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Palifermin, the first specific drug treatment for oral mucositis in bone marrow transplant

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Even though the target of chemotherapy and radiotherapy is the tumor cell, normal rapidly dividing tissues are affected and injuries of the upper and lower gastrointestinal tract are frequent. Oral mucositis (OM) is the most common complication following myeloablative therapy and Hematopoietic Stem Cell Transplantation (HSCT).[1,2] Almost all patients receiving chemotherapy and radiotherapy treatment experience some degree of OM. In particular, about 40% of patients receiving standard chemotherapy, 75-90 % of bone marrow transplant patients treated with high-dose conditioning regimen and nearly all patients treated with radiotherapy for head and neck cancers develop OM.[2,3]

The clinical presentation of OM varies from erythema and edema with soreness to severe and painful ulcerations of the mucosa that penetrate the submucosa and may require treatment with opioid analgesics. The pathogenesis of these lesions involves injury to the epithelium and the stroma, increased permeability of the vessels with consequent edema, infiltration of inflammatory cells and fibrosis. This process is sustained by the upregulation of transcription factors and proinflammatory cytokines that in turn lead to oral ulceration.

As a consequence of the severe pain from the OM, patients experience difficult or impossible oral intake of food and fluids with subsequent malnutrition and dehydration, rendering necessary the adoption of the total parental nutrition.[4,7] Other basic daily activities such as talking, sleeping and swallowing are also affected and produce a negative impact on patients' quality of life.[8] Because of these symptoms, postponements of scheduled treatment and dose reduction of the drugs are frequent and potentially jeopardize the treatment outcome. Moreover, the damage to the mucosa together with the damage to salivary glands with the consequent loss of saliva barrier function, increase the incidence of life-threatening infections from resident microflora in patients that already have bone marrow suppression and compromised immunologic functions.[9-13]

In order to prevent and treat OM several experimental therapeutic attempts have included oral cryotherapy,[14] allopurinol mouth rinses,[15] oral anesthetics, amifostine, sucralfate, glutamine, granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor mouthwash.[16-23] None of these have shown clear evidence of benefit.

In 2004 the US FDA approved Palifermin (Kepivance™) for reduction of incidence and duration of severe OM in patients receiving high dose chemotherapy followed by HSCT. Palifermin is a truncated, recombinant human form of keratinocyte growth factor (rHuKGF) that is member of the heparin-binding family of fibroblast growth factor 7 (FGF-7) and promotes cell proliferation in a variety of epithelial tissues with no effect on other cell types. Keratinocyte growth factor (KGF) was isolated in 1989 from conditioned medium of a human embryonic lung fibroblast cell line[24-25] and is produced by mesenchymal cells adjacent to the epithelium of many organs, such as epidermis, upper and lower gastrointestinal epithelium,[26] pancreas, liver lung, urothelium, etc, and it is also produced by dermal fibroblasts within the skin and by lamina propria cells of the intestine.[26-30] Increased levels of KGF mRNA have been observed within dermal wounds as compared to the intact skin[31] and also in the intestine of patients with inflammatory bowel disease,[32] indicating that the increased levels of KGF are a response to tissue damage.

Preclinical studies

Increases in proliferation, thickness and hyperplasia of some epithelia were shown in animal models, rodents and monkeys, after treatment with KGF, particularly the keratinizing mucosa of the oral cavity.[33]

In colorectal xenograft models, KGF was also shown to be able to protect the small intestine of the mice from the symptoms of the gastrointestinal radiation syndrome

and from the mucosal injury produced by treatment with fluorouracil (5FU). Protection was afforded without altering tumor growth rate or 5FU tumor cytotoxic effect.[34,35] In murine models, pretreatment with KGF, was also shown to improve survival as a result of protection of normal mucosa.[34-37]

Clinical studies

In order to evaluate the safety of recombinant human keratinocyte growth factor (KGF), Meropol *et al.*[38] performed a phase I clinical study in patients with metastatic colorectal cancer undergoing to 5FU treatment. In this multicenter, randomized, double-blinded, placebo-controlled study, 81 patients, enrolled in eight centers in the US, Canada and Europe, received KGF by intravenous bolus on day 1 to 3, followed by 5FU and leucovorin. OM was assessed by examination on days 1, 4, 8, 15 and 28. Daily self-assessment was provided by patients. The most common side effects were rash, flushing, and edema, and occurred in 13 of 18 patients treated with higher doses of KFG (60 and 80 μg/kg). The frequency of grade 2 to 4 mucositis was 43% in patients treated with KFG as compared to 67% in patients treated with placebo. KGF (palifermin) was well tolerated when administered for three days before a five-day course of flurouracil and leucovorin.

