

# Mucositis: Continuing Progress for a Continuing Need

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**D**espite the availability of the first agent approved by the US Food and Drug Administration to prevent mucositis in the hematopoietic stem cell transplant setting, many patients continue to suffer from this painful complication of anticancer therapy. This suffering is experienced not only by those undergoing stem cell transplants with non-total body irradiation (TBI)-based preparative regimens or by those in the allograft setting, but also by those receiving chemoradiotherapy for cancers of the head and neck or lungs. In addition, as more patients receive dose-dense chemotherapy or complicated combinations for gastrointestinal malignancies, intestinal mucositis caused by many neoplastic agents is being appreciated belatedly as a major cause of morbidity.

Emerging data show that regimens long thought not to cause significant mucositis actually do. Skeptics remain, but most investigators in the field agree that mucositis rates and severity continue to be underreported. This introduction discusses a number of significant studies of mucositis presented at major oncology meetings in 2006 and attempts to put these results in context with recently published literature. Hopefully, current trials and ongoing analyses of mucositis, such as those reported in this supplement to *The Journal of Supportive Oncology*, will focus increased attention on this painful and potentially lethal toxicity of anticancer therapy.

## Hematopoietic Stem Cell Transplantation

### IMPACT OF SEVERE MUCOSITIS

Many groups are examining the consequences of severe mucositis in patients who undergo both autografts and allografts as a prelude to or part of clinical trials. Data from the phase III study of palifermin (Kepivance), the first active agent approved for the

prevention of mucositis, indicate that TBI-based preparative regimens in the autograft setting are associated with the highest frequency of severe oral mucositis, with incidence rates as high as 98% when carefully assessed.<sup>1</sup> A follow-up publication from this trial detailed the significant impact mucositis has on both outcome and quality of life.<sup>2</sup> Although there was no increase in mortality in the phase III palifermin study, even for the 62% of those with grade 4 mucositis in this trial, several recent reports suggest that mortality is higher for those who develop severe mucositis in the transplant setting.

A recent retrospective report from Vera-Llonch et al<sup>3</sup> of 281 allografted patients, 96% of whom received TBI-based preparative regimens, details this risk. As in the palifermin autograft study,<sup>1</sup> days of fever, total parenteral nutrition use, narcotic use, and number of infections were higher as the mucositis became more severe. However, mortality also increased, from 8.8% for those without mucositis to 22% for those with the most severe form ( $P = 0.0422$ ). Although mucositis was seen with greater frequency among patients receiving prophylaxis for graft-versus-host disease (GVHD) with methotrexate as compared with those given sirolimus (Rapamune), the rate of severe mucositis was still 34% in this latter group (vs 66% in the methotrexate group). Costs of patient care also increased significantly, ranging from \$213,995 for those without ulcerative mucositis to \$437,421 for those with the worst mucositis.

Palifermin continues to be recommended as the only agent proven to be of clinical benefit in the transplant setting. Whether ongoing trials in the allograft setting or for mucositis caused by other severely mucotoxic regimens will indicate a survival benefit for palifermin is unknown.

### MELPHALAN-CONTAINING REGIMENS

One of the most debated issues in transplantation is the extent and severity of mucositis in patients who are autotransplanted with melphalan (Alkeran)-containing regimens. Although the most common preparative regimens for lymphoma or myeloma are based on high-dose melphalan, most

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investigators believe that these regimens only occasionally cause mucositis that is typically not severe, prolonged, or of significant impact to quality of life. However, recent studies indicate otherwise. Two studies of patients receiving single-agent melphalan ( $200 \text{ mg/m}^2$ )<sup>4,5</sup> showed ulcerative mucositis in  $\geq 65\%$  and severe mucositis (grade 3/4) in  $\geq 33\%$ . Notably, systemic narcotics were required for pain control for 2.6–6.5 days in these patients.

The most comprehensive analysis of oral mucositis due to melphalan-containing regimens in the transplant setting was presented by the European Group for Blood & Marrow Transplantation in 2006. Patients from 25 centers in 13 countries were evaluated using centrally trained observers. In this report, Blijlevens et al (page 50) found the incidence of severe mucositis was 46% in patients receiving high-dose melphalan and 41% in patients receiving BEAM (carmustine [BiCNU], etoposide, cytarabine, and melphalan) conditioning, with durations of severe mucositis of 5.4 and 5.3 days, respectively. Similar to that seen with TBI-based regimens, severe mucositis from these chemotherapies was associated with prolonged hospital stay and days of fever. The appropriate conclusion from these data is that mucositis associated with high-dose melphalan or BEAM chemotherapy requires our best efforts to ameliorate.

#### TREATMENT ADVANCES

Over the past 18 months, three new reports were published detailing the use of cryotherapy along with single-agent, high-dose melphalan in the transplant setting. Two were phase II studies, and the third was a phase III study of 20 patients in each arm.<sup>6-8</sup> Taken together, these studies validate the effectiveness of this therapy in reducing the incidence of severe mucositis; however, this approach has not been tested in multiagent regimens.

