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Original Research Article

Efficacy of topical Interferon Alfa- 2b used as an adjunct in the management of primary OSSN

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ABSTRACT

Objective: To assess the efficacy of topical interferon alfa-2b as an adjunct therapy in the management of primary ocular surface squamous neoplasia (OSSN).

Materials and Methods: Clinically visible OSSN on slit lamp examination in 21 patients (21 tumors) was managed with topical interferon alfa-2b, 1 million IU/mL, 4times daily for a period of one month, before subjecting the patients to definitive surgery. The patients were periodically observed, over a period of 6 months. Tumor control and complications were evaluated according to American Joint Committee on Cancer classification. A significant reduction in size, was noted in smaller tumors. Final diagnosis and staging was done after histopathological examination of the surgically excised tumour, which had been excised with a 4mm margin. Bigger extensive lesion did not show appreciable response in terms of appearance or reduction of size.

Results: Tumor size was found to be reduced significantly in 19 out of 21 tumors (%) following topical interferon alfa-2b treatment for a period of 1 month, from the presentation. Of the 19 tumors, tumor surface area was reduced 44% (median). Two patients (8.3%) did not respond to the treatment.

Based on American Joint Committee on Cancer classification, significant reduction was achieved in 2 of 3 Tis (67%), 17 of 20 T3 (85%), 19 of 23 N0 (83%), and 19 of 23 M0 (83%) category tumors.

Conclusion: According to American Joint Committee on Cancer classification, significant reduction with topical interferon alfa-2b can be achieved in 67% of Tis, 85% of T3, and 83% of all OSSN.

1. Introduction

Ocular surface squamous neoplasia (OSSN) includes a wide spectrum of neoplastic squamous epithelial abnormalities which include squamous dysplasia, squamous cell carcinoma in situ, and invasive squamous cell carcinoma.1-3 These neoplastic conditions can affect the conjunctival as well as the corneal surface and occasionally can invade into the surrounding areas such as globe, orbit, and nasolacrimal system.[1–5]

First proposed in 1995 as a distinct clinical entity,[6] ocular surface squamous neoplasia is an umbrella term which includes a spectrum of conjunctival malignancies. These range from mild epithelial dysplasia to invasive squamous carcinoma.[7] It is the most common non-pigmented malignancy of the ocular surface[8] It has an incidence ranging from 0.03–1.9 per 100,000/year in the Caucasian population,[9–12], to 3–3.4 per 100,000/year in African ethnicity populations.[13,14]

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Surgical excision is considered the gold standard of treatment here; however, due to the high rate of tumor recurrence, interest in conservative medical approaches has been progressively increasing in recent years.[15]

1.1. Risk factors

Risk factors for OSSN include both environmental and genetic factors. The strongest association was found to be exposure to ultraviolet (UV) radiation. As with cutaneous malignancies, UV can damage DNA and lead to the development of cancer promoting mutations.[16]

Individuals with XP are at a higher risk of UV-induced cell damage due to an inability to repair mutations in the DNA[17,18] and are therefore more susceptible to both ocular surface and cutaneous malignancies.[19] Another possible risk factor is the human papilloma virus (HPV) which has been found more frequently in OSSN specimens as compared to those of healthy conjunctiva,[20] although the frequency of detection varies with region.

HPV-induced carcinogenesis has been attributed to the ability of its oncoproteins, specifically E6 and E7, to target and interact with host cellular proteins, such as p53, and to enhance the degradation of normal proteins.[21]

2. Materials and Methods

A total of 21 patients receiving topical interferon alfa-2b as primary treatment for a clinically visible tumour were included in this study, after a signed informed consent was obtained from them. The treatment protocol included use of interferon alfa-2b (ReliFeron®) in a topical formulation of 1 million IU/mL. The eye drops were administered 4 times daily, for a period of 1 month.

The response to treatment was monitored on follow-up visits, and after a span of 1 month, all patients were subjected to definitive surgical management, irrespective of the response to interferon molecule. Surgical treatment – Excision biopsy was done, with a 4mm clear margin (except for the cases involving fornices), by No-touch technique to avoid tumor seeding. This was followed by cryotherapy of the conjunctiva, alcohol epitheliectomy for lesions involving the cornea, and amniotic membrane grafting (AMT). No recurrence was found at the end of follow up period.