In a phase II clinical trial, 129 patients with hematological malignancies undergoing total body irradiation and high-dose chemotherapy followed by autologous bone-marrow transplantation (ABMT), were randomized to receive placebo or palifermin 60 μg/kg/day for 3 days before TBI and/or 3 days after ABMT. Three groups of patients were generated: the placebo (pre and post) group, palifermin pre only group, and palifermin pre and post group. Palifermin recipients experienced a significant reduction in the duration of severe oral mucositis. In the pre/post palifermin group the mean duration of severe mucositis was 4 days vs 7.7 days in the placebo group and 5 days of the palifermin pre group. Improvement in the quality of life was observed as expression of reduced mouth and throat soreness, and other mucositis related symptoms such as difficulty in swallowing, drinking, eating, talking and sleeping. As a consequence, use of opioid analgesics and total parental nutrition was reduced.[39]

Supported by the encouraging results obtained in preclinical and phase I and II clinical studies Spielberger *et al.*[40] conducted a phase III double-blind study in order to compare the effect of palifermin with that of placebo on the development of oral mucositis in 212 patients with hematologic neoplasia who were undergoing total-body irradiation and high-dose chemotherapy followed by autologous bone-marrow transplantation. Patients were randomly assigned to receive palifermin (60 μg/kg per day) or placebo intravenously for three consecutive days, starting three days before the initiation of total-body irradiation. Then they received three additional doses of palifermin or placebo on days 0, 1 and 2 after transplantation. Total-body irradiation was delivered in 6, 8 or 10 fractions over a period of three or four days. Chemotherapy included intravenous etoposide (60 mg/kg) the day after the last radiation fraction and one dose of cyclophosphamide (100 mg/kg) two days before transplantation. Oral mucositis was assessed using the five grade World Health Organization (WHO) oral-toxicity scale (41), the five grade Radiation Therapy Oncology Group (RTOG) acute radiation-morbidity scoring criteria for mucous membranes,[42] and the four grade Western Consortium for Cancer Nursing Research (WCCNR) revised staging system for oarl mucositis.[43] In addition, patients were asked to complete the Oral Mucositis Daily Questionnaire (OMDQ)[44] every day from the day before the start of the conditioning regimen up to 28 days after transplantation in order to indicate the early manifestations of oral mucosa toxicity that are not detectable by clinicians but that can be felt by patients. The incidence of oral mucositis of WHO grade 3 or 4 was 63% in the palifermin group and 98% in the placebo group. The duration of mucositis was 6 days (range, 1 to 22) in the palifermin group and 9 days (range, 1 to 27) in the placebo group. Among all patients, the median duration of WHO grade 3 or 4 oral mucositis was 3 days (range, 0 to 22) in the palifermin group and 9 days (range, 0 to 27) in the placebo group. Patients receiving palifermin showed a significant reduction in the incidence of grade 4 oral mucositis, 20 % vs. 62 %, patient-reported soreness of the mouth and the throat, and a decrease in the use of opioid analgesics and use of total parental nutrition. Palifermin recipients had a lower incidence of febrile neutropenia as compared to placebo recipients (75% vs. 92%). Side effects were mild in severity and transient, and consisted of rash, pruritus, erythema, and taste alterations. Transient, asymptomatic increases in serum amylase and lipase were also observed. The clinical benefits deriving from palifermin treatment were confirmed by the patients' self-assessment with the OMQD that showed an improvement in patient overall and physical wellness.[45]

Conclusions

Oral mucositis is the manifestation of severe damage induced by chemotherapeutic agents and radiation therapy. In the transplant setting it is a major problem affecting quality of life in transplanted patients. Loss of integrity of the oral mucosa predisposes patients to infection, and this risk increases during the neutropenic period that follows the condition-

ing regimen. The severity of mucositis is correlated with days of therapy with injectable narcotics, antibiotics, total parental nutrition, long periods of hospitalization and mortality.

Patients that develop severe mucositis are more likely to experience pulmonary or multi-organ failure as a cause of death after ABMT as compared to patients with less severe mucositis.[9-13, 46] Mucositis may directly contribute to mortality risk and may also be a surrogate marker of other organ toxicities. A relationship between oral mucositis and hepatic veno-occlusive disease also has been reported.[47]

Palifermin has been shown to reduce the duration and severity of symptoms associated to oral mucositis after chemotherapy and radiotherapy for patients with hematologic neoplasias. In particular, palifermin significantly reduced the incidence of grade 4 oral mucositis, in which oral alimentation is impossible. The use of parenteral opioids as well as total parental nutrition and antibiotics was reduced. Patients' quality of life was improved by this treatment as well as a reduced mortality risk. Therefore by reducing the incidence of oral mucositis, palifermin might potentially decrease the costs of care and improve clinical outcomes.

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