



## PRECLINICAL AND CLINICAL ASPECTS OF ORAL MUCOSITIS: A SYSTEMIC REVIEW

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### ABSTRACT

Oral mucositis is characterized by erythema, inflammation and ulceration of oral mucosa as a result of neoplasm treatment like chemotherapy, radiation and patients undergoing transplantation including stem cell transplantation. During transplantation patients receiving higher dose of chemotherapy for immunosuppression like combination of busulfan and cyclophosphamide for prevent graft rejection. Oral mucositis is the second most vulnerable side effect of chemotherapy. The severity of disease is up to level that person who is affected may not be able to speak and chew solid food stuff. Sometimes because of much deliberate effect of oral mucositis, it

becomes compulsory to discontinue chemotherapy to prevent generation of oral mucositis. Many people get fungal infection during the course of oral mucositis and it will turn to even dangerous condition because of immunosuppressant effect of chemotherapy. Treatments available for oral mucositis majorly remain symptomatic relief except one palifermin, a keratinocyte growth promoting substance. The exact condition of oral mucositis is not easy to develop in animal models because of the difference in physiology of oral cavity much differ compare to human in sense of presence of keratin content in epithelium and highly resilience nature of oral mucosa. Many biological mediators are involved in oral mucositis which may provide future target for generation of newer, more effective and specific targeted delivery.

**Keywords:** Oral mucositis, Chemotherapy, Radiation, Palifermin.

## 1. INTRODUCTION

Cancer is one of the leading causes for mortality across the world. Among the various type of cancer, most of the death occurs due to oral cancer and lung cancer. The lancet news report expecting 75% of population will suffer due to cancer in 2030.<sup>1</sup> Cancer is defined as uncontrolled proliferation of cell with lack of differentiation and immortality of cells compare to normal cells due to multiple change in genetic expression which lead to imbalance between cell proliferation and cell death. It is a second leading disease in terms of the highest mortality. The cancer may be benign or malignant based on its ability of invading other tissue. For cancer treatment, three kinds of therapy like Chemotherapy (CT), Radiation therapy (RT) and surgical ablation are mainly used. Chemotherapy and Radiation therapy have many side effects as these therapies are unable to distinguish between normal and cancerous cells due to similar mitotic index. Chemotherapy may lead to bone marrow suppression, anemia, alopecia, cachexia, mucositis, nausea, vomiting, reduced fertility and chances of second cancer.

Oral mucositis is an inflammatory process of the oral mucosa due to radiation in head and neck cancer patients or chemotherapy or high dose of busulfan and cyclophosphamide used for prevention of graft rejection after bone marrow transplantation. It is characterized by atrophy of squamous epithelial tissue of oral mucosa, vascular damage and an inflammatory infiltrate after concentrated at the basement region. Epithelial atrophy is usually followed by ulceration. The development of oral mucositis is a complex process. Severe oral mucositis results from injury to rapidly dividing epithelial cells that line the oral cavity, causing physiological changes that range from mild atrophy to severe ulceration. This injury occurs as a consequence of CT and RT regimens, the roles of which are to target and eliminate rapidly dividing cancer cells.<sup>2,3</sup>

Oral and gastrointestinal mucositis can affect up to 100% of patients undergoing high-dose chemotherapy and Hemopoietic stem cell transplant, 80% of patients with malignancies of the head and neck receiving radiotherapy, 5-40% of patients receiving treatment for solid tumors with myelosuppressive chemotherapy and a wide range of patients receiving CT. Oral mucositis increases mortality and morbidity and many times contributes to rising health care costs. Because the patient is often neutropenic as well, the soreness may be aggravated by the development of fungal infections in the mouth, most commonly oral monilia, which shows up as small whitish patches on the mucosa and the surface of the tongue. These infections are

also common in people who are having steroids as part of their treatment. When mouth soreness develops it can also affect the sense of taste, so people often complain that things taste different, or that they cannot taste things so well whilst they are having their CT.

