Palifermin (Kepivance™) in the treatment of mucositis

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In patients undergoing high dose chemotherapy and hematopoietic stem cell transplant, oral mucositis (OM) is one of the most debilitating and annoying side effects. This complication results from cytotoxic injury to the epithelial lining of the oropharyngeal mucosa, although lesions of the whole gastrointestinal tract also occur.[1] The severity of OM varies from erythema and edema accompanied by mild soreness to full mucosal thickness ulcerations penetrating into the submucosa, often resulting in severe pain requiring narcotic analgesia and impaired swallowing, prolonged hospitalization, and increased risks for infections and potentially life-threatening sequelae.[2,3] Between 40% to 80% of cancer patients undergoing intensive treatment regimens requiring hematopoietic stem cell transplantation (HSCT) suffer the debilitating effects of OM during their cancer therapy.[4 7]

The clinical consequences of OM are multifaceted. From the patients' perspective, this is the most serious, painful, and detrimental condition leading to significant decreases in their quality of life due to the difficulty or inability to eat, drink, swallow, or speak. The consequences of OM often necessitate use of narcotic analgesics for pain control and/or some form of parenteral nutrition to allow hydration and caloric intake.[8] From the clinicians' point of view, severe OM may increase the patients' risk for life threatening infections and may prolong hospitalization.[9-12] The severity of OM in the transplant setting has been associated with increased mortality.1[3,14]

The most common interventions for OM management include good oral hygiene to minimize the risk of infections, pain medication, and parenteral nutrition if needed.[15,16] Experimental therapies under investigation include amifostine, sucralfate, glutamine, and GM-CSF mouthwash.[17-22] Until recently, there have been no approved medications to reduce the incidence and/or duration of OM.[23-25]

Discovered in 1989, keratinocyte growth factor (KGF) is a 28 kD member of the fibroblast growth factor family with epithelial cell proliferative properties.[26] Palifermin (Kepivance™) is a truncated, recombinant form of human keratinocyte growth factor (rHuKGF) that has been approved in the USA in 2004 to decrease the incidence and duration of severe OM in patients with hematologic malignancies receiving myelotoxic therapy requiring HSCT support. Palifermin (recombinant human keratinocyte growth factor) is an N-terminal, truncated version of endogenous keratinocyte growth factor with biologic activity similar to that of the native protein, but with increased stability 26 In animal models of chemotherapy, radiotherapy, and hematopoietic stem-cell transplantation[27,28] palifermin protected several types of epithelial tissues. A phase 1 trial indicated that palifermin at doses of up to 80 µg per kilogram of body weight per day for three consecutive days was not associated with major adverse events.[29] Early studies in colorectal cancer in patients receiving fluorouracil have documented feasibility but full safety and efficacy data are not available.

Pivotal randomized studies in autologous transplant patients

Randomized phase 1-2 studies in haematologic patients undergoing autologous transplant have established a safe dosage and have strongly suggested of a beneficial effect on mucositis (Amgen files) Finally, a large phase 3 blind multicenter randomized study involving 212 patients with hematologic malignancies undergoing HDC and autoslogous stem transplant was conducted and completed in the USA.[30] Patients were stratified according to diagnosis and center (13 centers were involved). Baseline characteristics for patients were similar across the treatment groups. The majority of patients were male (>56%) and white (>74%), with a median age of 49 years (range 18 to 69 years). A majority of patients in both treatment groups had Non Hodgkin's lymphoma or Hodgkin's disease,

