Palifermin: A keratinocyte growth factor for oral mucositis

Oral mucositis is an acute and distressing toxic sequel afflicting 70 to 80% of patients who receive chemotherapy and radiation.[1] It significantly impairs the routine functions like eating, swallowing, and talking, and thereby affects the quality of life of such patients. The biological basis of mucositis is complex involving sequential interaction of cytotoxic drugs or irradiation on the mitosis of proliferating epithelium, a number of cytokines and elements of oral microbial environment. In the past 10 years, more than 25 prophylactic or therapeutic treatment interventions based on biological attenuation has been tested for mucositis including opioid analgesics, NSAIDs, amifostine, prostaglandins, sucralfate, chlorhexidine, laser therapy etc.

In December 2004, the US Food and Drug Administration approved the use of Keratinocyte growth factor – Palifermin (KepivanceTM) for the prevention of severe oral mucositis in patients with hematological malignancies receiving high dose chemotherapy.

Chemistry

Palifermin is a human keratinocyte growth factor (r.hKGF) produced by recombinant DNA technology in *Escherichia coli,* manufactured by a biotechnology company Amgen, USA. Keratinocyte Growth Factor (KGF) is an endogenous protein of the family fibroblast growth factors. Palifermin is a water-soluble protein with 140 amino acids and a molecular weight of 16.3kD. It differs from endogenous human KGF in that its N–terminal amino acid has been truncated to increase the protein stability.[2,3]

Mechanism of action

Palifermin an r.hKGF protein binds to KGF receptor leading to proliferation, differentiation, and migration of epithelial cells in many tissues such as the tongue, buccal mucosa, esophagus, stomach, intestine and skin.[4] Palifermin increases epithelial thickening in the squamous epithelium of the oral cavity and increases the crypt depth and villous height of small intestine. Injured epithelium retains the ability to respond to KGF. Following irradiation, palifermin reduces atrophy, accelerates regrowth and decreases ulcer formation of oral epithelium. Palifermin also is thought to work by the reduction of reactive oxygen species through the activation of the transcription factor NRF2. Activation or stimulation of NRF2 results in the modulation of cellular response to stress by regulating several target genes through the antioxidant response element.[5]

Pharmacokinetics

The pharmacokinetics of Palifermin was studied in healthy human volunteers and in patients with haematological malignancies. After intravenous administration of 20 to 250 μg/kg (in healthy subjects) or 60 μg/kg (in cancer patients), palifermin concentration declined rapidly over 95% in the first 30 min. The elimination half-life was 4.5 h in both healthy patients and patients with cancer.[3]

No gender-related differences were observed in the doses tested (60 μg/kg or less). The pharmacokinetics of palifermin have not been assessed in pediatric or geriatric populations or in patients with hepatic or renal impairement.[3]

Preparations, dosage and administration

Palifermin is available as a white, lyophilized powder to be reconstituted with 1.2 mL of sterile water for IV injection. The recommended dosage is 60 μg/kg/day as IV bolus for 3 consecutive days, before and after myelotoxic therapy with a total of six doses. The first three doses should be administered before the myelotoxic therapy with the third dose 24 to 48 h before myelotoxic therapy. The last three doses should be administered after but on the same day of haemoatopoietic stem cell infusion and at least 4 days after the most recent administration of Palifermin.[3]

In a phase I, placebo-controlled, dose-escalation study, an intravenous palifermin dose of 40 μg /kg/day was recommended when administered intravenously for 3 days before a 5-day course of fluorouracil and leucovorin in patients (n = 81) with metastatic colorectal cancer. Dose-limiting oral and cutaneous toxicities were common at palifermin doses of 60 μg /kg/day and higher.[6]

Clinical studies

Two pivotal phase III studies conducted with Palifermin led to its FDA approval. Both the studies used randomized placebo controlled designs and enrolled a total of 381 patients (study 1 enrolled 212 patients and study 2 enrolled 169 patients).