Oral mucositis has a dramatic impact on the patient's quality of life. It also adversely influences the administration of an optimal CT cycle. Frequently, reduction of dose, late treatment and discontinuations of therapy is necessary to allow the oral lesions to heal. Also life-threatening infections with fungus and higher treatment costs are related to the severity of oral mucositis. These situation increase days of total parenteral nutrition, use of opioid analgesics, risk of fungus infection, total hospital expenditure linked to the severity of mucositis and degrade quality of life of patients.<sup>4</sup>

Mucositis secondary to radiation results from repeated tissue damage from multiple daily radiation therapy. It may begin to manifest at doses of nearly 1000 to 2000 cGy which is mostly limited to the area of radiation. Initial signs may include mucosal white patch due to transient hyper-keratinization followed by erythema, or erythema may occur first in some cases. Ulceration may occur typically at doses exceeding 3000 cGy. After the end of radiation treatment, it will take three to six weeks for oral tissue to heal that is in contrast to CT related oral mucositis occurs on non-keratinized oral mucosal tissue only so rapid healing taking place. The most severe oral ulceration tends to occur when the patient have very low level of their white blood cell count. Mostly healing will occur within two to three weeks after chemotherapy is ended but many other factors like protein intake, tobacco habit and fungal infection may affect the healing of ulcer of oral mucositis.

### 1.1.1 Patient oriented risks

Age has much impact on prognosis of oral mucositis. Children experience much frequent and debilitating mucositis due to high turnover rate and old age people develop severe mucositis due to insufficient DNA repair.<sup>5</sup> Female patients are more susceptible to develop oral mucositis than males after 5-fluorouracil (5-FU) treatment.<sup>6</sup> Nutritional status, type of malignancy, drug-induced xerostomia (dry mouth), presence of trauma and periodontal status also affect prognosis of disease. In addition, there has been a recent focus on genetic predisposition for oral mucositis. Enzymatic phenotypes probably play a key role in explaining the huge variation of inter individual tolerance to anticancer treatment. In patients undergoing high dose chemotherapy (HDC) for hemopoietic stem cell transplantation (HSCT) polymorphism in the 5, 10-methylenetetrahydrofolate reductase genes were

associated with a differential rate of oral mucositis after treatment with Methotrexate was found.<sup>7</sup>

### 1.1.2 Treatment oriented risk

Mucositis is second most dose-limiting toxicity in patients receiving chemotherapy.<sup>8</sup> Chemotherapeutic drugs affecting DNA synthesis are particularly stomatotoxic like 5-FU administration is associated with oral mucositis in about 40% of patients.<sup>9</sup> Cytotoxic agents are known to be very damaging to mucosa like alkylating agents such as anthracyclines and taxanes and folate-based drugs such as methotrexate.<sup>10</sup> It was observed that some drugs are excreted in the saliva, such as methotrexate and etoposide which also increase chances of oral mucositis.<sup>11</sup>

## 1.2 DIAGNOSIS: WHO SCALE FOR DEFINING SEVERITY OF ORAL MUCOSITIS

WHO has devised a scale which is useful for differentiating patients based on the severity of oral mucositis and helpful for relating which drug causes more serious ulcers compared to others.

WHO scale for Oral mucositis.

**Table-1**

Grade	Symptoms
0	No symptoms
1	Soreness and erythema
2	Inflammation, ulceration but patient able to eat solid food
3	Severe ulceration, patient dependent on liquid diet only
4	Patient not able to take food orally, difficulty in communication

## 1.3 PATHOPHYSIOLOGY AND PROGRESSION OF ORAL MUCOSITIS

The underlying picture and progression of oral mucositis is divided into 5 different stages. Normally the consequence of mucosa damage starts to appear after 3 to 4 days of initial CT as erythema which is later converted to ulceration as a result of progression of oral mucositis. The Oral mucositis remains as a troublesome side effect for at least 13 to 15 days which is followed by healing as a natural consequence of this phenomenon.

