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Therapeutic Evaluation of Interferon Alpha 2b in Ocular Surface Squamous Neoplasia

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KEYWORDS

Therapeutic Evaluation, Surface Squamous Neoplasia

ABSTRACT:

Background: To evaluate the efficacy of Interferon alpha-2b (IFN α-2b) in the management of Ocular Surface Squamous Neoplasia (OSSN), including its roles in immunotherapy, immunoreduction, and immunoprevention.

Methods: A retrospective observational study was conducted over a one-year period at a tertiary care hospital. The study included 30 patients diagnosed with OSSN who had received treatment with IFN α-2b and provided informed consent for participation. Medical records were reviewed to assess treatment outcomes and adverse effects.

Results: Among the 30 patients analyzed, immunotherapy was achieved in 13 patients (43.33%), immunoreduction in 6 patients (20%), and immunoprevention in 11 patients (36.66%). The treatment was well tolerated, with only minor side effects reported as conjunctival hyperemia in 2 patients (6.66%) and flu-like symptoms in 2 patients (6.66%). No adverse effects were observed in 26 patients (86.66%). Also, no recurrences of OSSN were noted during one year follow-up period.

Conclusion: Interferon alpha-2b appears to be a safe and effective treatment modality for OSSN, demonstrating potential as a primary approach for immunotherapy, immunoreduction, and immunoprevention. Given its favourable safety profile and efficacy, IFN α-2b may serve as a non-surgical alternative and could potentially replace surgery as the standard of care in OSSN cases.

INTRODUCTION

Ocular surface squamous neoplasia (OSSN) represents a spectrum of neoplastic changes affecting the squamous epithelium of the conjunctiva, cornea, and limbus, ranging from mild dysplasia and intraepithelial neoplasia (carcinoma in situ) to invasive squamous cell carcinoma (SCC).[1]The Primary risk factor for OSSN is ultraviolet B radiation. Other modifiable risk factors being smoking, chronic trauma, ocular inflammation, exposure to chemicals, vitamin A deficiency and local immunosuppression.[2] Human Immunodeficiency Virus and Human Pappiloma Virus have been strongly associated with the occurrence of OSSN. [3,4] OSSN usually presents unilaterally and rarely bilateral or multifocal presentations can occur. Lesion morphology may vary from gelatinous, leukoplakic, papillary, or nodular to nodular-ulcerative. [5]These lesions are typically located in the interpalpebral fissure medially or laterally and can be planar or textured, localized, or diffuse.[6] The common stains used to highlight OSSN are lissamine green, rose Bengal, and methylene blue stains. Commonly used imaging modalities to detect OSSN include High-resolution optical coherence tomography

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(HR-OCT), In vivo confocal microscopy and Exfoliative cytology.[7-11]

Surgical excision using the "no-touch" technique remains the gold standard for treating OSSN because of rapid resolution, but it has been associated with conjunctival scarring, symblepharon and limbal stem cell deficiency[LSCD].[12-14] A recent study by Bowen *et al.* reported that surgical excision is linked to recurrence rates of up to 31% when excised tissues have positive margins and 14% when margins are negative, based on a mean follow-up period of 42 months.[15]The most commonly used topical treatment options for OSSN are interferon alpha-2b (IFNα-2b), 5-fluorouracil (5-FU), and mitomycin C (MMC). [16-18] Other less frequently used agents are retinoic acid and anti-vascular endothelial growth factor (anti-VEGF). [19-22]

IFNα-2b is a naturally occurring glycoprotein of low molecular weight with antineoplastic properties. Its antineoplastic effects include promoting apoptosis, inhibiting angiogenesis, and extending the cell cycle duration in malignant cells. Interferons have also been used historically in the treatment of various conditions, such as cervical intraepithelial neoplasia, actinic keratosis, and metastatic malignant melanoma. [23-25]

