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Palifermin in Myelotoxic Therapy-Induced Oral Mucositis

A Viewpoint by Douglas E. Peterson

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Oral mucositis in patients receiving high-dose cancer therapies has historically been a frequent and expected adverse effect. The condition has often been viewed as an inevitable consequence of these cancer treatments, leading to supportive care measures that are implemented as needed prior to and during the acute phase. Despite the utility of these interventions, however, none has been directed to the specific pathobiology of oral mucositis.

Palifermin represents the first drug approved by the US FDA for the reduction of incidence and duration of oral mucositis in a specific cancer patient cohort. The drug's mechanism of action is based on the contemporary paradigm of mucosal injury in cancer patients. This achievement of regulatory approval based on a complex and current model of mucositis pathobiology is noteworthy.

These advances, as represented by palifermin, herald a new era of molecularly targeted therapy for patients at risk for clinically significant oral and gastrointestinal mucositis. Several other drugs are currently under development, including those administered via the enteral route. If ultimately approved for clinical use by federal regulatory agencies, the clinicians could be positioned to customise preventive and treatment drug interventions, based on anticipated severity and trajectory of mucositis in each patient. Furthermore, it is conceptually feasible that reduction in the inflammatory cascade within the oral mucosa could also mitigate severity of overall symptom clusters in these patients, including nausea, emesis and fatigue.

The efficacy of palifermin in the phase III trial is impressive from several perspectives, including a substantial reduction in grade 4 oral mucositis as well as in several patient-oriented and healthcare resource use measures. Some concerns exist regarding palifermin, however. These issues include potential safety considerations for other patient cohorts (e.g. allogeneic transplant patients), ease of route of administration (e.g. intravenous infusion), long-term safety regarding potential for tumour growth stimulation (e.g. patients being treated for oral squamous cell carcinoma) and cost of the drug (e.g. >$US8000 per patient at the present time). These and other issues warrant further studies. By comparison, however, the potential for designing combination therapies involving palifermin, as suggested above, provides an exciting opportunity for clinical studies at the phase IV level as well.

Modeling of development of drugs to manage oral mucositis parallels in many ways the evolution of drug development to reduce the incidence and severity of nausea and emesis in cancer patients over the past 20 years. In this latter model, advances in the understanding of molecular mechanisms of nausea and emesis, coupled with the development of single- and multi-drug therapeutic strategies, have enabled the clinician to effectively manage this prevalent toxicity in many cancer patients otherwise at risk for the condition. There is reason for realistic optimism that similar successes will emerge in the management of oral and gastrointestinal mucositis in cancer patients over the next several years. The science and regulatory approval represented by palifermin symbolises a key step in this strategic evolution. ▲