### 1.3.1 Initiation

The initiation stage of tissue injury occurs rapidly following the administration of CT or RT, resulting in DNA damage in basal squamous epithelial cells lining the gastrointestinal tract. The CT and RT used in conditioning regimens cause breaks to occur in DNA strands within target cells in the mucosal epithelium and in underlying submucosa. DNA strand breaks

interfere with normal cellular functioning of cells.<sup>2,3</sup> The CT or RT used in the conditioning regimens also generates reactive oxygen species (ROS), which can directly damage cells, tissues, and blood vessels by oxidative stress. ROS are also crucial mediators of downstream biological pathways that occur in the development and progression of oral mucositis. At this stage, the mucosa appears normal; however, a cascade of events is initiated in the sub mucosa that ultimately results in mucosal destruction.<sup>2,3</sup>

### 1.3.2 Signaling

During second phase of oral mucositis many events happen simultaneously. CT, RT, and ROS cause DNA damage and subsequent apoptosis (programmed cell death) in the epithelium of the mucosa. It also activate various transcription factors, leading to increased production of inflammatory cytokines such as tumor necrosis factor-alpha (TNF- $\alpha$ ) and interleukin 1-beta (IL-1 $\beta$ ), and apoptosis pathway.<sup>2,3</sup> DNA strand breaks result in the activation of several transduction pathways that activate factors such as p53 and nuclear factor- $\kappa$ B (NF- $\kappa$ B). NF- $\kappa$ B is significant because it results in the activation of nearly to 200 genes, many of which responsible for potentially effect on mucosal toxicity and damage. The upregulation of these genes results in the production of large quantities of various cytokines like TNF- $\alpha$ , interleukin (IL)-1, and IL-6. These damage the connective tissue and endothelium, ultimately resulting in epithelial basal cell injury and cell death. Fibroblasts are also targeted in this phase as result of the activation of metalloproteinase enzyme (MMPs) leads to the destruction of the collagenous sub epithelial matrix and the breakdown of the epithelial basement membrane. Some of the cytokines released in phase II not only damage tissue directly, but also provide a positive feedback loop that aggravates the injury which give rise to amplification. The released TNF- $\alpha$  activates NF- $\kappa$ B similar to IL-1. In this stage, mucosal erythema appears but tissue integrity remains intact and patients usually have mild symptoms.

Radiation and chemotherapy also hydrolyze the cell-membrane lipid sphingomyelin by stimulating the formation of sphingomyelinase or ceramide synthase, which activates the ceramide pathway leading to apoptosis.<sup>12</sup> Macrophages are activated by fibronectin breakup which further leads to activation of matrix metalloproteinase enzymes, which cause tissue injury and increased production of TNF- $\alpha$  in the squamous epithelium.

### 1.3.3 Amplification

In the amplification phase, the events of the first two stages are interlinked so that the proinflammatory cytokines amplify the mucosal damage that is initiated by radiation and chemotherapy. Transcription factor TNF- $\alpha$  activates the ceramide and caspase pathways leading to tissue damage and activates the transcription pathway mediated by NF- $\kappa$ B.<sup>13</sup> In a feedback loop, these processes result in increased production of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6. TNF- $\alpha$  and IL-1 $\beta$  also activate matrix metalloproteinase leading to direct tissue injury.<sup>12</sup>

CT and RT also activate the transcription factor NF- $\kappa$ B in epithelial, endothelial and macrophages which leads to the activation of genes and the production of pro-inflammatory cytokines, such as TNF- $\alpha$  and IL-1 $\beta$ . These cytokines amplify the primary signal or may activate NF- $\kappa$ B in other neighbor cells, that results in the activation of transcription of genes encoding mitogen-activated protein kinase (MAPK), cyclooxygenase 2 (COX2) and tyrosine-kinase signaling molecules. The above signaling pathways lead to activation of matrix metalloproteinase enzyme in cells of the squamous epithelium and lamina propria, results in tissue injury and amplification of previous signals.

### 1.3.4 Ulceration

The ulcerative phase of oral mucositis is the most significant to both patient and caregiver. Loss of mucosal integrity produces extremely painful lesions. Breaks in the mucosal epithelium may provide doorway of entry for bacteria, viruses, and fungi. Infectious bacterial cell wall products stimulate immune cells to produce cytokines which cause inflammation and apoptosis. As these patients are often neutropenic, ulcerated mucosa allows entry of colonizing microorganisms from the mouth to the systemic circulation causing life-threatening sepsis condition.

