Targeted management of cancer therapy induced oral mucositis.

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Abstract

Oral mucositis is the most common and painful complication of cancer chemotherapy and radiotherapy. It adversely affects the quality of life of the patients undergoing cancer treatment which can be a cause of discontinuation of therapy as well. There are several treatment options available for oral mucositis but the understanding of exact pathogenesis can lead us to provide a definitive treatment to the patients. This article discusses the targeted management of mucositis considering the events occurring in the pathogenesis of the same.

Key words:

Oral mucositis, chemotherapy, radiotherapy, hematopoetic stem cell transplant.

Introduction:

Oral mucositis is the most common and debilitating acute complication of cancer radiotherapy and chemotherapy. The patient suffering from oral mucositis usually complaints of burning sensation in mouth while eating to severe pain and dysphagia. Clinically it manifests as thinning of mucosa leading to erythma which further progresses to ulceration.

The occurrence of mucositis is highly variable in different individuals which may have a genetic predisposition. Usually 30 to 70% patients undergoing radiotherapy, 25 to 33% undergoing chemotherapy and 98% of patients receiving combined therapy develop mucositis. Initially there is mucosal whitening due to transient hyperkeratinization followed by mucosal thinning and erythma at cumulative doses of approximately 15 gray. As the radiation dose reaches to 30 gray irregular and severe ulcers occur which may be covered with pseudomembrane. In patients undergoing chemotherapy mucositis begins 4-5 days

following infusion. As WBC count goes down the severity of ulceration increases.

Oral mucositis adversely affects the quality of life of the patient. Apart from pain and discomfort it can cause systemic infection and sepsis in neutropenic individuals due to spread of oraganisms through oral ulceration which may require hospitalization. This along with parenteral nutrition, antibiotics and narcotic therapy adds to cost of treatment. In severe cases patient may take treatment breaks leading to suboptimal management of cancer. [1-4]

Pathogenesis:

The evidences given by Sonis has described a series of events taking place in epithelium as well as in submucosal tissue which provides a framework for development of more targeted and accurate management of oral mucositis. It is a five stage model.

Stage 1: initiation which accounts for 2 major events.

1. Direct damage to DNA of basal epithelial cells and submucosal cells such as fibroblasts and endothelial cells.
2. Generation of reactive oxygen species (free radicals/ ROS) also cause damage to cell membrane, connective tissue and DNA.

Stage 2: Primary damage response

1. The transcription factors mainly NF-kB plays an important role in activating pro inflammatory cytokines such as tumor necrosis factor (TNF), interleukin 6 (IL6) and IL-1B through gene regulation.
2. The ceramide pathway enhances the activity of sphingomyelinase and ceramide synthatase which in turn also increase apoptosis.
3. Direct injury to fibroblasts increases the secretion of matrix metalloproteinases which affect submucosa and disrupt basement membranes.

Stage 3: signal amplification

This stage is characterized by amplification of tissue damage by positive feedback loops.

1. TNF increases activity of NF-kB and sphingomyelinase.
2. The tissue injury initiates mitogen activated protein kinase signaling leading to C-JUN amino terminal kinase activation, which regulates AP-1 transcription factor affecting

matrix metalloproteinases (MMP) secretion.

These feedback loops cause damage, days after original chemo and radiotherapy insults to tissues.

Stage 4: ulceration

1. Characterized by wide and painful ulcerations which serve as a potent route for bacteremia.
2. The pseudomembrane contains degenerated cells providing a potent medium for both gram +ve and gram –ve bacterias.
3. The bacterial cell wall products act as stimulators of macrophage pro inflammatory cytokines and enhance release of MMPs.
4. ROS production in mitochondria activates a cytoplasmic complex named NLRP3 inflammosome which convert proinflammatory cytokines into their mature forms.

Stage 5: healing

Starts after 2-3 weeks following treatment completion.

1. Extracellular matrix initiates renewal of epithelial cell proliferation and differentiation.
2. COX-2 is believed to potentiate angiogenesis and has a key role in rebuilding of submucosa.[2-6]

Management of oral mucositis:

There are various palliative and symptomatic treatment modalities available for OM, such as improved oral hygiene, systemic analgesics, topical anaesthetics, antifungal agents etc but these are proved to have limited efficacy in prevention and complete management of the disease therefore in this article we have discussed treatment modalities which are targeted towards the pathogenesis of OM which include growth factors, antioxidants and newer therapies such as low level laser therapy, rapamycin and superoxide dismutase analogues.