Interferons are generally categorized into two types: Type I, which includes interferon alpha (IFNα), and Type II.[26] IFNα has demonstrated notable effectiveness in the management of OSSN. Among the clinically used forms of IFNα, interferon alpha-2a (IFNα-2a) and interferon alpha-2b (IFNα-2b) are the most common. [27]Recombinant IFNα-2b is frequently employed in OSSN treatment, administered either as topical eye drops or through subconjunctival or perilesional injections.[28] The standard concentration for topical IFNα-2b is 1 million IU/mL, typically instilled four times daily until complete clinical resolution, which generally occurs within approximately 12 weeks. [29-31]

The effectiveness of topical medications on OSSN ranges from 80% to 100% with MMC having the highest documented incidence of side effects at 76%, followed by 5-FU at 42%, and IFN α2b at the lowest with 15%. MMC has more severe and frequent side effects like pain,redness, allergic conjunctivitis, conujnctival hyperaemia, punctuate staining of cornea, punctual stenosis and LSCD. 5- FU is usually well tolerated with less side effects like pain, redness, eyelid edema, watering, keratopathy and superficial stromal melting. Topical IFN α2b drops are best tolerated among topical therapies of OSSN. Side effects are limited to mild irritation, conjunctival hyperaemia, reactive lymphoid hyperplasia and follicular conjunctivitis which resolve with discontinuation of treatment. [32-37]

MATERIALS AND METHODS

This retrospective interventional study was conducted at a tertiary care center in North Karnataka between April 2023 and April 2025. Institutional Review Board (IRB) approval was obtained, and the study adhered to the tenets of the Declaration of Helsinki.

Study Population

Medical records of all patients diagnosed with ocular surface squamous neoplasia (OSSN) who underwent treatment and follow-up during the study period were reviewed. Patients were included if they had a clinical presentation of OSSN with histological confirmation via impression cytology and provided informed consent. Exclusion criteria included prior treatment with Mitomycin C or 5-fluorouracil (5-FU), known allergy to interferon, non-compliance with treatment and patients who do not consent.

Data Collection

Demographic data, including age and gender, were recorded. Relevant systemic history, with specific attention to immunocompromised states such as HIV infection, organ transplantation, uncontrolled diabetes, chronic kidney disease (CKD), and other malignancies, was documented. A past history of similar ocular lesions, exposure to radiation, or tuberculosis were noted. Occupational history and potential ultraviolet (UV) exposure were also assessed.Presenting complaints and symptom duration (in months) were noted. Best-corrected visual acuity and refraction were recorded. A detailed slit-lamp examination was performed to assess:

- Tumor laterality (right or left eye)
- Location and extent of involvement (conjunctiva, limbus, cornea)
- Number of limbal clock hours involved
- Maximum basal tumor dimension (in mm)

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- Tumor morphology (leukoplakic, gelatinous, nodular, pigmented, or papillary)

Comprehensive ocular examination, including pupillary reflexes and fundoscopy, was performed. Locoregional lymph nodes were palpated, and systemic evaluation by a physician was done to rule out metastasis. Anterior segment optical coherence tomography (AS-OCT) was conducted in all cases to assess intraocular extension. Relevant serological investigations were performed.

Diagnosis and Treatment Allocation

Diagnosis of OSSN was confirmed via impression cytology. Patients were counselled regarding treatment options and potential side effects. Based on patient choice and clinical indication, two treatment arms were defined:

Arm 1: Interferon α2b-Based Therapy (Medical ± Surgical)

Patients received a combination of:

- Topical IFN α2b eye drops: Prepared by diluting 1 mL of recombinant human IFN α2b (5 million IU/mL) with 4 mL of sterile distilled water to achieve a concentration of 1 million IU/mL. Drops were dispensed in a sterile container, stored in a thermocol icebox, and administered 4 times daily. Patients were instructed to refrigerate the eye drops at 2–8°C.
- Perilesional IFN α2b injections: 5 million IU/mL was administered once monthly under aseptic precautions as an outpatient procedure after topical anaesthesia.

Patients were reviewed every 4 weeks. Treatment was continued for 3 months (i.e., three perilesional injections and continuous use of topical drops). Based on response to treatment, patients were classified as follows:

- **Immunotherapy**: Complete tumor regression after 3 months of therapy. Topical drops were continued for an additional 3 months as maintenance.
- **Immunoreduction**: Partial tumor regression after 3 months. These patients subsequently underwent surgical excision.
- **Non-responders**: No response or progression of lesion; these patients underwent surgery followed by adjuvant topical IFN α2b for immunoprevention.

