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RESEARCH ARTICLE

CHEMOPREVENTIVE AGENTS IN HEAD AND NECK CANCER

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ABSTRACT

Oral malignancy is the major health problem worldwide. Sixteen million new cases of cancers are estimated by 2020. Inspite of various advancement in treatment modalities including chemotherapy and radiotherapy, the survival rate has not been increased. Chemopreventive agents are essential micronutrients whose role is extensively known in physiological and also in pathological state associated with malignancy. This paper highlights the mechanism of action how chemopreventive agents suppress the carcinogenesis and also related to the clinical trials.

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INTRODUCTION

In 1976, Micheal B Sporn defined cancer chemoprevention as it uses natural, synthetic or biologic chemical agents to reverse, suppress or prevent carcinogenic progression. (Anne S. Tsao and Edward S Kim, 2004) The word chemoprevention means prevention of initiation, promotion and progression of cancer. (Ashish S. Bodhade and Alka M. Dive, 2013) Despite recent advanced treatment modalities for cancer including chemotherapy and radiotherapy the morbidity and mortality rate has not been reduced significantly. This indicates that the prevention of the cancer is the better way to address before or during carcinogenesis. (Ugbogu and Akubugwo, 2013) The concept of chemoprevention was initially proposed in 1920's with a great hope for cancer research. (Mohammad Aminur Rahman *et al*., 2010) Cancer develops from a multistep process called tumorigenesis or carcinogenesis. The carcinogenesis process is modified by various endogenous and environmental factors, which include tobacco in various forms such as chewing and smoking. Alcohol consumption is also considered to be an important risk factor. Potential malignant disorders such as Leukoplakia, Erythroplakia, Smoker's palate, Oral lichen planus, Syphilitic glossitis, Sideropenic dysphagia, Dyskeratosis congenita, Discoid Lupus Erythematosis and Oral submucous fibrosis also develops in multistep process. All these potentially malignant disorders have varying degrees of potential for turning into malignancy. (Ugbogu and Akubugwo, 2013; Ioana Scrobota and Silviu Valentin Vlad, 2016) In the past few decade many researchers have carried research in this field to prevent carcinogenesis and found that consumption of certain fruits and vegetables have reduced the risk of acquiring specific cancers in particular geographical regions. (Ugbogu and Akubugwo, 2013; Ioana Scrobota and Silviu Valentin Vlad, 2016; Thambi Dorai and Bharat B. Aggarwal, 2004) In this paper we have highlighted the various chemopreventive agents with their mechanism of action and their related studies.

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Hypothesis of carcinogenesis

There are various hypothesis of carcinogenesis which includes Genetic Theory, Epigenetic Theory and Multi-step Theory. (Ashwini Baliga and Raghavendra Kini, 2015)

Genetic Theory

This is one of the popular theory of carcinogenesis which suggests that the cells become neoplastic because of the alteration of the DNA within the cell. These mutated cells gradually transmit their characters to the next progeny of the cell. This theory has evidence from the carcinogenic agents which induce the changes. (Ashwini Baliga and Raghavendra Kini, 2015)

Epigenetic Theory

This theory is not well supported when compared to genetic theory but according to this theory, the carcinogenic agents

acts on activators or it will suppresses the genes and not on the genes themselves which results in abnormal expression of the genes. (Ashwini Baliga and Raghavendra Kini, 2015)

Multi-step Theory

This is the most commonly accepted and documented theory which states that carcinogenesis occurs in step wise and it is a multi-step process.

Mechanism of action of chemopreventive agents

Marcello Iriti and Elena Maria Varoni (2013) have concluded that transformation of normal cells into cancer cells through three distinct phases i.e, Initiation, Promotion and Progression.

Initiation

The initiation of normal cells into cancer cells is due to the exposure of the normal cell to carcinogenic and mutagenic agents. The known carcinogenic agents of oral cancer are mainly tobacco and its products. These initiated cells are irreversibly altered and they are at high risk for malignancy.

