Interferons in oral potentially malignant disorders, its effect and cure: A review

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Abstract
Potentially malignant lesion earlier known as a precancerous lesion is a morphologic alteration in the tissue which may progress into the development of malignancy. Similarly, a potentially malignant condition is associated with high risk of cancer. These lesions are commonly seen to occur after exposure to carcinogens, such as tobacco, areca nut, and alcohol, and they frequently progress to frank malignancy. Although, these lesions in the early stage (with hyperplasia and mild dysplasia) respond to retinoid therapy, advanced lesions (with moderate to severe dysplasia) are known to show resistance to the therapy. Bio-chemo-preventive therapy appears to be highly active in cases of advanced premalignant lesions, particularly those of the oral cavity. Interferons (IFNs) came into limelight with their use in hepatitis infections. It has been used in various cancer treatment modalities. IFNs and its uses have been less sought in cases of head and neck cancers. This review will demonstrate the critical importance IFNs and its mode of action with a translational approach toward advancing our understanding of the pathobiologic basis of tumorigenesis and therapeutic outcome of IFNs in oral potentially malignant disorders.

Keywords: Biological therapies, interferons, potentially malignant disorders

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Introduction
The term precancerous lesion has broadly been used in the literature to describe clinical presentations that have a potential to become cancer. The precancerous lesions and precancerous conditions have been categorized as depicted in Table 1.[¹]

Our understanding of the dynamic relationship between the host immune system and the process of carcinogenesis is evolving, as the molecular mechanisms operating in naturally occurring anti-tumor immune responses are being identified. It is now well established that the interferons (IFNs) act as central co-ordinators of these interactions. In fact, the fact that IFN-γ has a pivotal role in promoting anti-tumor responses became the topic of new interest in the process of cancer immune-surveillance. Adding to it, it is also established now that Type I IFNs too have distinct functions in this process. In this review, we shall highlight the role of the IFNs in premalignant diseases, in their occurrence and application in their treatment.

What are IFNs?
The IFNs are a group of multifunctional proteins involved in providing viral defense, cell growth regulation, and immune activation. They are broadly classified into two types. Type I IFNs, secreted in direct response to a viral infection, consist of IFN-α, predominantly synthesized by leukocytes, and IFN-β, synthesized by many cell types, but particularly by fibroblasts; and Type II IFN or IFN-γ, which is synthesized by activated T lymphocytes and natural killer cells in response to the recognition of infected cells as reviewed by Goodbourn et al.[²]

Antiviral Activity
IFNs stimulate an “antiviral state” in the target cell, wherein they either block or impair the viral replication via the synthesis of enzymes which interfere in the cellular and viral processes. Importantly, there are often differences in the requirements for the two types of IFNs in resolving specific viral infections, and the systems are not found to be redundant in most cases. Both the types of IFNs limit the viral spread by delaying the growth of targeted cells or by making them more prone to apoptosis. Along with this, IFNs have profound immunomodulatory effects and hence they are seen to stimulate the adaptive immune response. However, though IFN-α, β, and γ exert their influence on the
properties of immune effector cells, they do show significant difference in their actions, and thus these extended cytokine functions account for their different spectrum of antiviral activities [Table 2].[3,8]

**Anti-tumor Activity**

IFN-α is a pleiotropic cytokine of Type I IFNs family. It affects the tumor cell functions by many different mechanisms. In addition, it also promotes the activity and differentiation of host immune cells. Earlier studies on the mice tumor models have proved that a long-lasting anti-tumor response is sustained after treating the animals with IFN-α or β.[4] Subsequently, a group of studies conducted on tumor cells expressing IFN molecules and genetically modified, provided major information on the host-mediated anti-tumor mechanisms induced subsequent to the local synthesis of IFN-α. Since then, several studies have highlighted new immunomodulatory effects of IFN-α as its action on T cells and dendritic cells. Recent reports on cancer patients responding to IFN-α therapy add on to the importance of the immunomodulatory effects of IFN-α for the generation of a sustained anti-tumor response.[6]

IFNs can most probably be the treatment of choice for hairy cell leukemia and likely for symptomatic nodular lymphoma too. In addition, they also prove to be very beneficial in the treatment of papillomas and condylomas. No doubt the future of these magic bullets lies in the combination therapy as the "fourth arm" of cancer therapeutics. However, now the challenge lies in defining the role of these magic bullets. At pharmacological doses, they exert an anti-proliferative effect by inducing certain enzymes that cause stasis in targeted cancer cells.[7] Alternatively, they can also be used at physiological doses, wherein they exert immunologic and cell membrane effects. Thus, combination therapy with cytotoxic agents might require higher doses whereas they may be effective at much lower doses when combined with other biologic agents, such as monoclonal antibodies (mAbs). Thus in the coming years, it will be necessary to set their optimum biologic doses, in order to improve their usefulness in therapy instead of considering them as purely cytotoxic agents.[8]