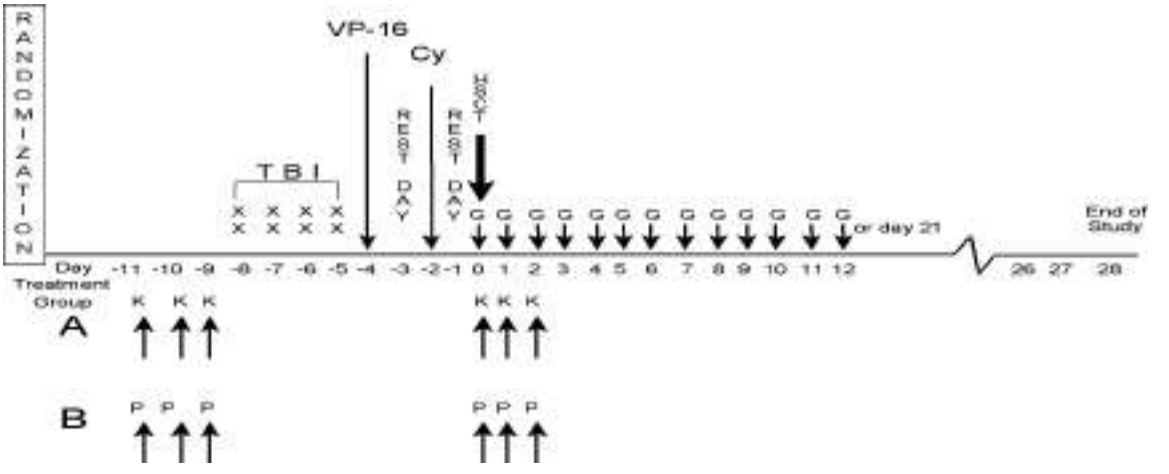


Figure 1. Palifermin administration during conditioning.
Conditioning regimen: TBI/etoposide (VP-16)/cyclophosphamide (Cy). Treatment Group A: K = palifermin 60 μg/kg/day IV bolus. Treatment Group B:P=placebo. TBI = fractionated total body irradiation: 12 Gy total dose in 6, 8, 0r 10 fractions over 3 to 4 days. VP-16 = etoposide: 1 dose of 60 mg/kg IV over 4 hours. Cy = cyclophosphamide: 1 dose of 100 mg/kg IV over 1 hour. G = Filgrastim: 5 μg/kg once daily starting on day 0 after hematopoietic stem cell transplantation and continuing until day 21 or engraftment.

a Karnofsky performance status >90.

Patients were randomly assigned to receive palifermin (60 μg/kg/day) or placebo intravenously for 3 consecutive days before the conditioning regimen (Total Body Irradiation, etoposide, and cyclophosphamide) and 3 consecutive days after HSCT (Figure 1). This schedule of Palifermin administration was based on the experience of a previous randomized phase II study (Amgen files) where it was documented to be safe and effective, whereas a different schedule that included palifermin administration coinciding with conditioning chemotherapy seemed to be ineffective. Total body irradiation was delivered in 6, 8, or 10 fractions over 3 or 4 days (beginning on day –8) for a total dose of 12 Grays (Gy). Chemotherapy included intravenous etoposide (60 mg/kg) on the day following the final TBI treatment and 1 dose of cyclophosphamide (100 mg/kg) 2 days prior to HSCT

The main mucositis tool was the WHO (World Health Organization) scale for oral mucositis which grades it as follows: grade 0=no OM; grade 1=soreness with or without erythema, no ulceration; grade 2=erythema and ulcers, patients can swallow solid diet; grade 3=extensive erythema and ulcers, patients cannot swallow solid diet; and grade 4=mucositis to the extent that alimentation is not possible. Daily oral assessments were done blindly by independet reviewer in most centers (usually a trained dentist). Additionally, two more clinical grading scales of oral mucositis (Radiation Therapy Oncology Group [RTOG], and Western Consortium for Cancer Nursing Research [WCCNR]) were used in the phase 3 study in order to obtain rigorous data. Furthermore, a patient self-reported daily questionnaire was used to measure the severity of mouth pain as perceived by patients and its impact on daily functional activities (drinking, eating, swallowing, talking, and sleeping). Patients were asked to complete the questionnaire, termed the Oral Mucositis Daily Questionnaire (OMDQ), every day from the day prior to the start of the conditioning regimen (day–12) up to 28 days after HSCT for a maximum of 41 days.

Results

A significant reduction of many parameters of oral mucositis was again documented in the palifermin group. Oral mucositis of WHO grade 3 or 4 developed in 67 of 106 patients in the palifermin group (63 percent) and 104 of 106 patients in the placebo group (98 percent, $p<0.001$) (Figure 2). In addition, the incidence of the most severe and debilitating oral mucositis (WHO grade 4) was reduced from 62% in patients receiving placebo to 20% in patients receiving palifermin ($p<0.001$). The median duration of oral mucositis of grade 3 or 4 among patients with this adverse effect was 6.0 days (range, 1 to 22) in the palifermin group and 9.0 days (range, 1 to 27) in the placebo group ($p<0.001$) (Figure 3). The median duration of oral mucositis of WHO grade 3 or 4 among all patients was 3.0 days (range, 0 to 22) in the palifermin group and 9.0 days (range, 0 to 27) in the placebo group ($p<0.001$) (Figure 3a). This result — the primary end