The demographic data recorded included age, sex, race, and skin color. History of risk factors, including smoking status, human papilloma virus infection, human immunodeficiency virus infection, chronic use of corticosteroids or other immunosuppressive medications, organ transplant, and corneal graft, was recorded. Any treatment modalities used before referral (excisional biopsy, cryotherapy, and topical chemotherapy) were documented.

Recorded clinical findings included best-corrected visual acuity, diagnosis (squamous cell carcinoma or CIN), tissues involved (bulbar conjunctiva, cornea, tarsal conjunctiva, forniceal conjunctiva, caruncle, and semilunar fold), number of tumors, maximal tumor basal diameter (in millimeters), tumor surface area (in millimeters squared), quadrant or location involved (superior, nasal, inferior, and temporal quadrants; upper tarsus; and lower tarsus), number of clock hours of limbal involvement, distance from the limbus, growth type (flat/sessile, dome, and pedunculated), presence of leukoplakia, presence of feeder and intrinsic vessels, presence of internal cysts, and color of the lesion.

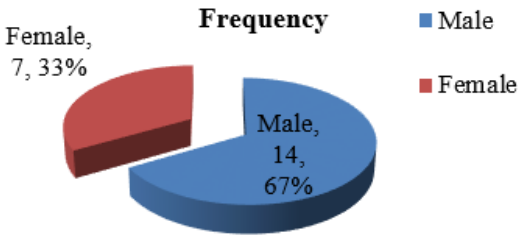
Based on clinical findings, the AJCC clinical stage of the tumor was determined (Table 1). The best-corrected visual acuity, maximal tumor basal diameter, tumor surface area, percentage of tumor remaining, and interferon alfa-2b–related toxicity were recorded at 1 month of follow-up visit. The tumor surface area was calculated using a geometric formula for area depending on the shape of the lesion. Irregular lesions were divided into smaller regular (rectangular, triangular, or circular) areas, and the tumor surface area was calculated by adding the surface area of these smaller components of the lesion. Slit lamp biomicroscopy was performed with documentation on large conjunctival drawings and clinical photographs at each visit.

Recorded treatment outcomes included recurrence of a tumor, appearance of a new tumor, characteristics of a recurrence or metastasis, site of metastasis of each of these outcomes. Metastasis to regional lymph nodes was assessed by palpation of preauricular, submental, submandibular, and cervical lymph nodes at each visit. Distant metastasis was assessed by additional imaging, wherever necessary.

The median patient age was 63 years (mean, 63 years; range, 22-89 years); 14 were male (70%) and 6 were female (30%). A history of risk factors for OSSN included smoking (6 [30%]), None of the patients in this series had human immunodeficiency virus infection or organ transplant. The median visual acuity at presentation was 20/30 in the affected eye.

2.1. Statistical analysis

For the statistical analysis, Paired - t test and Pearson correlation test were performed using commercial software (SPSS, version 20.0; SPSS Inc) to test the association of time of response with factors such as corneal involvement and initial tumor size.



21 patients data was collected over 6 month's period. Each patient was subjected to 1 month medical treatment. Paired t-test (2 sample for means) was conducted on 21 patients using statistical software SPSS version 20. Tumor area (mm2) was compared between "initial size" and "size after 1 month" of application of given medication.

The occurrence of tumor was double that in males (67%) as compared to that of females (33%).

Size	Mean	N
Initial (mm^2)	28.71	21
At 1 month (mm^2)	13.42	21

The average initial size of tumor amongst 21 patients was 28.71 mm2. While that after 1 month amongst the same 21 patients was 13.42 mm2. This indicated a significant reduction in tumor area after use of interferon 2-beta.

	N	Correlation	Sig.
Tumor initial size and size at 1month	21	0.878	.000

The variables "initial size" and "size after 1 month" showed a high degree of correlation.

Between these 2 variables, the hypothesis tested was as follows –

H0: The initial size of tumor and size of tumor after 1 month was same.