GROWTH FACTORS:

Growth factors are endogenous substances which are produced by a variety of cells in the body in small amounts. But these can be genetically produced in larger quantities to be used as targeted treatment at appropriate time of cancer therapy as they bind to target cells by specific receptors.[2,4,7] There are different types of growth factors like epidermal growth factor (EGF), granulocyte colony stimulating factor (G-

CSF), granulocyte monocyte colony stimulating factor (GM-CSF), transforming growth factor beta (TGF-B), interleukin 11, fibroblast growth factors (FGF) which can again be of three types, keratinocyte growth factor 1 (KGF-1), FGF-10, FGF-20.[2] The most studied and efficacious growth factor among these is keratinocyte growth factor.

KERATINOCYTE GROWTH FACTOR (KGF):

It is produced by mesenchymal cells located adjacent to the epithelium of several organs.[8]

Palifermin is a 28 KD heparin binding member of FGF-7 family. It is a N-terminal truncated version of endogenous KGF, which has multiple effects on oral mucositis.

1. Enhances mitosis and differentiation of keratinocytes, epithelial cells and submucosal cells such as fibroblasts and endothelial cells and increases their migration thus support barrier integrity.
2. Upregulates BCL-2 gene which is a suppressor of apoptosis.
3. Activates nerve growth factor 2 which is a transcription factor and enhances the expression of cytoprotective genes in cells and reduces oxidative stress by producing detoxifying enzymes for reactive oxygen species.
4. IL-13 which is an anti inflammatory cytokine and reduces the effect of TNF is upregulated by palifermin.
5. Downregulates the proinflammatory cytokines.

Palifermin is manufactured in E. coli and is a white lypophilized powder which has to be reconstituted in sterile water before IV infusion. It has been given IV in a dose of 60 ug/kg/day for 3 days prior to conditioning treatment and 3 days post transplantation in HSCT patients, and has produced significant reduction in incidence and duration of grade 3 and 4 OM and also reduction in pain, use of opioid and need for parenteral nutrition.[9-16]

In patients with cycled chemotherapy, palifermin was administered in dose range of 40-180 ug/kg/day 3 days prior to drug administration in different studies, which have concluded that palifermin significantly reduces incidence of ulcerative mucositis and mouth and throat soreness.[12]

In patients receiving chemoradiation for head and neck cancer studies have shown that weekly doses ranging from 120-180 ug/kg 3days before and throughout radiation

treatment reduced the duration of severe mucositis and also affected the incidence of mucositis.[12,17,18]

It can be associated with side effects such as rash, flushing, dysgeusia, nausea and vomiting.[17,19] Palifermin administration has a disadvantage of increasing the total cost of treatment.[14]

ANTIOXIDANTS:

Antioxidants are compounds which counteract free radicals and prevent them from causing tissue damage. Endogenous antioxidants are superoxide dismutase, glutathione peroxidase, catalases etc, which work to reduce the oxidative stress. Exogenous antioxidants include vitamins, minerals and polyphenols. Antioxidants work through following mechanisms:

1. Reduce formation of free radicals
2. Free radical scavengers
3. Repair agents which reconstitute cell membrane
4. Adaptation agents to generate required antioxidant enzymes.[20,21]

But previous reviews on efficacy of antioxidants in treating oral mucositis show that there is a possibility of these antioxidants to work as pro-oxidant in cancer cells in higher doses and they can provide a favourable condition for cancer cells to grow. Thus before using antioxidants as treatment options following points should be considered:

1. Dosage and type
2. Background and state of patient
3. Type of cancer and cancer therapy[20]

VITAMIN E (ALPHA TOCOPHEROL): Vit E is the most important antioxidant present naturally in human body which behaves as a scavenger for peroxyl free radical (HO2). It has an action of stabilizing cell membrane as well as has antioxidant effect. In addition it is well tolerated by the patient and is inexpensive as well.

Wadleigh et al reported daily dose of 1 ml of topical vit E application (400mg/ml) is effective in healing lesions of OM in patients undergoing chemotherapy.[22] It is recommended as oil based solution in a capsule which has to be dissolved in saliva and rinsed for 5 minutes immediately before every session of radiotherapy which reduces duration of severe mucositis.[23]

It is used topically because it's intestinal absorption is reported to be nonsignificant. This fact prevents it to hamper the effect of radiotherapy on tumour cells.[22-25]

MELATONIN:

N-acetyl 5-methoxy tryptamine is a hormone produced by pineal gland which is reported to have antioxidant properties. It's metabolites are also free radical scavengers. The actions of melatonin are to maintain mitochondrial homeostasis, anti-inflammatory action, downregulation of NLRP3 inflammosome activation and enhancement of antiapoptotic protein. It can prevent loss of proliferative progenitor stem cells caused by radiation and reduces radiation induced DNA degradation.

