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Supportive Care for Oncology Treatment: Not Just Icing on the Cake

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Oral mucositis (OM) is a frequent and, occasionally severe complication of chemotherapy and radiation therapy to treat cancer. The patient's experience of OM can range from mild odynophagia to severe tissue inflammation, edema, and mucosal bleeding which prevents all alimentation, and can require -- in its most severe form -- intubation to protect a patient's airway. As patients experience progressive mucositis during treatment, a vicious cycle can ensue, including worsening pain and dysphagia, resulting in reduced oral intake, leading to malnutrition, weight loss, fatigue and deconditioning. At the same time, ulceration in the oral cavity can lead to bacterial and fungal colonization and local infection, putting immune compromised patients at risk for systemic infection.

While best characterized in the setting of myeloablative high-dose chemotherapy for patients undergoing hematological stem cell transplantation (HCST), OM is a common toxicity of a wide range of chemotherapy agents used to treat cancers such as breast, lung, colorectal, and lymphoma.(1) The World Health Organization's scoring for grading OM ranges from 0 to 4, with 0 being no evidence of mucositis, grade 1 including soreness with or without erythema but no ulcerations, while grade 2 to 4 includes erythema and ulceration and a progressive loss of the ability to eat. Grade 2 classifies patients who can still swallow some solid foods, while grade 3 characterizes patients who cannot swallow any solid food. Grade 4 is reserved for those patients who are not able to tolerate any p.o. intake. (2) Despite its clinical impact, OM has not been studied with the fervor and intensity of new anti-cancer agents that are designed to eliminate tumor burdens and cure patients or prolong their survival. Hence, it has been viewed as the "icing on the cake" of cancer therapy, to the detriments of cancer patients who suffer from the complications of this very real clinical problem.

Given the severity and significant complications from oral mucositis, a number of interventions have been developed and tested to reduce the severity of this complication. Good oral hygiene, aggressive use of narcotic analgesics, and frequent physician evaluations are critical. Additional interventions that have been studied include cryotherapy using ice chips, and drugs such as benzydamine, amifostine, and more recently palifermin. Palifermin is a recombinant human keratinocyte growth factor (KGF) which targets the KGF/FGFR2b receptor. Stimulating this growth factor receptor can have a potent stimulating effect on epithelial cell proliferation. When initially tested in patients undergoing autologous HCST, palifermin was found to reduce the percentage of patients experiencing severe (grade 3/4) OM as well as its duration. (3) This positive study led to FDA approval in December, 2004. Subsequent studies of palifermin in colorectal patients treated with 5-fluorouracil as well as head and neck patients treated with radiation therapy have found improvements in mucositis,

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dysphagia and xerostomia in select patient groups. However, while approved as part of the conditioning regimen in HSCT, palifermin is not currently recommended for inclusion in other treatment modalities based on the consensus statements from groups such as the American Society of Clinical Oncology and the Multinational Association of Supportive Care in Cancer (1,2).

In this issue of the *Annals*, Vadhan-Raj and colleagues describe the effects of palifermin therapy in patients undergoing intensive treatment for solid tumor malignancies. (4) Using a randomized placebo-controlled phase II study design, they found that patients treated with doxorubicin-based chemotherapy for sarcomas had a significant improvement in the severity and duration of grade 2-4 mucositis. Patients in the trial received a single dose of 180 micrograms/kg instead of the standard three daily dosages prior to chemotherapy. Further, patients on the placebo arm were allowed to cross over to palifermin after treatment assignments were unblinded; all such patients experienced improvement in their OM in subsequent rounds of chemotherapy. In short, this is a positive study that met its endpoint.

The importance of supportive care in assisting patients undergoing intensive anticancer therapy cannot be overemphasized. Accordingly, we believe such supportive care interventions such as the use of palifermin should be assessed based on four principles.

First, do no harm

As the sobering experience from the use of erythropoiesis-stimulating agents has taught us, supportive agents can unexpectedly have negative impacts on patient outcomes. A central concern in the use of keratinocyte growth factor agonists such as palifermin is that they might initiate cell signals that lead to tumor proliferation or therapeutic resistance. Preclinical *in vitro* and *in vivo* research studies have yielded conflicting results that leave it unclear as to whether KGF agonists induce tumor growth, inhibit or induce apoptosis, induce cellular migration and/or invasion, or induce other tumorigenic properties (reviewed in 5). It is worth noting that past clinical studies of palifermin in hematological and solid tumor malignancies did not observe adverse clinical outcomes such as overall survival in patients (6,7,8). Importantly, the patients in the Vadhan-Raj study had sarcoma, which as a tumor of mesenchymal origin is not thought likely to be affected by KGF pathway signal activation. (5) Nevertheless, these cautionary preclinical studies must be considered, since uncovering the long-term adverse effects of erythropoietin stimulating agents required years of use in many thousands of patients.

Second, reduce suffering

Patients undergoing HSCT have reported that oral mucositis can be the worst complication of their entire intensive and prolonged treatment. (9) Given the inability to tolerate oral intake and the need for significant analgesics to treat OM, effective reduction of agents the severity and duration of this common toxicity clearly would have a significant impact on the quality of life and tolerability of current treatments. In the study by Vadhan-Raj, not only were the severity and duration of mucositis reduced, but patients themselves reported lower levels of suffering. Also, the requirements for narcotic analgesics were significantly reduced in those treated with palifermin. For example, patients required only one-sixth of the opioid analgesics in the palifermin treatment group compared to those in the placebo arm. This was an even more significant difference than that seen in the original trial in HSCT by Spielberger *et al.* (3).