Ha: The initial size of tumor and size of tumor after 1 month was different.

PAIRED T-TEST was conducted on the patient's data for 'before' and 'after' application of the interferon 2 beta at 95% confidence level. The null hypothesis was rejected as test was found to be statistically significant. The p-value was 0.000 much lower than 0.05 alpha.

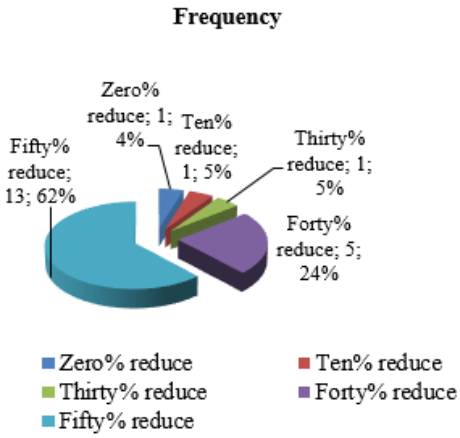
Percentage reduction in the tumor area was also analysed separately:

In 62% (n=13) of the patients, percentage reduction was around 50%.

In 24% (n=5) of the patients, percentage reduction was around 40%.

Thus, in 86% (n=18) of the patients, percentage reduction was around 40 to 50%.

One patient did not respond to the medication, one had only 10% reduction and another had 30% reduction.



3. Results

21 OSSN patients who were given topical interferon alfa-2b were included in the study. The characteristics including size and type of tumor are described in Table 1. Of the total 21, 6 were papillomatous, 8 were gelatinous, and 7 were leukoplakic. The median limbal involvement was 4 clock hours (mean, 5.58 clock hours; range, 2-12 clock hours). Of the 21 cases, 10 patients had 4 to 6 clock hours, and 4 had more than 180 degrees of limbal involvement.

18 tumors were clinically staged as T3 (tumors invading adjacent structures excluding the orbit) and 3 as T2. Median greatest linear diameter was 6 mm (range, 5.2-12 mm). No long-term complication or recurrence was found at the end of the follow-up period of the study.

The tumor characteristics are described in Table 2.

Table 1: Americanjoint committee on cancer classification of ocular surface squamous neoplasia clinical category (primary tumor) definition

TX	Tumor cannot be assessed
T0	Tumor absent
Tis	Tumor present as carcinoma in situ/conjunctival intraepithelial neoplasia
T1	Tumor present with largest basal _5 mm diameter
T2	Tumor present with largest basal diameter _5 mm, no invasion of adjacent structures
T3	Tumor invades adjacent structures excluding the orbit
T4	Tumor invades the orbit with or without further extension
T4a	Tumor invades orbital soft tissues, without bone invasion
T4b	Tumor invades bone
T4c	Tumor invades adjacent paranasal sinuses
T4d	Tumor invades brain

Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	Regional lymph node metastasis absent
N1	Regional lymph node metastasis present

Distant metastasis	
M0	Distant metastasis absent
M1	Distant metastasis present

Adjacent structures include cornea, forniceal conjunctiva, palpebral conjunctiva, tarsal conjunctiva, intraocular compartments, caruncle, lacrimal punctum and canaliculi, semilunar fold, anterior or posterior eyelid lamellae, and/or eyelid margin.

Table 2: Tumor Characteristics - Type of OSSN Tumor

Papillomatous	6
Gelatinous	8
Leukoplakic	7

Growth pattern	
Flat/sessile	20
Pedunculated	1

No. clock hours limbal involvement	
<3	3
4-6	12
7-9	4
10-12	2

Tissue involved	
Bulbar conjunctiva	21
Forniceal conjunctiva	1
Tarsal conjunctiva	1
Caruncle	1
Cornea	16

Mean greatest linear diameter, mm 7.23 + 2.28 (median, 6 mm)

HIV +ve	0
HBsAg positive	0
Smoking	11
UV exposure	21

HIV +ve indicates human immunodeficiency virus- positive ; HBsAg, hepatitis B surface antigen positive; UV, ultraviolet.