Moneim A et al used 3% melatonin gel in 0.3% ethanol in oral cavity 48 hrs before irradiation and upto 14 days after irradiation three times daily in rats. They reported reduced incidence of ulceration.[5,26,27]

ALOE VERA:

It is rich in flavonoids (polyphinols). Topical aloevera gel is known to show antioxidant, free radical scavenging, anti-inflammatory, anticancer, anti aging and wound healing properties. Along with this anti bacterial action has been reported by Kuzuyu et al.[28] Aloe vera enhances healing of tissue due to it's influence on fibroplasias, collagen synthesis and fibroblast proliferation. Ahmadi A in his review has hypothesized that 94.5% of aloe vera juice can prevent mucositis.[29] Puataweepong et al has studied the effects of aloe vera juice in patients undergoing radiotherapy and has concluded that incidence of mucositis was less in study group as compared to placebo.[30] Aloe vera can also slow down the progression of mucositis and reduces the severity by it's antifungal effects. Vit E and aloe vera together has greater ability to control inflammation as compared to placebo and also slows down the progression of mucositis.[31]

ZINC:

Zinc is required for more than 300 enzymes in our body to function normaly amongst which are certain antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase. It also contribute in repair of DNA damage. Zn sulphate capsules containing 50 mg zinc three times a day has been administered to radiotherapy patients in one clinical study which reported to reduce the degree of mucositis with no serious side effects and is inexpensive also.[32]

Zn L- carnosine oral rinse also has been reported to reduce oral mucositis, xerostomia, taste disturbances and pain severity in radiochemotherapy patients studied by Watanabe T et al.[25,32]

THIOL GROUPS:

They also act as antioxidants.. N-acetyl cystiene a thiol containing antioxidant, acts by stimulating synthesis of glutathione which is a free radical scavenger and prevents NF-kB response. It is administered in dose of 100mg/kg body wt. diluted in 500 ml dextrose solution 5%, IV infusion over 3 hr from starting day of HSCT upto 15 days after transplantation. It is reported to have significantly reduced oral mucositis.[33]

LOW LEVEL LASER THERAPY:

LLLT has a cyto protective effect during oxidative stress due to chemo and radiotherapy if pretreatment is done. This effect is based on conversion of laser light energy into energy usefull to cell. The chromophores in mitochondria absorb visible laser and increase ATP production resulting in increased proliferation and protein synthesis and in turn tissue repair.

Studies on LLLT have used mono chromatic narrow band relatively inexpensive diode lasers with low outputs in range of 10-100 mW. Almost all trials have used infrared wavelength, 830nm in doses of 1 to 6 J for at least 17 seconds per point. Alternate day LLLT needs to be performed for as long as mucositis ulcers are present. For prevention of OM ulcers LLLT is preferred at least 7 days before the start of cancer therapy. There is a definite reduction in severity, pain and duration of oral mucositis in various trials with no serious adverse effects.[25,34,35,36]

ANTI INFLAMMATORY AGENTS:

Benzydamine hydrochloride is a nonsteroidal anti inflammatory agent which is believed to suppress certain pro-inflammatory cytokines and thus reduces the progression of grade of mucositis. It is used in form of 0.15% oral rinse which is safe and well tolerated. It also acts as anaesthetic and antimicrobial agent.[37]

RAPAMYCIN:

It is a newer drug which inhibits mTOR (mechanistic target of rapamycin). It has a remarkable effect on controlling normal oral keratinocytes (NOKs), which have a self renewal capacity. Rapamycin has been shown to dramatically extend the replicative lifespan of NOKs. After treatment with rapamycin these cells can give rise to nearly 10^{17} progeny in contrast to their normal capacity which is 10^{6}.

Intra peritoneal injection of rapamycin has completely suppressed the development of radiation induced mucositis in mice.[38] Oral

mouthwashes of rapamycin may achieve higher local concentration with reduced systemic toxicities. But require evidence based studies in future for prevention of OM.

Conclusion:

There are three mainstay for definitive management of oral mucositis, that are scavenging the ROS, inhibition of inflammation through cytokines and inhibition of apoptosis.[41] The treatment options discussed in this article definitely have the potential to prevent and treat the oral mucositis effectively, but further studies and evidences are required, so that patients undergoing cancer therapy can be prevented from this deleterious complication.

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