Third, improve the efficacy of overall treatment

Given that mucositis can be a dose-limiting toxicity of some cytotoxic therapy regimens, a key impact of supportive care interventions could be an improvement in the delivery of anticancer treatment. For example, in the trial by Rosen *et al* of patients with colorectal cancer, dose reductions of 5-fluorouracil were more common in the placebo arm compared to those patients on palifermin. (7) The authors of the present study do not describe whether patients receiving palifermin required fewer dose reductions or less dose delays compared to those patients in the placebo arm. The authors promised a follow-on study that will include biomarker and pharmacokinetic results, and it is hoped that further information on patient treatment may be presented in the future.

Finally, be cost effective and comparatively effective

A critical issue in today's healthcare marketplace is whether new interventions -- which can be very expensive -- can be shown to be comparatively more effective than past interventions. (10) OM is a toxicity that can require significant resources to treat in terms of hospitalizations, neutropenic infections, and the use of total parental nutrition. Further, the patient experience in terms of pain, deconditioning, malnutrition, and reductions in quality of life can be profound. Thus, an important question of the clinical utility of agents such as palifermin is whether they are cost effective and comparatively effective. Such a question cannot be answered in a small phase II study. Follow-on larger phase III studies, as advocated by the authors, will need to be done, and hopefully will include measures necessary for comparative effectiveness analyses. It is worth noting that a past analysis of patients undergoing HSCT found a non-significant mean savings of \$3,595.00 per patient in those treated with palifermin. (11) Further studies and analyses are looked forward to with interest. Of course, if treatment with palifermin is shown to reduce suffering without increasing the cost of care, the overall benefit to patients would support its wider use.

In this era of combined aggressive cancer therapies that can include radiation, cytotoxic chemotherapy and biological targeted therapies, the incidence of toxicities, including mucositis is on the rise. These intensified therapies are meant to improve patient outcomes, but come at a cost of higher toxicities. Thus, interventions aimed at reducing these toxicities, and in turn enhancing the ability to deliver multimodality and multi-agent treatments, are necessary. Rigorous clinical studies of supportive measures such as those aimed at mucositis are as critical as clinical studies investigating new anticancer therapies. Vadhan-Raj and colleagues are to be commended for their well-designed and interesting study that is a valuable addition to a growing literature in the use of this and other supportive care agents that ameliorate the suffering, and improving the outcomes, of our patients. Such treatments are not "icing on the cake" but instead have a fundamental role to play in the care of the entire patient, and not just his or her cancer.

REFERENCES

1. Keefe DM, Schubert MM, Elting LS, Sonis ST, Epstein JB, Raber-Durlacher JE, et al. Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer*. Mar 1; 2007 109(5):820-31. [PubMed: 17236223]
2. Hensley ML, Hagerty KL, Kewalramani T, Green DM, Meropol NJ, Wasserman TH, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol*. Jan 1; 2009 27(1):127-45. [PubMed: 19018081]

3. Spielberger R, Stiff P, Bensinger W, Gentile T, Weisdorf D, Kewalramani T, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med*. Dec 16; 2004 351(25):2590–8. [PubMed: 15602019]
4. Vadhan-Raj S, Trest J, Patel S, Zhou X, Johnson MM, Araujo D, et al. Single dose palifermin prevents severe oral mucositis in cancer patients during multi-cycle chemotherapy: a double-blind randomized trial. *Annals Int Med* (NEED CITATION).
5. Finch PW, Rubin JS. Keratinocyte growth factor expression and activity in cancer: implications for use in patients with solid tumors. *J Natl Cancer Inst*. Jun 21; 2006 98(12):812–24. [PubMed: 16788155]
6. Levine JE, Blazar BR, DeFor T, Ferrara JL, Weisdorf DJ. Long-term follow-up of a phase I/II randomized, placebo-controlled trial of palifermin to prevent graft-versus-host disease (GVHD) after related donor allogeneic hematopoietic cell transplantation (HCT). *Biol Blood Marrow Transplant*. Sep; 2008 14(9):1017–21. [PubMed: 18721764]
7. Rosen LS, Abdi E, Davis ID, Gutheil J, Schnell FM, Zalcberg J, et al. Palifermin reduces the incidence of oral mucositis in patients with metastatic colorectal cancer treated with fluorouracil-based chemotherapy. *J Clin Oncol*. Nov 20; 2006 24(33):5194–200. [PubMed: 17075109]
8. Brizel DM, Murphy BA, Rosenthal DI, Pandya KJ, Glück S, Brizel HE, et al. Phase II study of palifermin and concurrent chemoradiation in head and neck squamous cell carcinoma. *J Clin Oncol*. May 20; 2008 26(15):2489–96. [PubMed: 18487568]
9. Bellm LA, Epstein JB, Rose-Ped A, Martin P, Fuchs HJ. Patient reports of complications of bone marrow transplantation. *Support Care Cancer*. Jan; 2000 8(1):33–9. [PubMed: 10650895]
10. Sox HC, Greenfield S. Comparative effectiveness research: a report from the Institute of Medicine. *Ann Intern Med*. Aug 4; 2009 151(3):203–5. [PubMed: 19567618]
11. Elting LS, Shih YC, Stiff PJ, Bensinger W, Cantor SB, Cooksley C, et al. Economic impact of palifermin on the costs of hospitalization for autologous hematopoietic stem-cell transplant: analysis of phase 3 trial results. *Biol Blood Marrow Transplant*. Jul; 2007 13(7):806–13. [PubMed: 17580258]