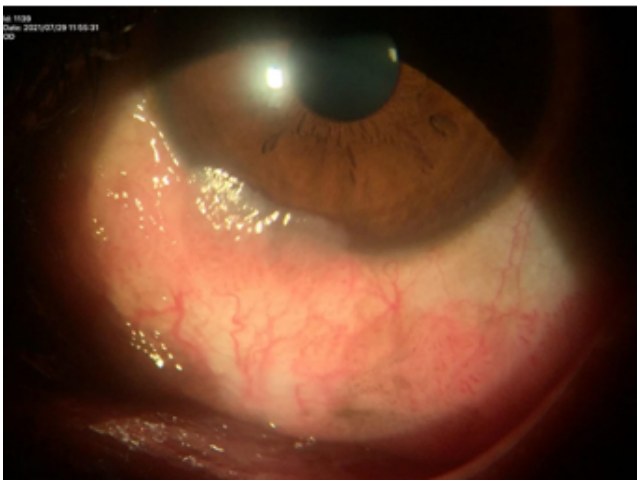


Fig. 1: Gelatinous lesion extending about 1.5 mm into cornea

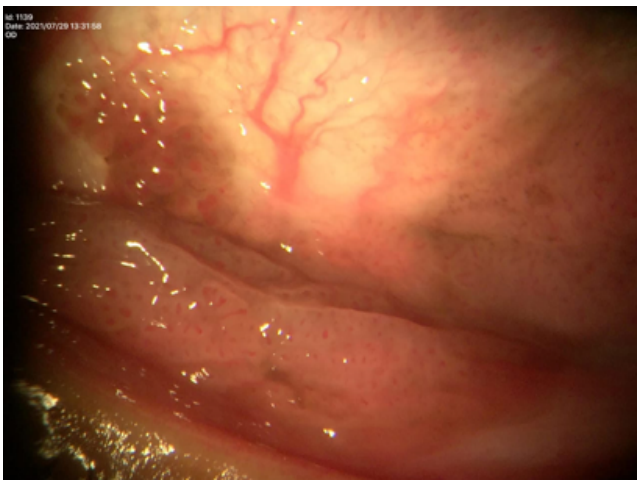


Fig. 2: Extensive OSSN involving the lower fornix and palpebral conjunctiva

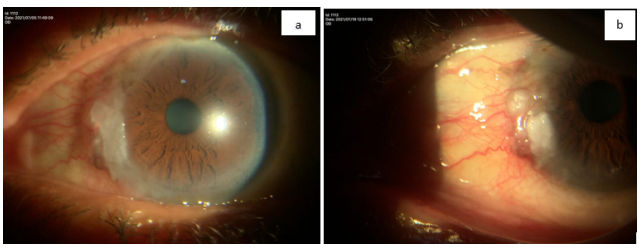


Fig. 3: a: Initial lesion at presentation; **b:** Shrinkage of lesion in size and clock hours after 1 month IFN-2 beta topical therapy

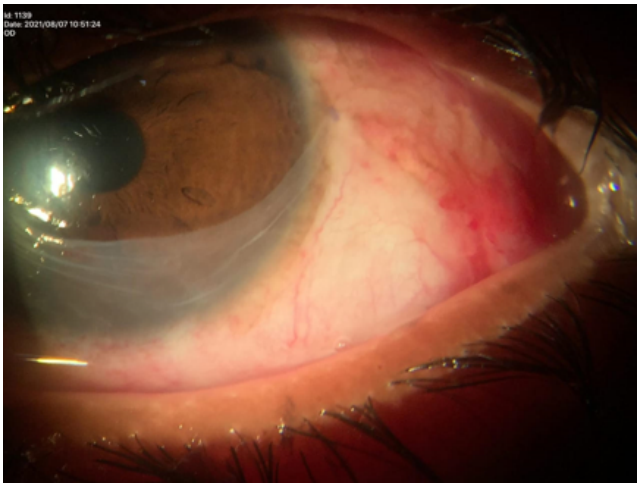


Fig. 4: Amniotic membrane graft in place done for extensive lesions

4. Discussion

Interferons are protein molecules which bind to cell receptors and trigger the synthesis of effector proteins. These can inhibit viruses, activate immunocompetent cells and also regulate oncogenes. They are a type natural defense mechanism.[22]