### 1.3.5 Healing

The extracellular matrix initiates the healing phase of oral mucositis by signaling a renewal of squamous epithelial cell proliferation and differentiation. Microbial flora of oral cavity is reestablished, and white cell counts return to normal level. The tissue also appears to return to normal in term of structure and function. However, epithelial tissue changes secondary to cancer therapy remain as it is and there is residual angiogenesis (formation of new blood vessels), increasing the patient's risk of developing oral mucositis with subsequent courses of anticancer therapy.<sup>2,3</sup>

## 2. FACTORS AFFECTING PROGNOSIS OF ORAL MUCOSITIS

**2.1 Matrix metalloproteinase activity of squamous cells:** Matrix metalloproteinase (MMP) which is also known as matrixins hydrolyze components of the extracellular matrix.<sup>14</sup> These proteinases play a crucial role in many normal physiological processes of embryogenesis, normal tissue remodeling, wound healing, angiogenesis, and in pathological condition like atheroma, arthritis, cancer, and ulceration of tissue. MMP are members of an enzyme family that require a zinc ion in their active site for catalytic activity. MMPs are important for maintaining tissue homeostasis. MMP are active at neutral pH and can therefore catalyze normal turnover of extracellular matrix (ECM) macromolecules such as the interstitial and basement membrane collagens, proteoglycans like aggrecan, decorin, fibromodulin and versican as well as accessory ECM proteins such as fibronectin. In the mucositis, the pathobiology of epithelial and extracellular collagen degradation is central feature of inflammatory connective tissue destruction leading to oral mucositis. In this regard, the MMP family of enzymes is involved in metabolic degradation of the ECM. MMP-1, 8 and 13 (members of the collagenase group of enzymes) are all involved in extracellular matrix degradation and remodeling during the course of periodontal disease and positively associated with the magnitude of connective tissue and attachment loss.<sup>15</sup> Hence, it might be postulated that MMPs could play an important role in the development of Oral mucositis.<sup>16</sup>

**2.2 Albumin level in saliva:** Serum albumin (AL) is one of the most predominant serum proteins in the oral cavity. It was found that at least 6–33-fold increase in whole salivary albumin concentration following allogeneic stem cell transplantation, which preceded the development of clinically detectable ulcers and correlated with its severity in patients.<sup>17</sup> The salivary AL serve as useful measuring tool and predictor of oral mucositis and an objective measure of lesion development.

**2.3 Trefoil factors of alimentary canal:** Trefoil factors are characterized by a specific trefoil domain that contains 3 loops. They are highly stable secretory proteins and expressed in gastrointestinal mucosa. Trefoil factors are believed to protect the mucosa from damage and to promote mucosal healing after injury. Trefoil factor 1 is a natural human protein found in the lining of the mouth and the intestine where it is involved in protecting and repairing the cells of gastro intestinal lining.

**2.4 Myeloperoxidase activity in tissue:** Myeloperoxidase (MPO) is member of the haem peroxidase-cyclooxygenase super family expressed in neutrophils in large quantities, in

monocytes up to smaller level and in certain type of macrophages. MPO participates in innate immune defense mechanism through formation of microbicidal reactive oxidants and diffusible radical species. A specific and wonderful activity of MPO is its ability to use chloride as a co substrate with hydrogen peroxide to produce chlorinating oxidants like hypochlorous acid which is potent antimicrobial agent. However, evidence has emerged that MPO-derived oxidants contribute to tissue damage as well as the initiation and propagation of acute and chronic vascular inflammatory disease.<sup>18</sup>

**2.5 Drug therapy used in malignancy:** All chemotherapy drugs capable of producing oral mucositis. If any agents affect DNA synthesis or affecting synthesis phase of cell cycle cause very severe oral mucositis like anthracycline drugs, cyclophosphamide and methotrexate compare to other.

**2.6 Level of epidermal growth factor in saliva:** During and after the course of radiation therapy the level of epidermal growth factor in saliva is inversely related to prognosis of oral mucositis. Epidermal growth factor present in body fluids and involved in maintenance and repair of epithelium.<sup>19</sup>

### 3. ANIMAL MODELS AVAILABLE FOR ORAL MUCOSITIS

Many animal models are available for induction of oral mucositis with the help of CT, radiation along with mechanical stress like scratching superficially for creating mucosal damage in animal like hamster. In most of animal models available, lots of side effects and toxicity are observed like higher mortality rate (due to inevitably exposure of brain during irradiating tongue of rodent), chances of infection (because chemotherapy target immune cells along with cancer cells), multiple usage of anesthesia and uncontrollable fractional irradiation, such that homogenous tissue irradiation is difficult to obtain, sometime anesthesia used during induction procedure may affect homeostasis of oral mucosa. In rat it is not possible to obtain symptoms of mucosal damage like vomiting and oral tissue available from rodent also limited in some animals like mice so these much drawback associated with animal models of oral mucositis.