Promotion

In this phase the initiated cells are actively converted in to preneoplastic cells which are more prone for malignancy.

Progression

Once the preneoplastic cells are formed, the preneoplastic cells will convert into the neoplastic cells in stepwise process. Finally the tumor mass acquires the aggressive characteristics such as invasion and metastasis. Many researchers have proposed the mechanism of chemopreventive agents in the past few decades. Various chemopreventive agents have its action at the molecular level to inhibit the cancer progression. Researchers over the past few decades differs with each other in mechanism of chemopreventive agents according to AshwiniBaliga *et al*. (2015)

- Inhibitors of Activated Protein -1 (AP-1) pathway.
- Inhibitors of cell proliferation and initiation of Apoptosis.
- Inhibitors of Cyclo-oxygenase-2(COX-2).
- Inhibitors of Angiogenesis.
- Inhibitors of cell cycling.

MECHANISM OF CHEMOPREVENTION

↓ ACTIVATION OF PROTEIN 1 ACTIVATION PATHWAY

↓CELL PROLIFERATION AND APOPTOSIS

↓COX-2

↓ANGIOGENESIS

↓CELL PROLIFERATION

Epidemiological data which provides evidence based information that cancer prevention is possible since it follows the common mechanism which includes DNA damage, oxidative stress and chronic inflammation. Silvio De Flora *et al*. (2005) overviewed the mechanism of Cancer Chemopreventive agents and proposed the following:

1. Primary prevention of cancer can be achieved by means of modifying either the extracellular environment or inside the cells. This can be done by modifying transmembrane transport, modulating metabolism, blocking reactive species, inhibiting cell replication, maintaining the structure of DNA, modulating DNA metabolism repair and controlling gene expression.
2. Secondary prevention when there is activated oncogenes, the prevention aims towards inhibition of the tumor progression through the same mechanisms and in addition by affecting the hormonal status and immune system in various ways and thereby inhibiting tumor angiogenesis.
3. Tertiary prevention is considered to the patients who had been affected by cancer and thereby aimed in prevention of invasion, metastasis and recurrence by the same mechanism.

According to Vikas Fotedar *et al*. (Ashwini Baliga and Raghavendra Kini, 2015) oral cancer develops as a multistep, multifocal disease resulting from the insults of various carcinogenic agents which involves a genetic or epigenetic damage. As a result of

A. Activation of proto oncogene
B. Inactivation of tumor suppressor genes
C. Or both (A & B)

In 1953, Slaughter *et al* proposed field cancerization which sets rationale for trying chemopreventive agents in cancer patients. They also proposed that surgical intervention is difficult in preventing cancer, since multiple sites are exposed to carcinogenic agents in the oral mucosa which tends to develop malignancy.

Oral cancer is an ideal model to consider chemoprevention strategies because

- It has known etiological factors.
- There is a strong association of potentially malignant disorders.
- It has well defined tumor progression (mild, moderate, severe dysplasia, ca in situ, frank carcinoma)
- The lesions can be effectively screened and can be subjected to histopathological examination before the usage of chemopreventive agents.
- It does not add financial burden to the patient.
- Appropriate actions can be directed towards early precursor's lesion.

Ideal requirement of chemopreventive agents

Till date around 400 compounds of chemopreventive agents have been tried in the laboratory with varying results. Also more than 40 agents had been investigated in the clinical trials but none of the chemopreventive agents satisfy the ideal requirements. (Ashwini Baliga and Raghavendra Kini, 2015; Vikas Fotedar and Shailee Fotedar, 2013) The ideal requirements for chemopreventive agents include little or no toxicity, high efficacy in multiple sites, capability of oral consumption, known mechanism of action, low cost and

human acceptance. (Ashwini Baliga and Raghavendra Kini, 2015; Vikas Fotedar and Shailee Fotedar, 2013) The clinical benefit of chemoprevention was approved by FDA for tamoxifen in breast cancer prevention and celecoxib for adenomatous polyposis. (Mohammad AminurRahman *et al*., 2010)