Interferon α-2b (IFNα-2b) specifically is a cytokine containing 165 amino acid residues which has immunomodulatory effects. Intralesional injections of IFNα-2b are known to enhance the production of IL-2and IFN-γ mRNA by the immune system. They also lower the production of IL-10. These mechanisms help in the recognition and targeting of neoplastic cells.[23]

Interferon alfa-2b is a recombinant form of interferon alfa that has been approved by the US Food and Drug Administration for the treatment of conditions that include chronic hepatitis B and C, malignant melanoma, hairy cell leukemia, multiple myeloma, follicular lymphoma, condyloma acuminata, and AIDS-related Kaposi sarcoma.[24,25]

Topical application of chemotherapeutic agents including mitomycin C, fluorouracil, or interferon alfa-2b has been used for control of OSSN.[24,26] According to a review by Poothullil and Colby,[27] the rates of CIN regression with these 3 agents are comparable (80%-88%). Esquenazi and associates[28] found that interferon alfa-2b is more expensive ($300 per treatment) than mitomycin C ($150 per treatment) and fluorouracil ($100 per treatment) in the treatment of CIN, but its superior safety profile makes it preferable over the others.

The standard dose of topical interferon alfa-2b is 1 million IU/mL. Galor and associates[29] compared this with a 3 million IU/mL dose and found no comparative difference in the tumor response, time to resolution, recurrence rate, and adverse effects. Topical therapy with interferon alfa- 2b (1 million IU/mL) has been reported in several publications[29,30] as being successful in achieving tumor control in 80% to 100% of OSSN classified as CIN.

There was no difference found in the recurrence rate of OSSN at 1- year between surgical excision (5%) and medical treatment with INF α2b (3%).[31]

Recurrence after interferon alfa-2b use was recognized in none to 29% of patients at intervals ranging from 2 to 28 months following treatment.[32,33] In the previous studies, recurrent tumors have been managed by retreatment with topical interferon alfa-2b or with topical interferon alfa-2b combined with mitomycin C.[34]

Karp and associates[35] have suggested the possibility of larger lesions requiring a longer time to resolve and that corneal lesions might respond more rapidly than the conjunctival lesions, based on their study of 5 patients.

The duration for which topical interferon therapy should be continued beyond tumor resolution is not well known as of now. It was continued to tumor resolution[36] up to 1 month beyond tumor resolution[37] and up to 4 months beyond tumor resolution[32] in various studies.

Studies investigating use of topical interferon alfa-2b (1 million IU/mL) for OSSN in human eyes have reported low rates of reversible complications like ocular discomfort and photophobia

in 10%, population, conjunctival hyperemia in 12%,[37] follicular conjunctivitis in 7% to 20%,[32,35,37] irritation in 10%, and superficial keratitis in 1 reported case.[35] These all were found to be self resolving complications.

A physician survey in 2005 which was conducted to assess the standard of care in the treatment of OSSN showed that less than 5% of the physicians had reported interferon alfa- 2b[38] as their primary choice of therapy and among those who routinely used adjunctive topical therapy after surgical excision , only 18% preferred interferon alfa-2b.

5. Conclusion

INF α2b is an effective adjunct to surgery, in suitable cases and is also used for immunoreduction, immunotherapy, or immunoprevention of OSSN.

Primary strategy for management of OSSN is surgical excision, it is the most common modality, surrounding cryotherapy, and alcohol keratectomy, with histopathologic confirmation of the tumor. However, there are circumstances in which surgical excision may not be feasible, especially with cases of extensive disease or elderly patients who are ineligible for surgical intervention.

In this clinical study, efficacy of topical interferon alfa-2b as an adjunct therapy in treatment of primary OSSN was found to have reliable results. Even though there are reports of using topical interferon alfa-2b as primary therapy for clinically diagnosed OSSN (without histopathologic confirmation), it is recommended to exercise caution and consider surgical excision wherever feasible, especially

for atypical lesions, for diagnostic as well as therapeutic purposes.

6. Conflict of Interest

The authors declare that there are no conflicts of interest in this paper.

7. Source of Funding

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