The following screenings are usually used for induction of oral mucositis

✓ A deep X-ray machine, (type F34-I; Dong Fang, Beijing, China) using an acceleration voltage of 210 kV, working current of 12 mA, a target distance of 40 cm, an irradiation field

of  $10 \times 15 \text{ cm}^2$ , a 4-mm aluminum filter system, and a delivered dosage of 100.75 cGY/min was used to irradiate the dorsal surface of rat's tongue for induction of oral mucositis.<sup>20</sup>

✓ The standard regimen used for hematopoietic stem cell transplantation Busulphan 6mg/kg by oral route and cyclophosphamide 120mg/kg by intravenous route used for induction of oral mucositis.<sup>21</sup>

✓ Methotrexate 2.5mg/kg was used for 3 days by subcutaneous route also used for induction of oral mucositis and mucositis.<sup>22</sup>

✓ Busulphan 6mg/kg for 4 days and intermittent infrared irradiation (within 15 days) directly targeted to dorsal surface of rat tongue.<sup>23</sup>

#### 4. DIFFICULTIES OF ANIMAL MODELS IN ORAL MUCOSITIS

✓ Following administration of the chemotherapy and radiation, the mucosa of the rat required to be mechanically scratched in order to induce mucositis.

✓ In the rat it will not possible to successfully induce visible oral mucositis due to highly keratinized nature of epithelium so it make difficult to successfully investigate oral mucositis with chemotherapy compare to hamster.

✓ Higher dose of chemotherapy required for inducing mucosal injury, due to highly resilience nature of rat GIT. The higher dose of chemotherapy affect liver, kidney, and lung so the treatment for induction of mucositis also lead to toxicity of the major organ and animal may die before mucositis properly developed.

✓ Toxicities associated with chemotherapy includes localized or regional includes ulcer, xerostomia, abdominal pain, malabsorption and other more generalized systemic toxicities includes fatigue, lack of appetite, nausea, and cognitive impairment.

✓ Rats do not have chemoreceptor trigger zone (CTZ) and emetogenic reflex so it cannot vomit. Vomiting is symptoms of mucosal injury so this is disadvantage as measuring tool in rat, but it is possible to use pica (eating non eatable things) as an indirect indicator for nausea and vomiting symptoms.<sup>24</sup>

✓ Anesthesia given to animal during different procedure having effect on mucosal homeostasis and saliva secretion so it will alter healing process in oral mucositis.

✓ Sprague Dawley rats are more sensitive for induction of oral ulcer compare to Wistar rat so selection of appropriate species before experiment having effect on induction of disease.

#### 5. TOXICITIES ASSOCIATED WITH CHEMOTHERAPY IN RAT

Any chemotherapeutic drug consider as cytotoxic and it will interfere with many normal

biological process which leads to toxicity. The following kinds of toxicity often seen by author when they were standardizing animal model of oral mucositis in rat

**5.1** Following image showing haematuria associated with Cyclophosphamide administration.

**5.2** Nasopharyngeal infection and nasal bleeding due to immunosuppression in rat by busulfan



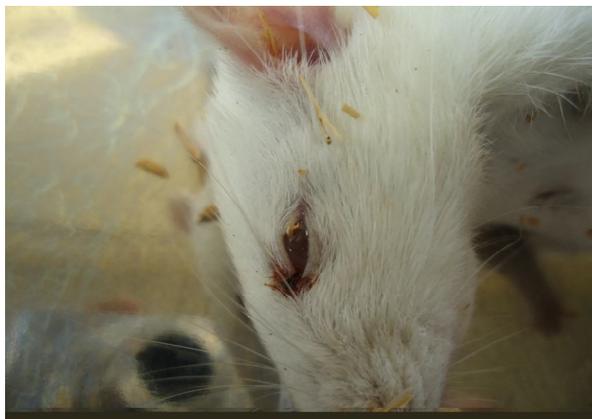
**Figure-1 Urinary toxicity**



**Figure-2 Respiratory infection**

**5.3** Severe diarrhea associated with methotrexate administration

**5.4** The following picture indicate clotting problem after retro orbital puncture done for estimation of hematological count. This hemorrhage due to decline in platelets count called as thrombocytopenia.