Arm 2: Primary Surgical Excision with Adjuvant Interferon α2b

Patients choosing primary surgery underwent tumor excision under local anaesthesia by a single experienced surgeon. The surgical procedure included:

- No-touch technique with 4 mm tumor-free margins
- Partial lamellar kerato-sclero-conjunctivectomy
- Application of an alcohol-soaked sponge to the cornea for safe epithelial elevation.
- Surgical instrument and drape change post-excision
- Double freeze-thaw cryotherapy to tumour base and conjunctival margins
- Amniotic membrane grafting was done and secured with 8-0sutures

Postoperatively, patients received topical IFN α2b eye drops (1 million IU/mL) four times daily for 3 months as **immunoprevention**. Follow-up was conducted every 4 weeks for 6 months to assess for side effects or recurrence. After complete tumor regression, patients were monitored every 3 months for 1 year.

RESULTS

A total of 30 patients with ocular surface squamous neoplasia (OSSN) were enrolled in this study. The demographic characteristics are summarized in Table 1. The median age of the patients was 61.5 years (mean: 62.33 years, range: 55–70 years). A male predominance was observed, with 21 patients (70%) being male and 9 patients (30%) female. There were 6 patients with Immunosuppression(4 patients with HIV seropositive and 2 patients post renal transplant)

Clinical Presentation

The clinical features at presentation are detailed in Table 2. The most common presenting complaint was the appearance of a fleshy conjunctival mass, reported in 63.33% of patients (n=19), followed by redness in

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26.66% (n=8), diminution of vision in 6.66% (n=2), and ocular pain in 3.33% (n=1). The mean duration of symptoms prior to presentation was 5.77 months (median: 6 months, range: 1–12 months).

The most frequently involved site was the conjunctivo-limbal region (63.33%, n=19), followed by the bulbar conjunctiva (20%, n=6) and then cornea (16.66%, n=5). All patients presented with unilateral OSSN. The mean maximum basal tumor dimension was 9.1 mm (median: 8.5 mm, range: 5–17 mm).

Treatment Outcomes

Of the 30 patients:

1. **19 patients were treated under Arm 1** (interferon α2b therapy ± surgery)
    - 13 patients (68.42%) achieved complete tumor resolution (immunotherapy) with interferon alone and did not require surgical intervention.
    - 6 patients (31.58%) had partial tumor resolution (immunoreduction) after 3 months of interferon therapy and subsequently underwent surgical excision of the residual lesion.
2. **11 patients chose Arm 2** (primary surgical excision followed by immunoprevention). All patients in this group were successfully treated with surgery followed by topical interferon therapy to prevent recurrence.
3. The 6 patients from Arm 1 who underwent surgery after immunoreduction also received postoperative topical interferon therapy for immunoprevention.

In total:

- Immunotherapy (interferon only, no surgery) was achieved in 13 patients (43.33%)
- Immunoreduction followed by surgery was required in 6 patients (20%)
- Immunoprevention with postoperative topical interferon was administered in 17 patients (56.66%), which included 6 from Arm 1 and 11 from Arm 2

Thus, surgical intervention was successfully avoided in 13 patients (43.33%), thereby significantly reducing the surgical burden. Minor adverse effects were reported in 4 patients (13.33%),Conjunctival hyperemia in 2 patients (6.66%), Flu-like symptoms in 2 patients (6.66%),no adverse effects were reported in 26 patients (86.66%), no recurrences were observed in any patient during the 6-month follow-up period as seen in Table 3. Therapeutic efficacy of Interferon alpha 2b has been graphically depicted in Figure 1. As seen in Figure 2a and 2b, Pre and post treatment results of Interferon alpha 2b after surgical excision of OSSN which shows complete resolution. Figure 3a and 3b shows OSSN with a large basal diameter was treated surgically with cryotherapy and amniotic membrane transplantation. Post operatively, Interferon alpha 2b used as immunoprevention.