**IFNs in Potentially Malignant Lesions**

IFNs and its association with premalignancies have been sparsely discussed in the English literature. To name a few studies which have introduced the role IFNs in developing a premalignant state were done by Urata et al. and Sato et al. IFN activity in the sera of patients with oral potentially malignant lesions has been highlighted by Urata et al. wherein the IFN assay was tested on oral premalignant lesions by the plaque-reduction assay in the sera of 26 patients. On acid treatment, a significant increase in the number of acid-stable IFNs was found in the patients as compared to the controls. The titer of IFN-γ (n = 17, P < 0.002) showed a significant increase as compared to the controls (n = 20). All patients were treated with topical HuIFN-β. When the correlation between the disease prognosis and titers of serum IFN was studied, all patients with good prognosis showed decreased levels of IFN-γ (P < 0.01). On the other hand, acid-stable IFNs increased after the therapy (P < 0.05). It was thus concluded that the endogenous IFN system may have a role in the pathophysiology of oral mucosal lesions.[9]

To study the effect of HuIFN therapy on oral premalignant lesions, a pilot study was done by Sato et al.[10] wherein he topically applied HuIFN-β to 20 oral premalignant lesions for 1 h twice a week. The 14 oral lesions with mucosal erosion or ulceration showed complete healing after approximately 10 successive applications. In the other 6 patients, subjective symptoms such as irritation, the pain had subsided, but hyperkeratotic patches did not show completely remission.[10]

**IFNs in Oral Sub Mucous Fibrosis (OSMF)**

OSMF is characterized by fibrosis at the submucosal level, that ultimately leads on to progressive restricted mouth opening. In a study by Haque et al., it was highlighted that IFN-γ is an anti-fibrotic cytokine. They conducted this study to investigate in vitro the action of IFN-γ on fibroblasts stimulated by arecoline in OSMF patients (n = 5). Furthermore, they also studied the effect of intra-lesional administration of IFN-γ on the fibrosis in those patients (n = 29). They also analyzed the inflammatory cell infiltrates and the cytokine levels before and after the treatment in the lesional tissue. The results revealed that the increased collagen synthesis in response to arecoline was inhibited by IFN-γ (0.01-10.0 U/ml) in a dose-related
manner. In an open uncontrolled study, administration of intra-lesional IFN-γ showed improvement in the patients' mouth opening, with a net gain of 8 ± 4 mm (42%). In addition, the patients also reported reduced dysesthesis and improved suppleness of the buccal mucosa. Reduction in the inflammatory cell infiltrate, and cytokines level was observed in the post-treatment immunohistochemistry. Hence, the effect of IFN-γ on collagen synthesis acts as a key-factor in the treatment of such patients, and thus intra-lesional injections of IFN-γ might act as a significant therapeutic modality in OSMF.[11]

OSMF is a chronic disease known to affect any part of the oral cavity and showing juxta-epithelial inflammatory reaction, leading to fibrosis of the lamina propria; which ultimately causes trismus. IFNs are seen to have profound effects on collagen synthesis. IFN-α, β, and γ suppress the collagen synthesis by fibroblasts. Inhibition of collagen synthesis by IFN-γ occurs via the inhibition of transcription of genes for Types I and III collagen. IFN-γ inhibits the increased collagen synthesis, characteristic of fibroblasts which were derived from scleroderma patients. IFN-γ is also seen to inhibit the collagen synthesis by myo-fibroblasts and synovial fibroblast-like cells. In addition to this, IFN-γ is also known to suppress the pro-collagen mRNA levels and Type II collagen synthesis in human articular chondrocytes. In vivo studies in mice have shown that IFN-γ inhibits the collagen synthesis in the process of fibrosis due to an implanted foreign body, in cases of bleomycin-induced pulmonary fibrosis, and during the healing response to cutaneous thermal burns. In the latter case, it was also observed that while the collagen content of the wound scar was reduced, hyaluronic acid on the contrary, was found to be increased in mice receiving IFN-γ. Similar results have been obtained in in-vitro studies showing that, while IFN-α and β decrease the production of glycosaminoglycans, IFN-γ increases their production. It has also been observed that acute inflammation was also suppressed in mice treated with IFN-γ. Thus, it was established that IFN-γ inhibits collagen synthesis via regulating the process of transcription. One report has also highlighted the effect of IFN-α in decreasing the size of a keloid in a patient. Thus, as the IFNs can inhibit collagen synthesis, further studies are required to evaluate their usefulness in the treatment of disease states with abnormal fibrosis and also their potential in altering the healing response in many therapeutic interventions.[11-13]

IFNs in Oral Lichen Planus (OLP)

OLP is an immunologically mediated lesion with distinct clinical appearance and characteristic distribution, but may also present in a wide variety of patterns which can mimic other lesions. Erosive or erythematous lichen planus have a 0.8% chance of turning into malignancy.[14,15]