Classification of chemopreventive agents (Silvio De Flora and Lynnette R. Ferguson, 2005)

Pharmacological and chemical structural classification of promising chemopreventive agents:

1. Antimutagens / carcinogens blocking agents:
   - Phase II metabolic enzyme inducers
   - N-acetly-L-cysteine
   - Polyphenols
   - Curcumin, dehydroepiandrosterone (DHEA)
2. Antiproliferatives
   - Retinoids/Carotenoids – Beta carotene, 13 cis-retinoic acid, vitamin A
   - Glucose-6-Phosphate dehydrogenase inhibitors
   - Aspirin.
3. Antioxidants

Commonly used Chemopreventive agents in Oral cancer Prevention

- Vitamin A and other Retinoids
- Beta carotene
- Vitamin E
- Dietary agents
- Newer agents

Vitamin- A and Retinoids

Vitamin A consists of retinoid molecule in the form of retinol, retinal, retinoic acid and other pro-vitamin A like carotenoids. Vitamin A is readily available in vegetables and animal sources which includes cod liver oil, egg, butter, milk, carrot, spinach as a precursor to retinol. Retinoids has a protective role in maintaining both physiological and pathological state of human body. It acts as a signal modifying factor in controlling the gene expression, which influences the enzymes, proteins, hormones and growth factors to maintain the activity between the disease and the normal being.[11] Retinoids have been widely studied as a chemopreventive agents since it is capable of inducing apoptosis, decrease the growth rate of epithelial cells and free radicals and also regulates transcription through receptors and suppresses the activity of Activator Protein (AP-1).

Meir Gorsky *et al* had reported the use of topical Vitamin A in the treatment of Oral Leukoplakia. 10-27% of the patients have complete response were 54-90% of patients have only partial response. The recurrence was also reported with 50% of the patients after the withdrawal of the medication. (Meir Gorsky and Joel B. Epstein, 2002)

Stich *et al* conducted a comparative study of vitamin A (200000 IU/wk for 6 months) with placebo in tobacco users and betel nut with leukoplakia. 57.1% of patient's showed complete remission and 3% of patient's showed complete remission in placebo. (VikasFotedar and ShaileeFotedar, 2013)

In 1986 **Hong *et al*** conducted a prospective, randomized, double-blind clinical trial in 46 oral leukopakia patients and he reported that the patient's taking vitamin A showed significant clinical improvement and histological improvement when compared to placebo. (VikasFotedar and ShaileeFotedar, 2013)

Another trial conducted by **Koch** achieved complete or partial remission in 45% of the patient with premalignant lesions treated with 1 of 3 retinoids after 6 years follow up. (VikasFotedar and ShaileeFotedar, 2013)

In 1988 **Chiesa *et al*** conducted randomized trials of systemic synthetic retinoid 4-Haptoglobin Protein Related (HPR) as maintenance therapy versus laser after removal of leukoplakia and he reported that 8% of the patients in systemic retinoid group, 29% with laser group found relapses or new lesions. Haptoglobin related protein shows well tolerated and minimal toxicity. (VikasFotedar and ShaileeFotedar, 2013)

Betacarotene

Betacarotene is the precursor of retinoids which occurs naturally and has a high antioxidant activity. (Thambi Dorai and Bharat B. Aggarwal, 2004) It had been thought that the cancer rate reduces significantly with the dietary supplement of betacarotene. (John *et al*., 2004) Topical application of betacarotene in animal studies shows significant response.