Table 1: Demographic Characteristics of Patients with Ocular Surface Squamous Neoplasia (n = 30)

Features	**n (%)**
Age (years) Median (mean, range)	61.5 62.33, 55 – 70
Gender: Male Female	 21 (70 %) 09 (30%)

Table 2: Clinical Features of Patients with Ocular Surface Squamous Neoplasia (n = 30)

Features	**N**	**Percentage**
Presenting complaints		
Diminution of vision Fleshy mass Pain Redness	2 19 1 8	6.66% 63.33% 3.33% 26.66%

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Site of OSSN :		
Cornea	5	16.66%
Conjunctivo limbal	19	63.33%
Bulbar conjunctiva	6	20%

Table 3: Treatment Modalities and Clinical Outcomes in Patients with Ocular Surface Squamous Neoplasia (n = 30)

Features	N	Percentage
Clinical outcome to Interferon α-2b therapy		
Immunotherapy	13	43.33%
Immunoreduction	6	20%
Immunoprevention	11	11%
Side Effects		
Flu like symptoms	2	6.66%
Conjunctival hyperemia	2	6.66%
Tumor recurrence	nil	nil

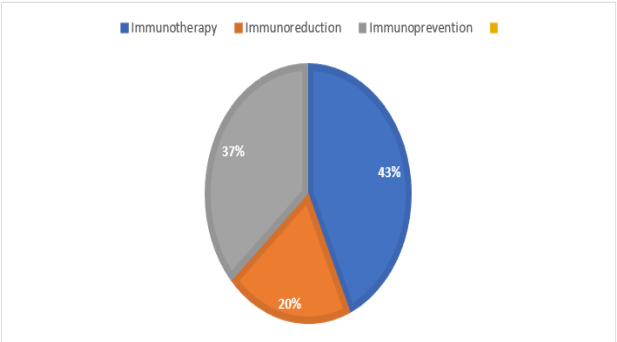

Figure 1: Therapeutic efficacy of Interferon alpha 2b as immunotherapy, immunoreduction and immunoprevention.

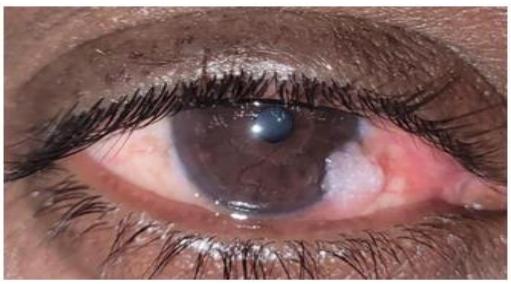

Figure 2a

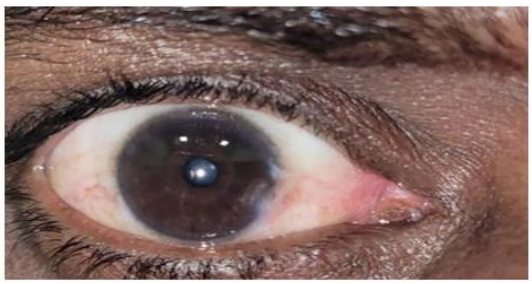

Figure 2b

Figure 2a and 2b: Before-and-after image demonstrating the immunotherapeutic effect of IFN alpha-2b, showing complete lesion resolution

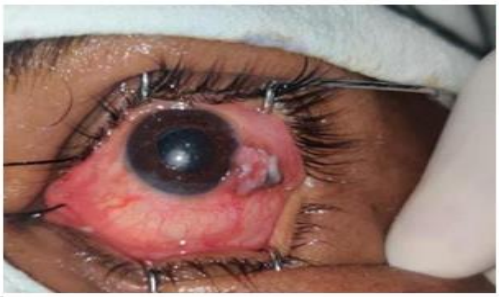

Figure 3a

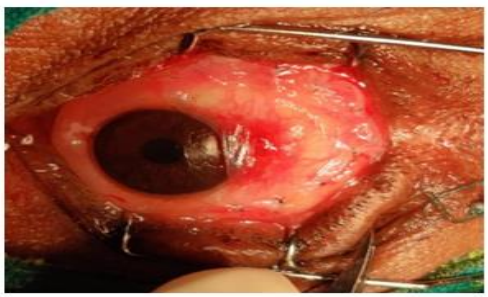

Figure 3b

Figure 3a and 3b: OSSN with a large basal diameter was treated surgically with cryotherapy and amniotic membrane transplantation. Post operatively, Interferon alpha 2b used as immunoprevention.

