Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: November 30, 2022

Citation: Shrivastava N., 2022. Growth Factors and Effects of Palifermin in Management of Cancer Therapy Induced Oral Mucositis, Medical Research Archives, [online] 10(11). https://doi.org/10.18103/mra.v10i11.3349

DOI:

https://doi.org/10.18103/mra.v10i11.3349

ISSN: 2375-1924

RESEARCH ARTICLE

Growth Factors and Effects of Palifermin in Management of Cancer Therapy Induced Oral Mucositis

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ABSTRACT

Amongst the various hazards of chemotherapeutic drugs and radiation in cancer patients, oral mucositis is the most commonly encountered and troublesome complication so far. It can be a cause for discontinuation of therapy and may add to the cost of treatment. In this article, pathogenesis of oral mucositis and role of recombinant human growth factors in management of it have been discussed, as we need to achieve a guideline for proper treatment of this painful side effect of cancer treatment. Palifermin, a keratinocyte growth factor has been shown to give promising results in cases of severe mucositis in hematopoetic stem cell transplant patients undergoing combined chemoradiotherapy. Other exogenous growth factors are also effective in the management of mucositis when administered topically or subcutaneously, but there is need for more number of studies with a large sample size for establishing a proper treatment plan which is cost effective as well as helpful in reducing patient's discomfort.

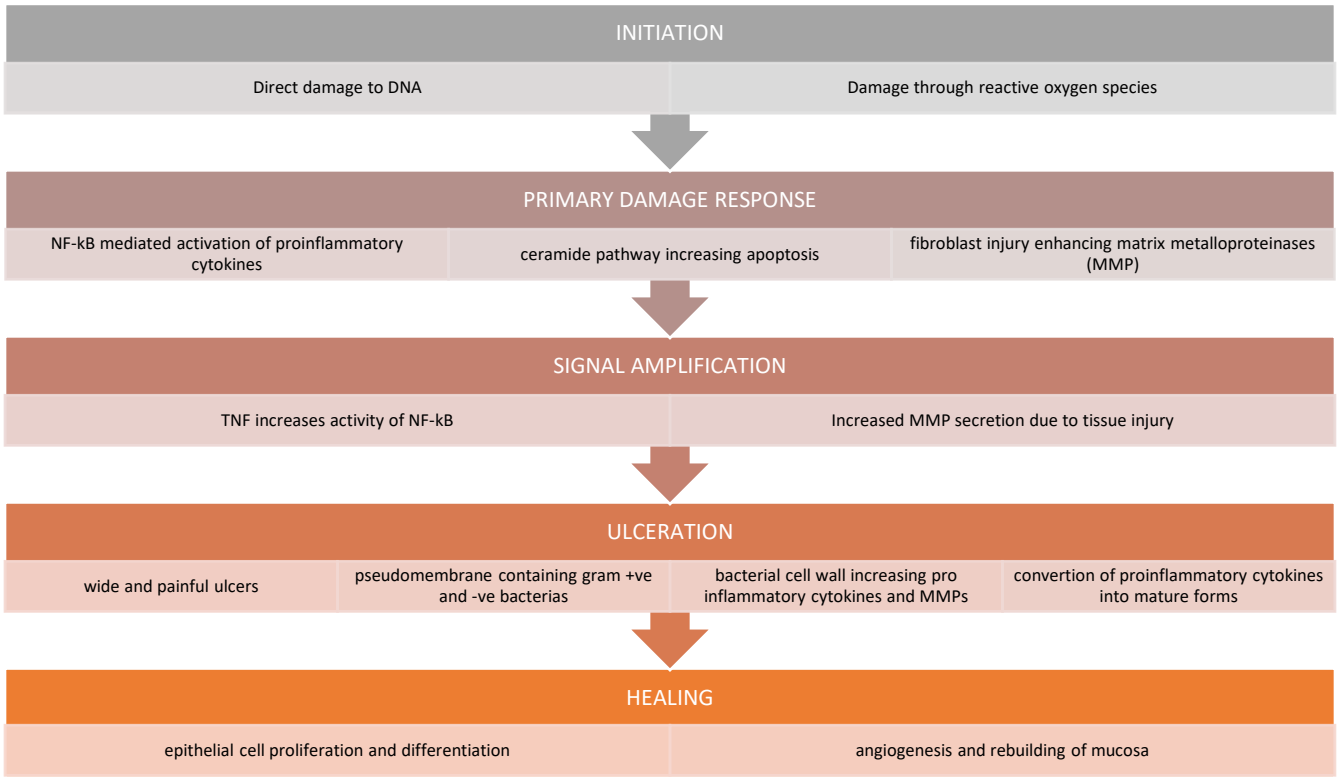
Keywords: Chemotherapy, Radiotherapy, Growth factors, Oral Mucositis, Hematopoietic stem cell transplant.