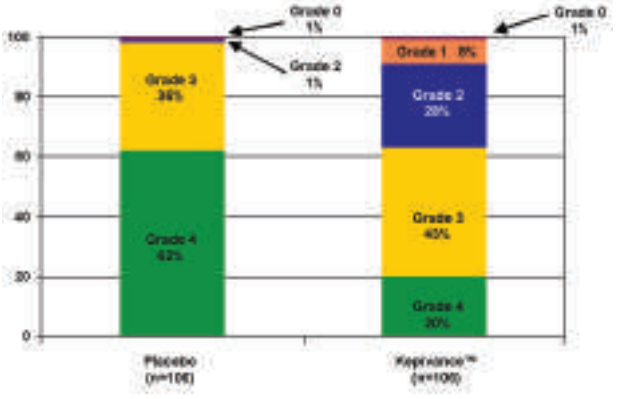
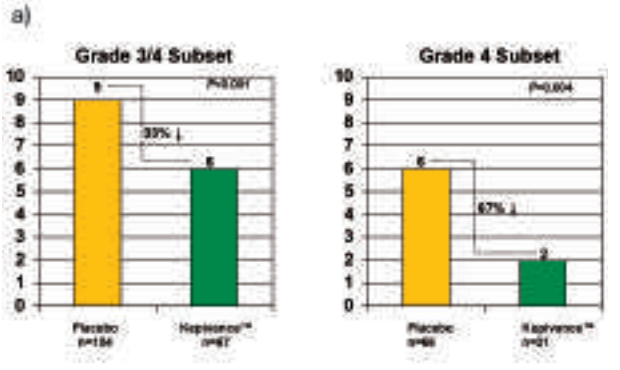


Figure 2. Incidence of oral mucositis in the 2 treatment groups. Adapted from Spielberger R, new Engl J Med. 2004;351:2590-8.



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Kepivance™ Product Information

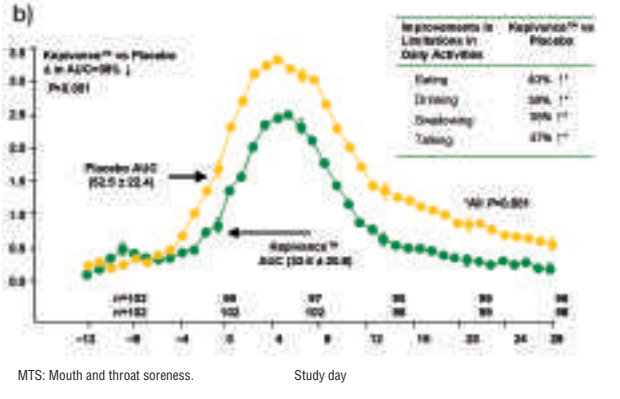

Figure 3. Improvement of objective mucositis (a), and subjective symptoms (b), by palifermin. a. Kepivance™ (palifermin) Reduced the Duration of Severe Oral Mucositis in the Subset of Patients Who Experienced this Severity. b. Palifermin improved oral mucositis-related patient-reported outcomes in the HSCT. *Adapted from Emmanouilides C, et al. Blood, 2003;102:251a and Spielberger R, N Engl J Med 2004;351:2590-8.*

point — was reproducible when the analysis was performed according to center, type of hematologic cancer, or number of fractions of irradiation. Similar esults were seen for other measurements of oral mucositis among all patients, including the median duration of oral mucositis of WHO grade 2 or higher (8.0 days [range, 0 to 28] in the palifermin group and 14.3 days [range, 0 to 37] in the placebo group, $p<0.001$), the median duration of oral mucositis of RTOG grade 3 or 4 (0.0 days [range, 0 to 24] and 6.0 days [range, 0 to 54], $p<0.001$), and the median duration of lesions of WCCNR grade 2 or 3 (1.0 day [range, 0 to 36] and 7.0 days [range, 0 to 56], $p<0.001$).

Effect on resource utilization

The reduction of mucositis resulted in significant associated reduction of supportive resources.[31] Palifermin recipients used less parenteral or transdermal opioid analgesics for mucositis than did placebo recipients, as measured by the median cumulative dose administered (212 mg of morphine equivalents [range, 0 to 9418] vs. 535 mg of morphine equivalents [range, 0 to 9418], $p<0.001$) and the median duration of administration (7.0 days [range, 0 to 28] vs. 11.0 days [range, 0 to 32], $p<0.001$). Palifermin recipients had a lower incidence of febrile neutropenia than did placebo recipients (75 percent vs. 92 percent, $p<0.001$). Exploratory analysis revealed a trend toward a lower incidence of blood-borne infections in the palifermin group than in the placebo group (15 percent vs. 25 percent). The incidence of the use of total parenteral nutrition during the study was also lower among palifermin recipients than among placebo recipients (31 percent vs. 55 percent, $p<0.001$).

These findings were confirmed by the statistically significant improvement of patient self reported mouth and throat pain and its impact on daily functioning in patients receiving palifermin. This was demonstrated graphically (Figure 3b) as well as numerically using the AUC scores (Table 1).