A recent small, placebo-controlled study by Antunes et al<sup>9</sup> validated earlier reports that low-level helium-neon laser therapy in the autograft setting did decrease severe mucositis, but there was no difference in pain scores, possibly because the technical nature of the therapy did not effectively treat the lower pharynx. Amifostine (Ethyol) continues to be studied in patients receiving high-dose melphalan, with a suggestion that the optimal pretreatment dose is  $910 \text{ mg/m}^2$ . At this level, a 2005 study<sup>5</sup> showed a decrease in grade 3/4 mucositis from 33 to 12% ( $P = 0.02$ ) in patients ( $n = 90$ ) receiving melphalan ( $200 \text{ mg/m}^2$ ).

New studies of palifermin in both the autograft and allograft settings are starting to appear. In the autograft setting, a retrospective comparison<sup>10</sup> of mucositis in 34 patients receiving high-dose melphalan or BEAM combined with standard doses of palifermin showed that palifermin reduced grade 3/4 mucositis from 44% to 17%. A downstream benefit of lower narcotic use was not seen in this analysis. A similarly designed study was also reported by Nasilowska-Adamska et al (page 56) in 53 patients who received either an allograft (45%) or an autograft and an ablative regimen. The patients were matched to historical controls, and a decrease in grade 3/4 mucositis was seen along with a suggestive decrease in acute GVHD in 25% versus 50% in favor of the palifermin group. However, because there were only 24 allografted patients, and it is not clear what GVHD prophylaxis was administered to these patients, a claim of improved GVHD control is tenuous.

Results from the first allograft trial with a GVHD endpoint were published recently by Blazar et al.<sup>11</sup> Based on animal models of GVHD, patients in this phase I study received palifermin post transplant at increasing durations. A dramatic difference in mucositis outcomes was not detected, although an interaction with methotrexate given on day +1 may have affected the efficacy of palifermin. At the February 2007 meeting of the Center for International Blood and Marrow Transplant Research and the American Society for Blood and Marrow Transplantation, data presented by our group showed that palifermin was effective in preventing oral mucositis in patients receiving umbilical cord blood transplants (without methotrexate GVHD prophylaxis) and TBI-based preparative regimens.<sup>12</sup> Only 2/11 patients developed any mucositis in the palifermin treated group versus 12/15 in the historical controls.

Additional phase III transplant trials with mucositis endpoints are underway to define the value of palifermin in the autograft setting in BEAM-treated patients and in the allograft setting using standard ablative regimens. It is anticipated that studies utilizing the other fibroblast growth factor (FGF-20; velafermin) currently being tested in the transplant setting will be available for review in the next several years. Unique to this agent is its potential benefit when administered after completion of the transplant regimen. In 2006, Schuster et al (page 58) examined the efficacy of varying doses of velafermin (0.03, 0.1, or 0.2 mg/kg) in preventing oral mucositis after stem cell transplant, with or without TBI.

## Head and Neck Cancer

Severe mucositis is seen in > 90% of patients receiving chemoradiotherapy for head and neck cancer. The burden of mucositis in this setting—both on patient quality of life and healthcare resources—is significant, as detailed in the study by Isitt et al (page 54). Given its severity and duration, a number of trials testing everything from topical antibiotics to growth factors have been tried to alleviate the suffering, reduced quality of life, and depression in these patients. A series of phase III treatment trials have recently been published, most with unfavorable results. Topical agents such as pilocarpine and hematopoietic growth factors such as granulocyte macrophage-colony stimulating factor (sargramostim [Leukine]) were found to be inactive.<sup>13,14</sup>

On the other hand, a small, preliminary study of intravenous L-alanyl-L-glutamine showed a decrease in mucositis among 14 patients compared with 15 controls.<sup>15</sup> Favorable results were also seen in a 30-patient randomized trial of low-energy helium-neon laser therapy administered daily to nine intraoral sites preradiotherapy.<sup>16</sup> Grade 3 mucositis dropped from 35.2% to 0.6%, and there was a concomitant decrease in pain that persisted throughout the treatment period. Palifermin studies are underway in this setting and, hopefully, will be reported in 2007. However, given the severity of the local mucosal damage, it is likely that a combined approach, including a growth factor such as palifermin and a local therapy such as low-energy lasers, will be most effective for these patients.

## Conclusion

Thanks to the efforts by organizations such as the Multinational Association for Supportive Care in Cancer and well conducted surveys taken by dedicated investigators, the severity of mucositis for even “mild” BMT regimens is being recognized. Now that effective therapy has been approved or is in development to prevent mucositis in these various settings, it is imperative that patients reap the benefits. Unfortunately, the efforts at many centers are being implemented too slowly for effective and comprehensive cancer care.

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