Introduction

Radiotherapy and chemotherapy alone or in combination are the mainstay of nonsurgical management of cancerous lesions. These therapeutic options affect not only the malignant cells but also the normal mucosal cells, which are rapidly dividing, giving rise to many short as well as long term effects. Amongst these oral mucositis is the most common and debilitating complication of cytotoxic effects of radiation and chemotherapeutic drugs. Severe oral mucositis can be a reason for abandoning or interrupting the treatment, which in turn may increase the risk of residual tumor cell proliferation, worsening the prognosis. Along with this, oral ulceration can cause starvation and bactereamia, causing severe pain and may require hospitalization. In patients receiving radiotherapy, approximately 70-80% suffer from oral mucositis, ulceration and pseudomembrane. 25-30% patients undergoing chemotherapy develop oral mucositis, more so in younger patients because of higher mitotic rate and more number of epidermal growth factor receptors. Among the patients receiving combined therapy approximately 98-100% develop oral mucositis.[1-2]

Pathogenesis:

There are a series of events taking place in epithelium as well as in submucosa which are responsible for various grades of oral mucositis. These events are categorized into five stages that are initiation, primary damage response, signal amplification, ulceration and healing. (Fig 1)



(fig 1: MMP- matrix metalloproteinases, NF-κβ- nuclear factor kappa beta)

The tissue damage in this process is amplified by positive feedback loops. Understanding the biological complexity at the molecular level, that lies behind the damage of oral mucosa in patients receiving cancer therapy can give us new directions for the management of the same.[1,3]

Management:

The management can be divided into palliative and symptomatic treatment. There are multiple treatment options which have been proposed for this deleterious side effect of cancer therapy but all have limited efficacy. In this article we will be discussing the role of growth factors in management of cancer therapy induced oral mucositis in detail.

Growth factors:

Growth factors are endogenously produced chemicals by variety of cells in our body. They have a tendency to bind target cells by specific receptors. These substances can be produced in larger quantities genetically for the treatment of different stages of mucositis. The different types of growth factors are:

1. Epidermal growth factor (EGF)
2. Granulocyte colony stimulating factor(G-CSF)
3. Granulocyte macrophage colony stimulating factor(GM-CSF)
4. Transforming growth factor beta(TGF-β)
5. Fibroblast growth factors: which are of various types.
    I. Keratinocyte growth factor-1 (KGF-1)
    II. Fibroblast growth factor-10 (FGF-10)
    III. Fibroblast growth factor-20 (FGF-20)

1.Epidermal growth factor:

EGF is a single chain amino acid polypeptide which binds to EGF receptors and initiates a chain of biochemical events that alter gene regulation resulting in division and proliferation of oral epithelial cells. Endogenous EGF is present in body fluids such as saliva, milk and deudenal fluids. It was first discovered by Cohen in 1962 from submaxillary gland of rats. It has an important role in tissue homeostasis as well as angiogenesis.[4]

Recombinant human EGF (rh-EGF) can be given topically in form of mouthwashes. It can cause resolution of oral ulcers, delayed onset and reduced severity of recurrent oral ulcerations.[5] It can be used as a rescue therapy after chemotherapy and radiotherapy to speed up the healing of oral ulcers.[6-7] rh EGF is thought to increase the proliferation of fibroblasts.

