifermin was performed in lymphoma patients who received high-

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dose chemotherapy (BEAM regimen: BiCNU [carmustine], etoposide, ara-C [cytarabine], and melphalan [Alkeran]) with an autologous peripheral blood stem cell transplant [8]. Placebo or active study drug (palifermin) was administered intravenously either daily for 3 days before the BEAM regimen or with an additional 3 days, starting on the day of stem cell infusion. The maximum tolerated dose was 60 μg/kg, as several patients receiving 80 μg/kg daily developed what were considered to be moderate skin and oral reactions. At a dose level of 60 μg/kg, no WHO grade 4 mucositis was seen, and less than 10% of patients experienced grade 3 toxicity. In addition, no differences in outcome were seen when the WHO scale was compared with the OAG scale. Also seen was an improvement in patient-reported mouth and throat soreness.

PHASE II STUDIES

Based on these promising results, a randomized phase II trial of palifermin was performed in the transplant setting, using a TBI-based preparative regimen [9]. Severe mucositis was significantly improved, as measured by WHO grade and duration, in those patients who received palifermin 60 μg/kg daily for 3 days before the preparative regimen began and also after the infusion of stem cells at its completion. Patients' perception of mouth and throat soreness and their analgesic requirements were significantly reduced in the palifermin-treated arms of the study.

A similar trial design was used in patients with advanced colon cancer in which palifermin was administered on days 1–3 and 5-fluorouracil and leucovorin calcium were given on days 4–8 [10]. Again, there was a significant decrease in moderate-to-severe mucositis and a shortening of the duration of mucosal symptoms in those patients who received palifermin, compared with the placebo-treated group.

PHASE III STUDIES

The successful phase II BMT trial led to the phase III trial reported by Stiff et al (page 75). Once again, the incidence and severity of WHO grade III/IV mucositis were significantly better in patients who received palifermin, as opposed to placebo, with most of the benefit being a reduction of grade IV mucositis. The WHO scale was as accurate for measuring the severity of mucositis as the RTOG comparator scale, and, as in the previous phase II study, there was a significant reduction in analgesic use as well as total parenteral nutrition requirements in the palifermin-treated group. In addition, there was a significant reduction in patient-reported mouth and throat soreness, as well as improvement in quality of life, as measured by the Functional Assessment of Cancer Therapy-General questionnaire.

The result is that for the first time, we have an effective agent for mucositis that significantly improves pain and function. Moreover, during the process of evaluating this new agent, we have developed a road map for how to perform further mucositis studies.

Additional clinical trials of palifermin are scheduled, and, based on beneficial effects observed in an animal model of graft-versus-host disease, exploratory studies in allogeneic BMT recipients are starting. Finally, patients undergoing mucotoxic therapies may be able to look forward to relief.

References

1. Bellm LA, Epstein JR, Rose-Ped A, Martin P, Fuchs HJ. Patient reports of complications of bone marrow transplantation. Support Care Cancer 2000;8:33–39.
2. Stiff P. Mucositis associated with stem cell transplantation: current status and innovative approaches to management. Bone Marrow Transplant 2001;27(suppl 2):S3–S11.
3. Sonis S, Oster G, Fuchs H, et al. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. J Clin Oncol 2001;19:2201–2205.
4. Peterson DE. Research advances in oral mucositis. Curr Opin Oncol 1999;11:261–266.
5. Sonis ST, Eilers JP, Epstein JB, et al. Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. Mucositis Study Group. Cancer 1999;15:2103–2113.
6. Rubin JS, Osada H, Finch RW, et al. Purification and characterization of a newly identified growth factor specific for epithelial cells. Proc Natl Acad Sci USA 1989;86:802–806.
7. Farrell CL, Rex KL, Kaufman SA, et al. Effects of keratinocyte growth factor in the squamous epithelium of the upper aerodigestive tract of normal and irradiated mice. Int J Radiat Biol 1999;75:609–612.
8. Durrant S, Pico JL, Schultz N, et al. A phase I study of recombinant keratinocyte growth factor (rHuKGF) in lymphoma patients receiving high-dose chemotherapy with autologous peripheral blood progenitor cell transplantation [abstract]. Blood 1999;94(suppl 1):708a.
9. Speilberger RT, Stiff P, Emmanoulides C, et al. Efficacy of recombinant human keratinocyte growth factor (rHuKGF) in reducing mucositis in patients with hematologic malignancies undergoing autologous peripheral blood progenitor cell transplantation (auto-PBPCT) after radiation-based conditioning—results of a phase 2 trial. In: Program/Proceedings of the 37th Annual Meeting of the American Society of Clinical Oncology; May 12–15, 2001; San Francisco, Calif. Abstract 25.
10. Clarke SJ, Abdi E, Davis D, et al. Recombinant human keratinocyte growth factor (rHuKGF) prevents chemotherapy-induced mucositis in patients with advanced colorectal cancer: a randomized phase II trial. In: Program/Proceedings of the 37th Annual Meeting of the American Society of Clinical Oncology; May 12–15, 2001; San Francisco, Calif. Abstract 1529.