Garewal *et al* in phase II trial described that there was high response with the use of beta carotene in leukoplakia. Out of 24 patients treated, 17 patients had a major response with a response rate of 71%. (John *et al*., 2004)

Suda *et al* in 1989 also conducted a phase II trial in Oral leukoplakia patients with beta carotene, reported that the response rate was 44.4% without toxicity. (John *et al*., 2004)

Sankaranarayanan *et al* in a double blind study with vitamin A or Beta carotene in 160 patients for 12 months showed that 33% of the patients responded with beta carotene and 52% of the patients responded with Vitamin- A. (John *et al*., 2004)

Kaugars *et al* in a study conducted with 79 leukoplakia patients, were treated with Beta Carotene 30 mg/day , 1000 mg of Acscorbic Acid and 800 IU of Tocopherols for 9 months. (John *et al*., 2004) Clinical improvement of the oral lesion was noted in 55.7% of the patients. Carotenoids are relatively non toxic. In the physician's health study constituting 22,071 male physicians with twelve years of carotene supplementation showed no benefit nor harm in the incidence of malignant neoplasm.

Beta Carotene in combination with retinol (CARET) is removed from the chemopreventive trials since it showed the risk of development of lung cancer and cardiac death. (John *et al*., 2004)

Vitamin – E

Vitamin-E is a fat soluble vitamin in the major chain-breaking antioxidants present in our body. It consists of four forms of Tocopherols in which alpha-Tocopherol is actively maintained in the body. It acts as a first line of defence against lipid peroxidation, protecting cell membranes from free radical attacks through its free radical quenching activity. (Fatima

Imounan *et al*., 2012) It also inhibits the carcinogenic nitrosamine formation by stimulation of p53, down regulation of p53, activation of heat shock proteins and anti-angiogenetic effects. Vitamin E is readily available in vegetable oils (primarily soy, sunflower and corn oils), sunflower seeds and nuts.

Benner *et al* in phase II trials with 400IU of vitamin E for 24 weeks twice daily in 43 patients and reported that 46% of the patients showed clinical responses and 21 % had histological responses without toxicity. (Fatima Imounan *et al*., 2012)

Abhijit Nayak *et al* studied the efficacy of lycopene in combination with vitamin E in the management of Oral Submucous Fibrosis of 72 patients and concluded that lycopene in combination with vitamin E was found to be significantly efficient in reducing the signs and symptoms of OSMF. (Abhijit Nayak and Anitha, 2015)

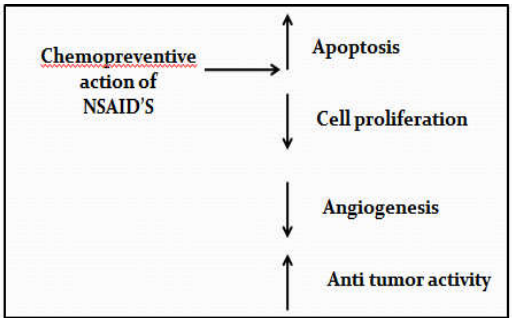
Biochemoprevention

Biochemoprevention can be achieved by giving the combination of the drugs together for the prevention of carcinogenesis. High dose combination of isotretinoin, alpha-TF with IFN-alpha has been tried since alpha-TF has synergistic effects with retenoids as well as minimal side effects and markedly better inhibition of cell growth compared with each single agent or two drug combination. (VikasFotedar and ShaileeFotedar, 2013; John *et al*., 2004)

Shin *et al* conducted phase II trials with isotretinoin alpha-TF and IFN-alpha for 12 months in patients with locally advanced head and neck cancer and reported that among 44 patients; 9% developed locoregional recurrence, 5 % developed locoregional recurrence in distant metastases and one patient developed a second primary malignancy. The overall survival rate was 98%, 89%, and 81% for 1 year, 3 year and 5 year follow up suggesting that bioadjuvant therapy is long lasting. (John *et al*., 2004)

NSAID's

NSAID's have also been tried as a Chemopreventive Agents. Topical delivery is commonly used for chemoprevention where it acts on the mucosa. Celecoxib, Nimesullide and Ibuprofen are known to have high chemopreventive action. It remains the agent of choice which targets COX-2 in oral epithelium. (Ashwini Baliga and Raghavendra Kini, 2015)