In patients receiving radiotherapy, intermittent administration of EGF can prevent mucosal damage during irradiation and enhance healing between radiation doses. It can be applied topically in spray form, twice daily for 7 days in a dose of 25µg/day.[8] Also low concentration diluted rh-EGF as a mouthwash thrice a day can delay initiation of mucositis.[5]

In chemotherapy induced oral mucositis rh-EGF is shown to reduce the limitations in swallowing and drinking at a dose of 50µg/day. Also duration of total parenteral nutrition and opioid analgesics is reported to be shorter in WHO grade 3 mucositis in

patients receiving cytotoxic drugs.[9-10] There is no report of cancer cell growth or increase in tumor size by exogenous EGF.[11-15]

The rh-EGF has the capacity to increase the turnover rate of basal epithelial cells. This increases the possibility that if it is administered during chemotherapy it can worsen the incidence of oral mucositis, as chemotherapeutic drugs affect rapidly dividing cells. This fact suggests that rh-EGF should be administered during recovery period after high dose chemotherapy.[9-10]
In combined chemoradiotherapy (CCRT), the most effective dose is 1mg/kg/day for 3 consecutive days subcutaneously after administration of CCRT for epithelial recovery and cell proliferation.[16]

Various studies have shown that rh-EGF has a therapeutic role in cancer therapy induced oral mucositis but optimal dose fractionation schedule and application method require more studies.

2.Colony stimulating factors:

Colony Stimulating Factors (CSFs) are hematopoetic growth factors required to convert bone marrow progenitor cells to mature blood cells.[17] These are effective in mucosal healing. This is achieved by:

1. Stimulation and proliferation of macrophages and neutrophils.
2. Proliferation and migration of endothelial cells enhancing angiogenesis.
3. Promote keratinocyte proliferation.
4. Chemotaxis of inflammatory cells.[18]

In patients receiving cancer therapy, neutropenia is a predisposing factor for other oral infections which can aggravate the severity of mucositis. CSFs have been proved to improve neutropenia in bone marrow transplant patients and enable quick healing of mucositis. The response of CSFs are dependent on concentration of receptors present in area treated.[19]

G-CSF has been shown to reduce oral mucositis in patients undergoing chemotherapy for genitourinary cancer.[20] Basically it has a myelocytic recovery effect in patients having chemotherapy induced myelotoxicities. G-CSF mouthrinse has shown to reduce the duration of hospitalization but has minimal effect in severity of oral mucositis.[19]

GM-CSF is generally produced endogenously by few hematopoietic as well as non-hematopoietic cells such as fibroblasts, keratinocytes and endothelial cells in response to inflammatory mediators such as IL-1 (Interleukin-1) or TNF (tumor necrosis factor).[21-23]

GM-CSF in particular has positive effect on epithelial cell proliferation by enhancing Interleukin-1 transcription and translation.[24-25] It also shows an effect on basal epithelial stem cell stimulation and can induce vascular cell proliferation and migration.[18]

It has been observed in previous studies that GM-CSF has a benefit on mucositis pain and on weight loss in patients of head and neck neoplasms undergoing chemotherapy and radiotherapy.[26-31]It can be applied topically in

mouthwash form or subcutaneously.[32-33] The topical route of administration in form of mouthwash is comparatively simpler and it has less adverse effects such as nausea, vomiting and bone pain. But the bioabsorption of subcutaneously administered GM-CSF is better and has a higher effect on increase in WBC count.[18] The subcutaneous dose of 4μg/kg for 10 days in patients undergoing chemotherapy (from 5th to 14th day after drug administration) has shown to reduce incidence, duration and mean area of grade 3 oral mucositis by regenerative effects on oral mucosa.[24]

It has to be noted that studies have documented increase in mucositis and myelotoxicity, if G-CSF and GM-CSF are administered concurrently on day 1 with chemotherapeutic drug.[34-35] The explanation for this is that the CSFs stimulate the proliferation of bone marrow progenitor cells and now higher number of precursor cells are available and susceptible to chemotherapy.[36-37] Also CSFs cause autocrine stimulation of tumor growth.[23]

However there is reduction in severity of oral mucositis has been reported in the second part of split radiotherapy as well as second cycle of chemotherapy by continued treatment of GM-CSF. This might be because of clonogenic cell repopulation causing preconditioning of mucosa before second cycle.[38-41.]