Study 1 was a double blind placebo controlled study enrolling 212 patients with Hodgkin's disease, non-Hodgkin's lymphoma, acute myelogenous leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, or multiple myeloma who received total body irradiation (total, 1200 cGy) and chemotherapy treatment with etoposide (60 mg/kg) and cyclophosphamide (100 mg/kg) before autologous peripheral stem cell transplantation. Patients were randomized to receive placebo (n=106) or intravenous palifermin 60 μg /kg/day for 3 consecutive days before total body irradiation, and 3 consecutive days after peripheral blood stem cell transplantation (n=106). Oral mucositis was assessed before transplantation and daily for 28 days following transplantation or until severe oral mucositis had resolved. The assessment

was based on 3 scales: the 5-grade World Health Organization (WHO) oral-toxicity scale, the 5-grade Radiation Therapy Oncology Group (RTOG) acute radiation- morbidity scoring criteria for mucus membranes, and the 4-grade Western Consortium for Cancer Nursing Research (WCCNR) revised staging system for oral mucositis. The primary end point was the duration of oral mucositis of WHO grade 3 or WHO grade 4. At the end of the study, the palifermin therapy was associated with an improvement in the primary end point, duration of oral mucositis of WHO grade 3 or 4. The median duration was 3 days with palifermin therapy and 9 days with placebo therapy. Palifermin therapy was associated with a reduced incidence and duration of WHO grade 3 and 4 oral mucositis and reduced clinical sequelae, opiod analgesic use, and total parenteral nutrition. Improvements in quality of life, as assessed using daily diaries and the functional assessment of cancer Therapy-general (FACT-G), also were observed.[7]

Study 2 was also a randomized double blind placebo controlled study designed to compare varying schedules of palifermin administration in 169 patients with hematological malignancies. These patients were all treated with high-dose cytotoxic therapy (fractionated total body irradiation with a total dose of 12 cGy, etoposide 60 mg/kg, and cyclophosphamide 75 to 100 mg/kg) followed by peripheral blood progenitor cell support. The reduction in median days of WHO grade ¾ oral mucositis was 4 days with palifermin therapy and 6 days with placebo therapy. The incidence of WHO grade ¾ oral mucositis was 67% with palifermin therapy and 80% with placebo therapy, and the incidence of WHO grade 4 oral mucositis was 26% and 50%, respectively.[3]

Contraindication and precautions

Palifermin is contraindicated in patients with known hypersensitivity to *E.Coli*–derived proteins. Carcinogenic potential of palifermin is unknown. No mutagenic or clastogenic effects were observed. Palifermin is classified as pregnancy category C. It is embryotoxic in animal models. There are no studies in pregnant women. It is also unknown if palifermin is excreted in human milk; therefore caution is advised if palifermin is administered to a breast- feeding woman.[3]

Adverse effects

The most common adverse reactions observed in the Palifermin-treated patients were skin rashes, erythema, edema, and pruritis. In a phase I, placebo controlled, dose escalation study, abdominal pain, altered taste, anorexia, and vomiting occurred more often in patients who received palifermin compared to placebo. Tongue thickening or discolouration has occurred in 17% of patients, which was attributed to palifermin therapy.[7] Although hypertensive events were reported in 7% of patients receiving Palifermin, they were transient and did not require treatment after discontinuation.[7]

The safety and efficacy of Palifermin in nonhematological malignancies has not been established.

Conclusion

Palifermin is effective in reducing the incidence of severe oral mucositis. An important finding from various studies was that Palifermin drastically reduced the incidence of WHO grade 4 mucositis, which is the most debilitating consequence of radiotherapy and high dose chemotherapy requiring parenteral nutrition. Therefore, Palifermin appears to be a promising treatment option for radiotherapy- or chemotherapy-induced mucositis.

K.S. Pinakini*, K.L. Bairy

*Department of Pharmacology, Melaka Manipal Medical College (ICHS), Manipal and Department of Pharmacology, Kasturba Medical College, Manipal- 576104. India
E mail: pimochi@yahoo.co.in

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