Aspirin

Aspirin which is also known as acetylsalicylic acid (ASA), is a nonselective COX inhibitor that blocks the action of COX-1 and COX-2, which in turn inhibits the prostaglandin synthesis, particularly PGE_2. Thun *et al* examined and reported that some categories of Aspirin reduced 30% nonsignificant risk in buccal cavity and pharyngeal cancers. In another study conducted by Bosetti *et al* there was 67% of risk reduction in patients with aerodigestive cancer who took aspirin for more than 5 years. In a hospital based study aspirin showed a significant reduction of risk about 25% in head and neck cancer. (Joydeep Ghosh *et al*., 2016)

Vitamin-C

It is a water soluble antioxidant which has an action in Chemoprevention. Vitamin C is required for the recycling of glutathione, which is an endogenous antioxidant present in the body. It has an ability to protect the tissue from the invasion of cancer cells by strengthening the cellular matrix. (Ashwini Baliga and Raghavendra Kini, 2015; John *et al*., 2004)

Selenium

Selenium which is obtained from yeast is used for cancer prevention, which shows reduced incidence of cancer in human trials. There are several proposed mechanism of selenium but probably the mechanism remains the modulation of the immune system and cytochrome p450 which prevents cancer. (Ashwini Baliga and Raghavendra Kini, 2015; John *et al*., 2004) Supplement of selenium 200ug per day enhances the immune response. Decreased levels of selenium increases the cancer potential in humans.

Dietary phytochemicals agents

Phytochemicals are those which naturally occurs by means of plants which has a natural defence mechanism with known anticarcinogenic effects. Many dietary agents are known for suppression of transformative, hyperproliferative and inflammatory processes that acts as an initiative for carcinogenesis. Most of the dietary agents are safe since they are derived from the natural sources. Population based studies in South East Asian countries indicated that they are less commonly affected by colon, gastrointestinal, prostate, breast and other cancers when compared to the Western countries because their dietary constitutes Broccoli, Lettuce, Cabbage, Spinach, Grapes, Garlic, Ginger, Soy, Curcumin, Onion, Tomato, Cruciferous Vegetables, Chillies and Green Tea plays a significant role in inhibiting carcinogenesis. (Ugbogu and Akubugwo, 2013; Ashwini Baliga and Raghavendra Kini, 2015) The dietary phytochemical agents have been classified according to their mode of action either by blocking or suppressing the activity of carcinogenesis. (Abhijit Nayak and Anitha, 2015)

Blocking agents: These agents usually act by inhibiting the metabolic activity of carcinogenesis and also enhances their detoxification. (Ugbogu and Akubugwo, 2013)

Suppressing agents: These agents usually act by interfering the promotion and progression of the carcinogenesis by cell proliferation, integration and initiating apoptosis. (Ugbogu and Akubugwo, 2013)

Curcumin

Curcumin has a considerable anti-tumor effect and it is one of the most extensively investigated phytochemical, with regards

to chemoprevention. Curcuma longa has a long history of use in treating the inflammatory condition in Southeast Asia and China. Many authors had described the anti-inflammatory mechanism of curcumin. It was suggested that curcumin inhibits the oxidative stress through keap1-Nrf2 pathway. Due to its chemical structure curcumin acts as a natural free radical scavenger. It is also capable of inhibiting COX-2 through suppression of NF-kB. (Reason Wilken and Mysore S Veena, 2011; Ashwini Baliga and Raghavendra Kini, 2015; Vikas Fotedar and Shailee Fotedar, 2013) The molecular target of curcumin acts by Inhibition of NF-kB activation, Suppression of interleukins, Cell cycle inhibition, Suppression of vascular endothelial growth factors and involves in combination of anti-inflammatory, antioxidant, immunomodulatory, proapoptotic, and antiangiogenic properties. Synergistic effects have been demonstrated with curcumin when it is combined with some cytotoxic drugs or certain other diet-derived polyphenols. (Reason Wilken and Mysore S Veena, 2011; Ashwini Baliga and Raghavendra Kini, 2015)