There is definitely a need for further studies with greater number of patients to confirm curing effect of GM-CSF on cancer therapy induced oral mucositis. Also the cost effectiveness of regular use of GM-CSF mouthwash has to be checked.[42]

3.Transforming growth factor- β:

Transforming growth factor-β (TGF-β) is a growth factor which has three isoforms, out of which TGF-β1 is predominant in keratinocytes. It signals through type I and II receptors. It has been identified as immunosuppressive, anti inflammatory molecule, but it also has a proinflammatory effect as it recruits leukocytes at injury site. These leukocytes in turn secrete chemokines and inflammatory cytokines. TGF-β activates NF-κβ which increases inflammation in oral mucosa.

Smad7 a nuclear protein, is a TGF-β antagonist. It promotes cell proliferation and survival, once reached a sufficient level to block TGF-β signaling, thus promoting wound healing. Also it directly antagonizes NF-κβ.
The natural cellular location of Smad7 is in nucleus. Pertaining to this exogenous Smad7 has been developed as recombinant protein with an N- terminal Tat tag, to allow it to permeate the cell membrane and enter into the nucleus.[43]

In previous studies on mice Smad7 has shown to reduce surrogate markers of TGF-β and NF-κβ, reducing the severity of mucositis. Over expression of Smad7 has been shown to accelerate epithelial proliferation and reduce apoptosis.[44] It also accelerates epithelial migration.[45] Tat Smad7 can be applied topically to the oral mucosa. The dosage and time of administration need to be assessed carefully so as to minimize the antagonistic

effect on growth inhibitor mechanism of TGF-β on cancer cells.

In a recent study truncated human Smad7 protein fused with Tat tag has been used to treat oral mucositis in radiotherapy treated dogs. It has successfully been shown to reduce the duration of grade 3 oral mucositis. The Tat-PYC Smad7 was applied topically which penetrated the epithelial cells but was undetected in serum. The molecular changes included reduced inflammation and cell death as well as increased cell growth and DNA repair. There was also reduction in DNA damage and neutrophil infiltration. There was significant reduction in TGF-β and NF-κβ signaling. Also IL-1B and TNF-α were lower in the mucosa.[46]

In another study Han et al used K5- Smad7, which is Smad7 transgene by keratin5 promoter mice. The animals became resistant to radiation induced mucositis. Smad7 reduced both TGF-β and NF-κβ pathways to attenuate inflammation, growth inhibition and apoptosis. In addition it promoted oral epithelial keratinocyte migration. There was also consistent reduction in infiltrated neutrophils, macrophages and lymphocytes in transgenic mice. Apoptotic cells were reduced significantly.[45]

It has been noted that Smad7 incompletely blocks NF-κβ and TGF-β signaling pathways and does not reduce these below their normal physiological value, thus beneficial to healing of mucositis, as complete blockade of either pathway can lead to excessive inflammatory response.[47-49]

In contrast to growth factors, which have potential risk for promoting cancer cell growth, anti smad associated cell migration and proliferation would not affect cancer cells as majority of cancer cells tend to lose TGF-β signaling.[50]

4.Interleukin 11:

The recombinant human interleukin 11 (rhIL11) glycoprotein is a pleotropic cytokine which has been widely used to treat bone marrow suppression in patients undergoing cancer chemotherapy and radiotherapy.[51-52]
IL 11 has multiple therapeutic effects on oral mucositis:

1. Promotes proliferation and migration of endothelial cells.
2. Enhances activity of angiogenic factors.
3. Promotes healing of mucosa by proliferation of oral epithelial cells.[53-54]
4. Stimulates myeloid, erythroid and megakaryocyte differentiation.[55]
5. Modulates T cell inflammatory reaction.
6. Inhibits apoptosis induction.[56]

RhIL11 binds to colony stimulating factor receptors in epithelial cells and promote growth of keratinocytes and fibroblasts.