**Figure-3 Coagulation disorder**



**Figure-4 Gastro intestinal toxicity**

Many times it is possible that animal may die because of the above toxicity and side effect before the completion of practical period so inducing oral mucositis with chemotherapeutic agent is great challenge. Occurrence of infection is also common during induction of oral mucositis because of immunosuppression.

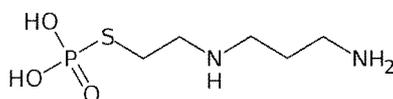
## 6. TREATMENT OPTION AVAILABLE FOR ORAL MUCOSITIS

For oral mucositis two variety of treatment are available.

**6.1 Pharmacological treatment:** It includes different drugs and chemical provide symptomatic relief in oral mucositis by affecting various targets. The following drugs are available for oral mucositis but they provide only symptomatic relief except palifermin, a keratinocyte growth factor for oral mucosa and promote rapid proliferation of damaged squamous stratified cells while analgesic and local anesthetic relieve pain associated with ulceration.

- ✓ Bland oral rinses: 0.9% saline solution, 0.9% Sodium bicarbonate solution.
- ✓ Topical anesthetics (Local anesthetic): Lidocaine, Benzocaine
- ✓ Mucosal coating agents: Amphojel, Kaopectate.
- ✓ Analgesics: Benzydamine hydrochloride (topical)
- ✓ Opioid analgesic drugs: Fentanyl, Codeine
- ✓ Growth factor (keratinocyte growth factor): Palifermin, Granulocyte macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF)
- ✓ Miscellaneous: Cryotherapy, Allopurinol, Amifostine, Antimicrobial and antifungal agent, Chamomile, Glutamine, Interleukin-11.

Palifermin was approved by the U.S FDA in December 2004 for decreasing the incidence and duration of severe oral mucositis in patients undergoing high-dose chemotherapy with or without radiation therapy followed by bone marrow transplant in hematologic cancers. Palifermin have many useful biological effects on mucosal epithelial like increase mucosal proliferation; migration and formation of newer cells which is provide rapid healing of ulceration.<sup>25</sup> Palifermin found to be more effective as prophylaxis in CT and RT induced oral mucositis.



### Amifostine

Amifostine is act as cytoprotective and help to protect normal cells during chemotherapy cycle. Amifostine work by scavenging free radical during radiation of head and neck so act as anti oxidant and also protect normal cells from hazardous effect of radiation while not providing any cytoprotection to cancer cells.<sup>26</sup>

Cryotherapy is especially useful following 5-fluorouracil treatment because smaller half life of drug. In cryotherapy, ice chips are kept in oral cavity before 5-10 minutes before CT administration. By this therapy it will possible to reduce exposure of oral mucosa to 5-fluorouracil by inducing vasoconstriction, reducing metabolic rate and sensitivity of oral mucosa epithelium. Many time cryotherapy cause numbness and headache which is minor and not affecting patient's compliance.

Glutamine having many beneficial properties like Anti oxidant, immunoenhancer, aiding in gastrointestinal function provide advantage for healing in oral mucositis. Glutamine found in highest amount in the human body.<sup>27</sup> which normally comes under category of non essential amino acid but in some clinically conditions the natural production of glutamine not sufficient for maintaining tissue structure and behave in such case as conditionally essential amino acid.<sup>28</sup> Trauma, inflammation, and mucosal injury increase demand of glutamine. Glutamine required for formation of new cellular structure and prevents damage to cell component by providing anti oxidant property which leads to rapid healing phase in oral mucositis. Beside above property it also has immunoenhancer property which prevents arising of fungal infection on mucosal surface by enhancing immunity of oral environment. Glutamine is main fuel for rapidly dividing cells like gastrointestinal tract and haematopoietic cells like lymphocyte and macrophage which lead to improved immunity.