Gingerol

Ginger (Zingiber Officinale) also has a long history in many cultures as a folk remedy for GIT discomfort and nausea. Researches have demonstrated that ginger may be effective as an anti-nauseative agent, in particular it has been posed as a possible agent for anti-cancer activity by inhibiting the tumour promotion. (Wolfgang M Marx and LaisaTeleni, 2013; Ashwini Baliga and Raghavendra Kini, 2015) However the exact mechanism of gingerol is unknown. Multiple constitutes within the ginger have been identified as potentially beneficial agent. The active ingredients in ginger includes gingerols, shogoals, zingiberene, zingerone, and parado. Numerous studies based on clinical trials and animal models had shown that ginger and its constituents have significant role in the prevention of diseases via modulation of genetic and metabolic activities (Arshad H Rahmani and Fahad M Al Shabrmi, 2014).

Epigallocatechingallate (EGCG)

It is a phenolic antioxidant and one of the essential fatty acids in human blood monocyte and neuroblastoma cell lines. The potential neuroprotective effects of this phenolic compounds are currently being extensively investigated with regard to ageing as well as reactive oxygen species mediated processes. Experimental animal studies as well as cell lines of carcinogenesis models demonstrated its potential anti-tumour activity and suppression of malignant transformation. (Ugbogu and Akubugwo, 2013; Ashwini Baliga and Raghavendra Kini, 2015; Vikas Fotedar and Shailee Fotedar, 2013) One of the most widely consuming beverage in worldwide is tea which contains Polyphenols with rich antioxidant properties.

Tsao *et al* in his phase II randomized trials of short term study in Green Tea extract in oral premalignant patients reported that there was a significantly higher response rate than placebo, providing rationale for testing Green Tea extract in longer term clinical trials. (Mohammad Aminur Rahman *et al*., 2010)

Spirulina fusiformis

It is a blue green micro algae that is found in the natural sources of proteins, carotenoids and other micronutrients. Research was made in animal studies and model which suggested that these are capable of inhibition of the oral carcinogenesis progression. (Ashwini Baliga and Raghavendra Kini, 2015; Vikas Fotedar and Shailee Fotedar, 2013)

New targets &biomarkers of head and neck squamous cell carcinoma

Head and neck squamous cell carcinoma develops after accumulation of genetic changes in the epithelium that exposed to carcinogenic agents which led to the investigation of biomarkers that may represent distinct alterations.[12]This leads to the development of new chemopreventive agents that includes:

- Oncogenes
- Growth factors.
- Growth factor receptors.
- Tumor suppressor genes.

Cyclooxygenase – 2(cox-2) inhibitors

Cyclo-oxygenase-2(COX-2) is overexpressed in all the premalignant conditions involving the Colon, Liver, Pancreas, Breast, Lung, Bladder, Skin, Stomach and almost all the cancers including Head and Neck. (John *et al*., 2004; Thambi Dorai and Bharat B. Aggarwal, 2004) Cox-2 have properties of enhancing the production of vascular growth factors, leading to neoangiogenesis, as well as to mediate cytokines which involves in the chronic inflammation. This results in the increased epithelial carcinogenesis. Cox-2 also have capability of catalysing the conversion of procarcinogens to carcinogens. (John *et al*., 2004; Thambi Dorai and Bharat B. Aggarwal, 2004) Hence inhibitors of COX-2 eg, celecoxib, valadecoxib, refecoxib, resveratrol, curcumin, catechins helps in cancer prevention.