In a study on animal model rhIL-11 has been shown to attenuate pro inflammatory cytokine expression thereby modulates acute radiation induced mucositis.[57]

In study conducted by Hangping Wei et al rhIL11 mouthwash was administered to patients receiving systemic chemotherapy. The mouthwash was prepared by dissolving 3mg lyophilized powder of rhIL11 in distill

water and 100ml normal saline was added. Patients were asked to gargle 10ml of mouthwash 4 times a day for 2-3minutes. After 1 week of treatment rhIL11 proved to be better treatment option in severe grades of mucositis.[55]

Subcutaneous administration of rhIL11 has also been shown to attenuate mucositis induced by 5-fluorouracil when given twice daily on the first day and continued for 14 days. It has a favourable impact on weight loss and survival in animal models.[58]

Thus this cytokine has the ability to modulate a variety of cellular responses within various tissue compartments of oral mucosa.

5.Keratinocyte growth factor:

Keratinocyte growth factors (KGFs) are expressed by fibroblasts and endothelial cells in response to pro- inflammatory cytokines. KGFs regulate epithelial mesenchymal interactions and maintains epithelial integrity via Fibroblast growth factor receptor 2b (FGF2b).[59]

Palifermin is a recombinant human keratinocyte growth factor (rhDeltaN23-KGF). It is a truncated derivative of KGF with higher stability.[60] It is manufactured in Escherichia Coli and supplied as white, preservative free, lyophilized powder which has to be reconstituted with sterile water for IV infusion.[61] It is smaller than endogenous KGF.[2] Various preclinical studies have shown that KGF increases epithelial proliferation and decreases rate of apoptosis. In addition it has a positive effect on neovascularisation and collagen deposition.[2,62] It also modulates cytokine profile.[64-65]

Palifermin has multiple mechanisms of action which are useful for management of oral mucositis. These are:

1. Induces differentiation of epithelial cells.
2. Upregulation of Th2 cytokines and IL13.
3. Inhibition of apoptosis.
4. Prevents DNA strand breaks and enhances tissue remodeling.
5. Activates radox sensitive transcription factor (Nrf-2).
6. Increases expression of cytoprotective genes in cells.[2,64-66]

The adverse effects caused by palifermin which have been noted so far are:

1. Temporary alteration in taste.
2. Thickening of tongue and buccal mucosa.
3. White coating of tongue.
4. Skin erythema, burning, rashes, pruritis.
5. Transient changes in blood amylase and lipase levels.
6. Palmar- plantar erthrodysaesthesia which is severe cutaneous toxicity reported in few cases.[67-69]

In multiple animal studies palifermin is shown to protect oral and intestinal epithelium from negative effects of radiation and cytotoxic drugs by preserving it's integrity.[70-74] Mucosal biopsies have shown epithelial hyperplasia with increase in proliferative marker Ki67 after administration of first dose of palifermin.[75] Palifermin is first mechanistically based intervention of oral mucositis. It's efficacy in patients receiving hematopoietic stem cell transplant (HSCT) has been proven.[61] The use of palifermin has been approved by US Food and Drug Administration in 2004 to reduce incidence and duration of oral mucositis in

patients with hematological malignancies receiving myeloablative therapy.[2,60]

Multiple studies have shown in which palifermin significantly reduced the incidence of severe oral mucositis in patients receiving concurrent chemoradiotherapy for head and neck cancers. In one such study palifermin in dose of 60mcg/kg once weekly for 10 doses has been shown to reduce mucositis, dysphagia and xerostomia. The effect was noted to be higher when hyperfractionated radiotherapy was administered.[76-77] In another study weekly dose of 120mcg/kg of palifermin was given 3 days before and throughout chemoradiotherapy. The incidence and duration of severe mucositis was significantly reduced. There was reduction in serum amylase level which returned to normal by 3rd week.[78]

Palifermin given at a dose of 180mcg/kg weekly for 7 weeks in patients receiving chemoradiotherapy with no prior surgical treatment has reduced mean duration of severe OM from 26 to 5 days and also delayed onset of OM. It has been documented that collapsed dosing of palifermin with 180mcg/kg has been well tolerated by the patients.[79-80] In patients receiving allogenic stem cell transplant palifermin treated patients have shown shorter time and lower grade of OM. Also duration of total parenteral nutrition and incidence of febrile neutropenia is reduced.[81]