The study was conducted to investigate the potential involvement of IFN-γ in the pathogenesis of OLP. On the biopsy specimens from 10 OLP patients, the topographic distribution of cells expressing IFN-γ mRNA was determined by an in situ hybridization technique. Approximately 1% or fewer lesional cells were found to be IFN-γ mRNA-positive, and the majority of these cells were found lining the basement membrane. A slightly higher number of phytohemagglutinin (PHA)-induced IFN-γ-producing cells were found in the blood from 11 other OLP patients. IFN-γ response toward Candida albicans was same in OLP and control blood cells, highlighting normal immunological function in the OLP patients. These findings suggest that T-cells activation and IFN secretion occur locally and are not seen to reflect in the peripheral blood. It is also inferred that the disease is regulated by less number of T cells.[16-17]

OLP is common in patients infected with hepatitis C virus (HCV). The study conducted by Nagao et al. to study the occurrence and progression of OLP in HCV patients treated with IFN to investigate the role of HCV in OLP pathogenesis. 24 hepatitis C patients were examined for oral lesions before, during and after IFN treatment and OLP was observed in 16.7%. Hence it was concluded that OLP can occur, exacerbate or persist during IFN treatment for HCV, even after the serum HCV RNA turns negative. Thus, it was established that OLP in these patients is not due to HCV infection per se but is associated with the host factors due to HCV infection. So, the physicians should be aware of OLP occurrence or its exacerbation during IFN therapy in hepatitis C patients, but IFN therapy per se is not contraindicated in such patients.[18]

Wenzel et al. conducted an immunohistochemical analysis of the skin biopsies of OLP using mAbs against various targets. It was revealed that MxA protein was significantly expressed, which is specific to Type I IFNs, hence indicating the involvement of Type I IFNs.[19]

OLP and chronic liver diseases are the extrahepatic manifestations of HCV infection. The treatment modality of such HCV-related chronic liver diseases has evolved over the years from the use of only IFNs to the combination therapy of IFN and ribavirin. A case report of treating erosive OLP, cutaneous lichen planus and Leukoplakia of the vocal cord with IFN and ribavirin in a man with chronic HCV infection has been published.[20] The patient was initially treated with IFN-β (6 MU/day for 2 weeks), then a combination of IFN-α2b (6 MU/day for 2 weeks and 3 times a week for 14 weeks) and ribavirin (400-600 mg/day). The combination therapy was stopped after 18 weeks because of aggravation of the OLP. Aminotransferase levels returned to normal during the therapy. However, 7 weeks after discontinuation, they rose to 10 times the normal. 5 months after discontinuation, the OLP lesions appeared. 8 months after discontinuation, the OLP erosion gradually reduced. However, serum HCV RNA was still noted. Hence, this study reaffirmed that caution should be exercised during IFN and ribavirin therapy to chronic hepatitis C patients having prior erosive OLP lesions.[20,21]
Interferons in oral potentially malignant diseases

It is now well established that there is an association between human papillomavirus (HPV) virus and proliferative verrucous leukoplakia. HPV being a virus has the capability to induce IFNs. Li et al. studied the effects of E6 proteins of HPV on IFN signaling pathway and they noticed that the expression of the “malignant” type of HPV-18 E6 proteins in human HT1080 cells inhibited the activation of JAK-STAT pathway in response to IFN-α but not so with IFN-γ. Furthermore, this inhibition was not noticed due to the “benign” HPV-11 E6. This was due to the fact that when the cells expressed HPV-18 E6 after IFN-α treatment, there was decreased tyrosine phosphorylation of STAT1, STAT2, and Tyk2, which resulted in the reduced DNA-binding and transactivation capacity of ISGF3. In addition to this, HPV E6 proteins were also seen to interact with Tyk2, wherein HPV-18 E6 was seen to interact more than HPV-11 E6. Hence, it was established that HPV-18 E6 has an inhibitory role on the IFN-α induced JAK-STAT pathway which in turn effects the growth of the cells. As various dosages of cytostatic drugs have been proven to show beneficial effects in reducing tumor size; IFN-α seems to support the therapy by delaying the growth of the tumor but does not take the place of surgery alone.

This is supported by a study done by Risse et al. wherein a cumulative dose of 45 million IU of IFN-α2b was administered in one of the cases, lesion size was seen to be stabilized but unfortunately, the patient died after discontinuation of the treatment due to hepatic toxicity. In an another case of a giant condyoma acuminatum of the penis, stabilization of the disease was attained with a cumulative dose of 522 million IU of IFN α-2a with no evidence of recurrence after surgical treatment. Hence, IFNs can be used as an adjuvant therapy in verrucous lesions for reducing the size of the tumor.

Conclusion

Oral premalignant lesions serve as a useful medium for developing chemopreventive trials for lesions of the oropharynx. Although these lesions in their early stages respond to single-agent retinoid therapy, but advanced lesions show resistance to these single agents. The combination of retinoids and IFNs has shown to enhance the induction of cell differentiation and suppress the process of cell proliferation in various preclinical and clinical studies. However, still IFNs have not been used to treat these conditions due to their known side effects. Although IFNs have shown promising results in interventions involving OSMF, so far, this review will help a researcher to get an insight into the current concepts of therapeutics of IFNs and indulge in further promising studies involving IFNs in potentially malignant disorder.

References