Benzydamine hydrochloride is topical local analgesic and anaesthetic non steroidal anti inflammatory agent work by inhibition of pro inflammatory biomediators generation and not helpful in tissue protection in oral mucositis. Interleukin 11 found very effective in CT and RT induced oral mucositis and in preclinical testing it also shown reduction in mortality of animal and increase in cell proliferation in gastrointestinal tract during high dose of chemotherapy.<sup>29</sup>

Beside the role in proliferation and differentiation of hematopoietic precursor cells, G-CSF and GM-CSF also regulate migration and proliferation of endothelial cells.<sup>30</sup> RT and CT create xerostomia, a dryness of mouth due to suppression of saliva secretion from salivary gland. Saliva consists of immunoglobulin A. CT disturbs normal oropharyngeal microbial flora balance which result in colonization by abnormal bacteria. Mostly aerobic gram negative bacteria responsible for irradiation induced oral mucositis.<sup>31</sup> Lozenges containing antibiotic like polymyxin E, tobramycin and amphotericin B able to reduce severity of oral mucositis and confine to erythema after radiation treatment.<sup>32</sup>

**6.2 Non pharmacological treatment:** This strategy provides mainly supportive care and aid up in pharmacological treatment. It includes

- ✓ Good oral care: 2-3 times brushing with good soft brush with smooth handling, use of alcohol free mouthwash gargle, frequent examine oral cavity for symptoms of oral mucositis like erythema and ulceration helpful for checking of side effect. Caries should be treated in well advance of CT otherwise it will prone to late healing and arising of candidiasis (fungal) infection due to moist nature of oral cavity.
- ✓ Good nutrition: Spicy and other foods which irritate the mucosa must be avoided, intake of frozen foods like ice cream, cold fruit juices and milkshakes often helpful by providing calmness to oral mucosa and nutrition at the same times. Citrus fruits having acid in the juice and nicotine containing product like tobacco should be avoided. Foods consist of high protein diet helpful for rapid healing so its amount in diet should be increased.

## **7. DRAWBACK ASSOCIATED WITH AVAILABLE THERAPY AND NEED OF NEW MOLECULES**

- ✓ Cost of therapy with palifermin, amifostine and glutamine is very high so it will increase cost of therapy.
- ✓ Analgesic and local anesthetics provide relief from pain only but it has no effect on mucosal proliferation and rapid healing of ulcer and also higher dose of these drug associated with many side effect.
- ✓ Cryotherapy include orally administration of ice chips inside of buccal cavity and remain there during chemotherapy cycle which protect mucosal cells of oral cavity by decreasing its metabolic activity but cryotherapy effective against 5-Flurouracil chemotherapy cycle only.
- ✓ Topically applied drug may get inside of body and create systemic effect which is not desirable.
- ✓ Many time severe oral mucositis make it necessary to stop chemo cycle until oral mucositis become less in severity, which ultimately affect prognosis of disease, hospital stay and pharmacoeconomics of patient.

## **8. NEWER ADVANCES IN ORAL MUCOSITIS**

Recently Soligenix initiated phase 2 clinical trial of SGX942, to treat oral mucositis occurring as side effect of chemotherapy of head and neck cancer. SGX942 is innate defense regulator having short synthetic peptide structure and working by concurrent action of anti inflammatory and anti infective. SGX942, lacking direct antibiotic activity and capable of

modulating host defense response. The molecules also showed good anti bacterial activity against broad spectrum of pathogens.

## 9. CONCLUSION

Oral mucositis is result of unintentional damage to squamous epithelial of tongue and other lining of oral mucosa during treatment of cancer. It is ultimately result in inflammation and ulceration of tongue, lip and buccal cavity which is collectively known as stomatitis. This condition lead to interruption of chemotherapy cycle, increase in hospital stay, chances to get secondary infection and increase in cost of treatment. The conventional drugs for oral mucositis are less effective. Palifermin, epidermal growth factor although showing promising result but it increases the economic burden on patient with risk of side effects. In the future many new molecules may arrive which will target proinflammatory mediators of signaling and amplification phases like Cytokines and transcriptional factor of oral mucositis. Various animal models are available for screening newer test drug for oral mucositis. The induction of disease in animal is not so easy. The main reason behind is toxicities associated with chemotherapy and radiation. Many times it has been observed that animal may fall into morbidity and then mortality after administration of chemotherapeutic agents and radiation.

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