High dose myelotoxic chemotherapy can cause most debilitating form of oral mucositis. This is also common during conditioning regimen for HSCT in patients having acute lymphoblastic leukemia. In hematological malignancies palifermin has been administered in 3 doses before the preparative regimen (60mcg/kg/day) and 3 doses after stem cell infusion, which has shown to reduce the incidence and severity of OM.[66,82-83] The third dose of premyelotoxic therapy should be administered 24-48 hrs before administration of myeloablative drug. The first dose of post myelotoxic therapy should be given on the same day of hematopoetic stem cell infusion, because the protection of oral mucosa provided by palifermin varies with conditioning regimen.[2,69]

In study conducted by Lucchese et al palifermin was administered intravenously in a dose of 60mcg/kg for 3 days before and 0, +1 and +2 post autologous HSCT infusion. There was marked reduction in severity, incidence of grade 3 and 4 OM, duration of hospitalization, use of parenteral nutrition and use of opioid analgesics.[75] Similar results were found in other studies.[84-87]

It has been documented that palifermin given before initiation of OM causes transient increase in proliferation and differentiation of epithelial cells thus increases the thickness of mucosa.[88] A dose after chemotoxic regimen promotes re-epithelialization of wound and causes healing.[89-90] Single dose palifermin can be used as primary prophylaxis in patients receiving multicycle chemotherapy. In addition it can be used as secondary prophylaxis to prevent recurrence of severe mucositis.[75]

The use of palifermin does not guarantee to eliminate mucositis but has an definite effect on improving the quality of life of patients

who are highly debilitated by cancer and chemoradiotherapies.[91-92]

There is a potential concern about palifermin usage before chemotherapy, is that it can render mucosa more sensitive to chemotherapy because of it's proliferative ability, but it is noted that along with increased proliferation there is also increased expression of cyclin E, which is a putative G-1 marker suggesting that the cells are not in S phase and are not dividing actively just before administration of chemotherapeutic drugs.[76] The timing of administration of palifermin is of crucial importance. Suboptimal timing of post dose may influence tissue repair negatively.[93] It should not be given within 24 hrs of chemotherapy as it can result in increased duration and severity of OM.[2]

An additional concern for it's usage in epithelial tumors is that many of these tumors express FGFR2b receptor and palifermin acts as a mitogen for these cells which might promote tumorigenesis.[60] A 15 year long term safety outcomes for palifermin use was observed by Stiff et al and it has not shown higher incidence of secondary malignancies or increase in tumor size.[94] Additionally palifermin has not been shown to promote growth of two carcinoma cell lines that express functional KGF receptors and also it has not been shown to protect tumor cells from antitumor effect of chemotherapeutic regimen.[95]

In patients receiving total body irradiation based allogenic HSCT palifermin was well tolerated in a dose of 60mcg/kg and had a positive influence on severity, duration and management of OM.[96]

Other members of KGF family are FGF20 (velafermin) and human recombinant KGF-2 (Repafermin) have overlapping actions as palifermin in management of oral mucositis.[97]

Conclusion:

Oral mucositis is the most debilitating side effect of radiation and chemotherapy in cancer patients. It's pathogenesis is well known. Several modalities of management of oral mucositis have been discussed previously but studies show conflicting results. Hence there are no specific guidelines proposed so far. The understanding of pathogenesis of OM can be used to administer more targeted management towards this deleterious side effect. However further clinical studies are warranted for the proposal of guidelines for use of each of these growth factors. The benefits of these recombinant human growth factors in minimizing the severity of OM and their cost effectiveness needs to be analysed. For accomplishment of this goal clearly defined study designs with clinically meaningful end points are required. Also the response of the patients to these interventions is not the same always thus the study population has to be large enough for confirmatory results.

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Conflict of Interest Statement

None

Funding Statement

None

Acknowledgments:

None

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