Epidermal Growth Factor (EGFR) receptors

It is a trans-membrane protein that is most commonly found in the epithelium. It plays a role in the tissue homeostasis, oroganogenesis, proliferation and survival of cancer cells. Over expression of this protein was found in many cancers including head and neck cancer which suggested that blocking of this protein can prevent the carcinogenesis. Increased production of COX-2 derived prostaglandin can impact several mechanisms that have been linked to carcinogenesis, including cell proliferation, apoptosis and angiogenesis. Eg: Gefitinib, Erlotinib. (John *et al*., 2004; Thambi Dorai and Bharat B. Aggarwal, 2004) Trials in cell lines with combination of EGFR, TKI and Celecoxib had shown inhibition of Head and Neck Squamous Cell Carcinoma and has great future promise in chemoprevention of head and neck squamous cell carcinoma. And also in patient trials with Gefitinib 500mg in 47 patients the response rate was 10.6%. (John *et al*., 2004)

P53 gene

It is the tumour suppressor gene that is located in the short arm of the chromosome 17. It is commonly seen in the head and neck cancer in more than 43% of the patients with mutation. Since over expression of this gene is seen in most of the cases it also acts as a predictive factor for short survival and risk of recurrence or in second primary tumours. P53 also indicates the response of neoadjuvant chemotherapy. ONYX-015 which is a known adenovirus that lacks the gene encoding E1B 55kd,

binds and inactivate the p53. This ONYX-015 was used in phase II trial as a mouthwash in potentially malignant condition with oral dysplasia. The results were satisfactory. Out of 10 patients treated weekly; resolution was seen in 3 patients, as well as histological improvement in another 2 patients without toxicity. (John *et al*., 2004; Vikas Fotedar and Shailee Fotedar, 2013)

H-Ras gene

It is a protein which plays an important role in cell division, the process by which the cell mature to carry out the specific function. H-Ras gene mutation is seen in about 27-61% of the squamous cell carcinoma cases and about 30% in leukoplakia. Farnesyl transferase inhibitors, L-778,123 and radiotherapy was studied in phase I where 2 of 3 patients with head and neck squamous cell carcinoma had no recurrence in the follow up with CT and nasopharyngoscopy with acceptable toxicity. (John *et al*., 2004)

Limitations of the chemopreventive agents (Rajendra G. MEHTA, 2014)

- Lack of the animal models for demonstration of the chemopreventive agents.
- Lack of perfect co-relation between in vitro in cancer cells and in vivo experimental animals.
- Lack of exact mechanism of action of the chemopreventive agents.
- Clinical trials are more expensive.
- Lack of patient awareness.
- Lack of Industrial participation.
- Difficulty in early screening of cancer and selection of chemopreventive agents.

Conclusion

Chemoprevention is an attractive strategy in Head and Neck cancer management, although past trials have not fully demonstrated its feasibility. Single agent retenoids are active against oral premalignant lesions demonstrating a proof of that Head and Neck cancer chemoprevention is possible. Biochemoprevention with Isotretinoin, IFN-α, α-TF is a promising approach, but its efficacy need to be determined. Molecular targeted agents EGFR, TKIs, FTIs and COX-2 inhibitors are important potential treatment options. Seventy percent of oral cancers appear from potentially malignant disorders. The process of carcinogenesis is a multistage and multistep process with phases of initiation, promotion and progression. It is therefore possible to intervene and prevent the process of carcinogenesis during these phases since it takes several years to reach invasive stage. Progression of precancerous stages can be stabilized, arrested or reversed by chemopreventive strategies. Prevention of cancer through chemoprevention and or by the use of systemic medications is a new strategy and continues to hold promise in the field of oncology.

Even after decades of research the significant outcome of the problem was still questionable. "Prevention is better than cure" accordingly chemopreventive agents has evolved in past few decades which is promising for the future management. Inspite of its limitations chemopreventive agents finds its application among precancer and cancerous patients in an attempt to reduce the disease progression and morbidity.

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