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DISCUSSION

A study by Venkatesh *et al.* compared 5-FU and IFN eye drops as primary treatment options for OSSN and concluded that both achieved high tumor resolution rates and low recurrence, confirming their effectiveness as treatment modalities for OSSN.[38] In our study, 43.33% of tumors showed complete response to IFNα-2b, while 20% demonstrated a partial response. Additionally, 56.66% of tumors were managed with IFNα-2b as immunoprevention. Notably, a 100% cure rate was achieved using IFNα-2b, either alone or in combination with surgery. These findings align with previous studies that report success rates ranging from 81% to 100% for IFNα-2b in the treatment of OSSN. [39-41]

IFNα-2b can be utilized for immunoreduction in extensive lesions, particularly those with a basal tumor diameter of 20 mm or more, or involving more than 6 clock hours of the ocular surface.[42,43]A study done by Kim *et al.*. noted that out of 18 patients with extensive OSSN, immunotherapy achieved in 13 (72 %) patients and immunoreduction achieved in 28 % with mean duration of 6 months (37). However, in our study 6 patients achieved immunoreduction with tumor basal diameter 12- 17 mm and immunotherapy was achieved in 13 patients with basal tumor diameter ≤ 10 mm. In a study by Karp *et al.*., among five patients, two patients had corneal OSSN. Both patients had complete tumor regression with topical INF α-2 b as immunotherapy by a median duration of 2 months [23]. In our study five patients had corneal OSSN in whom, INF α-2 b served as immunotherapy with median duration of 3 months.

According to published literature, topical IFNα-2b is effective at a dose of 1 MIU/cc administered four to six times daily [32,41,44]. A comparative study evaluating the efficacy and side effect profile of two concentrations of topical IFNα-2b (1 MIU/cc vs. 3 MIU/cc) in the treatment of OSSN found no significant difference between the two dosages [29]. However, there is no established consensus regarding the optimal dose or regimen for perilesional IFNα-2b. Some studies have used 3 MIU/0.5 cc one to three times per week until clinical resolution[40,45], while others have reported using 10 MIU/cc once a month. [41-43] In our study, topical IFNα-2b was administered at a dose of 1 MIU/cc four times daily until clinical resolution, while perilesional injections were given at a dose of 5 MIU/cc once monthly until the conjunctival component of the tumor resolved. Additionally, the literature shows no consensus on the duration for continuing topical IFNα-2b after clinical resolution, with recommendations ranging from 1 to 4 months. [29,32,41] In our study, all patients were advised to continue topical IFNα-2b for 3 months beyond complete clinical resolution.

There is no difference in the recurrence rate of OSSN at 1-year between surgical excision (5%) and medical treatment with INF α2b (3%).[32] In our study, no tumor recurrence was noted in any patient in the follow-up period of 12 months.

INF α2b has fewer side effects than other topical agents used in OSSN. Ocular side effects include conjunctival hyperemia (5%), ocular irritation (4%), superficial punctate keratitis (4%), and follicular conjunctivitis (1%).[41] Systemic side effects include post injection flu-like syndrome for 1 day (9%).[41] In our study, the side effects included transient conjunctival hyperemia (6.66 %) and flu-like syndrome (6.66 %), which were comparable with other studies. [29,40,41]

LIMITATIONS

The limitations of this study include its retrospective design, a relatively small patient cohort, and a shorter follow-up duration. Treatment with IFNα2b also requires more follow-up visits compared to primary surgical intervention. However, medical management helps avoid additional surgeries for limbal stem cell deficiency, which may result from extensive surgical excision and cryotherapy in cases of large lesions.[46]

CONCLUSION

Interferon α-2 b can be used for immunotherapy, immunoreduction or immunoprevention for management of OSSN. Interferon α-2 b may replace surgery as the standard of care in the future in treating OSSN.

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Conflicts of interest: There are no conflicts of interest.

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