Overall, palifermin provided a 38% reduction in moth-throat soarness (MTS) AUC score compared to placebo. Similar reductions in limitations (or improvements) were seen in swallowing (38%), drinking (38%), eating (40%), talking (47%), and sleeping (40%) AUC scores. ($p\leq0.01$ for all comparisons). As shown in Table 1, the mean duration (in days) of patients suffering from at least moderate amount of MTS (≥2) was greater than 5 days shorter in the palifermin group as compared to the placebo group. For functional impairment related to MTS, including swallowing, drinking, eating, talking, and sleeping, the use of palifermin resulted in a reduction on average of 4.4, 4.5, 6.1, 4.5, and 3.7 days, respectively, in the duration of these limitations.

Table 1. Duration (days) of mMouth – throat soreness (MTS) and MTS related limitations (≥2) by treatment group.

	Placebo (N=106)	Palifermin (N=106)	Difference (Days)	P-Valuea
MTS				
Mean (SD)	13.7 (5.7)	8.6 (6.5)	5.1	< 0.001
Min, Max	0.0, 25.0	0.0, 29.0		
MTS Related Limitations on Daily Activities				
Swallowing Mean (SD)	12.2 (6.2)	7.8 (7.1)	4.4	< 0.001
Drinking Mean (SD)	11.8 (6.0)	7.3 (7.0)	4.5	< 0.001
Eating Mean (SD)	15.6 (7.0)	9.6 (7.7)	6.1	< 0.001
Talking Mean (SD)	9.9 (5.7)	5.4 (6.8)	4.5	< 0.001
Sleeping Mean (SD)	8.8 (5.7)	5.1 (5.9)	3.7	< 0.001

Toxicity

The incidence, frequency, and severity of adverse events were similar in the two groups, and most were attributable to the underlying cancer, cytotoxic chemotherapy, or total-body irradiation, with the exception of few adverse events consistent with the pharmacologic action of palifermin on skin and oral epithelium (e.g., rash, pruritus, erythema, paresthesia, mouth and tongue disorders, and taste alteration). All these events were mild to moderate in severity, transient (occurring approximately three days after the third dose of palifermin and lasting approximately three days), and not a cause for the discontinuation of study drug. Transient, asymptomatic increases in serum amylase (primarily of salivary origin) and lipase concentrations were observed in both groups, with the peak value for amylase occurring on the last day of irradiation and the peak value for lipase occurring after the third dose of study drug. The increases were higher in the palifermin group (median maximal increases from baseline, 166.5 U of amylase per liter and 17.5 U of lipase per liter) than the placebo group (92.0 and 12.5 U per liter, respectively) This was not associated with any pancreatic pathology and was believed to be related to stimulation of salivary glands. No additional increase was observed for either enzyme, and concentrations returned to near-baseline values by the day of transplantation. After a median follow up of 23 months no adverse effects on morbidity or survival were noted (data submitted for publication).

Conclusions

Palifermin is the first FDA approved drug for the reduction of severe oral mucositis in a group of haematologic patients with pretreatment high-risk for this complication. For the clinicians involved in the study, it was really rewarding to see several patients who despite having received total body irradiation and high dose chemotherapy were able to complete the transplant process without pain and with full diet.

The results of the randomized study confirms beyond doubt the observations of earlier studies in patients undergoing HDC and autologous transplant, demonstrating a clinically meaningful and perceptible benefit in reduction of oral mucositis. Because of the somewhat subjective evaluation of this outcome, several objective scales and subjective measures were used, all confirming the advantage conferred by Palifermin. Beyond the clear benefit in improving the quality of life by reducing oral pain and maintaining the ability to eat, swallow and speak, the reduction of the mucositis results in objective benefits, such as possibly less blood-borne infections, less pain medication administration and less sedation due to opiates, and particularly less need for parenteral administration. On the other hand, the regimen, which includes 3 intravenous administrations before the initiation of the TBI and three just after the infusion of stem cells is simple and devoid of significant toxicity. . Palifermin is a growth factor. Keratinocyte growth-factor receptor is not known to be expressed in hematologic cancers, nevertheless, the growth of second tumors that express this receptor is theoretically possible. Evaluation of this risk requires long-term follow-up, which is ongoing. At 23 months, the progression-free survival rates for palifermin and placebo were identical (data submitted for publication). Iti s unlikely that an adverse long-term effect in the hematologic population will be observed. It is however not impossible that such a concern will prevent the use of palifermin in the protection from mucositis occurring with irradiation or chemoirradiation in patients with solid tumors. There

is no question that palifermin offers a great benefit in the population undergoing TBI-containing high dose chemotherapy. More studies will be performed in cohorts of patients with less pretreatment probability of severe mucositis to better assess the benefit in such cases. Meanwhile the medical community and particularly the patients who are candidates for palifermin could enjoy the clinical and quality of life benefit conferred by this growth factor.

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