Original Article

Recombinant Interferon Alpha-2b as Primary Treatment for Ocular Surface Squamous Neoplasia

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Abstract

Purpose: To investigate the effects of topical and perilesional interferon alpha-2b as primary treatment for ocular surface squamous neoplasia (OSSN).

Methods: In this prospective interventional case series, topical interferon alpha-2b (3 MIU/mL) was used as the initial treatment of OSSN, with perilesional interferon alpha-2b (3 MIU/mL) added based on clinical response. The primary outcome was complete tumor resolution. Spearman's rank correlation test was used to investigate the association of complete tumor resolution and time to resolution with baseline tumor characteristics and the American Joint Committee on Cancer (AJCC) classification for OSSN.

Results: Ninety-two patients (92 OSSN tumors) were included in the study. The total follow-up duration was 13.57 ± 2.14 months (median: 12, range: 3–23). The median basal tumor diameter was 4 mm (mean: 4.13 ± 1.37). Complete tumor resolution was achieved in 89 cases (96.73%), with a median time to complete tumor resolution of 5 months (mean: 4.64 ± 1.92). Complete tumor resolution was 57 of 57 in T1 (100%), 8 of 9 in T2 (88.88%), and 21 of 23 in T3 (91.30%). There were statistically significant correlations between AJCC classification and complete tumor resolution (Spearman's $r = -0.22$, $P = 0.03$) and maximal basal tumor diameter and the time to complete resolution (Spearman's $r = 0.35$, $P = 0.001$). There were no recurrences during the study follow-up period.

Conclusion: Topical interferon alpha-2b is effective and well tolerated as a primary treatment for OSSN, with a high rate of tumors responding completely to therapy.

Keywords: Ocular surface squamous neoplasia, Recombinant interferon alpha-2b, Topical chemotherapy

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Introduction

Ocular surface squamous neoplasia (OSSN) is the most prevalent malignant ocular surface neoplasm with a prevalence of 0.2–3.5 cases per 100,000 population.[1,2] The spectrum of OSSN includes a range from minimally invasive disease to invasive squamous cell carcinoma that could involve the ocular surface, eyeball, its appendix, and the orbital cavity in advanced cases.[3]

The classical surgical approach for the treatment of OSSN has been wide surgical excision using the "no-touch" technique and cryotherapy of conjunctival margins.[4] On the other hand, topical chemotherapy with agents such as mitomycin C (MMC), 5-fluorouracil (5-FU), and interferon alpha-2b are the effective and less invasive treatments for squamous neoplasia of ocular surface, with the advantage of treating all over the ocular surface.[5] MMC has been shown in studies to be highly effective. Still, its application for treatment of OSSN has been associated with short-term and long-term complications such as conjunctival hyperemia, photophobia,

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punctate epithelial erosion, punctual stenosis, corneal erosion, scleral thinning, and limbal stem cell deficiency.[6-10] Interferon alpha-2b and 5-FU are similarly effective, with interferon alpha-2b being an extremely well-tolerated and effective treatment.[5]

The reported success rate of interferon alpha-2b for the treatment of OSSN varies between 81% and 100% in previous studies.[5,11-16] However, differences in risk factors and etiology of OSSN in different populations could be a factor impacting the response to treatment, highlighting the role of the evidence provided by studies including large sample sizes in diverse populations. Our objective was to report the outcomes of local therapy with interferon alpha-2b in an Iranian population.

Methods

This study was a prospective interventional case series conducted at a single institution. The study was conducted between January 2016 and January 2019. The Ethical Committee of Farabi Eye Hospital (Tehran University of Medical Sciences, Tehran, Iran) approved the study protocol (IR.TUMS.FARABIH.REC.1397.048). The study adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants in the study.

Patients with a clinical diagnosis of ocular surface squamous neoplasms (carcinoma *in situ*/squamous cell carcinoma) presenting to the cornea and ocular surface clinic at Farabi Eye Hospital were included in the study. Patients presenting with signs of scleral, intraocular, or orbital invasion; incomplete follow-up; or follow-up <3 months were excluded from the study.

All patients underwent complete ophthalmic, local lymph node, and medical examination to evaluate the extent of ocular involvement and rule out local lymph node or systemic metastasis. Impression cytology was done for all the patients. However, clinical findings were considered more accurate when there was a discrepancy between impression cytology' result and clinical observations. The demographic details, including age and gender, were reviewed. Systemic history regarding risk factors including smoking, occupation, history of human immunodeficiency virus (HIV), and systemic comorbidities was obtained from all patients. The recorded clinical features included presenting complaints, morphologic features (leukoplakic, gelatinous, papilliform, and mixed), tumor location (conjunctiva, cornea, and conjunctival-limbal-corneal surface) and quadrant, and maximum basal tumor diameter. A clinical modification of the seventh edition American Joint Committee on Cancer (AJCC) classification for OSSN was used for the staging of tumors.[17] According to this classification, OSSN is classified as T0 (no evidence of primary tumor), Tis (carcinoma *in situ*), T1 (tumor 5 mm or less in the greatest dimension), T2 (tumor more than 5 mm in the greatest dimension without invasion of adjacent structures), and T3 (tumor invades adjacent structures including cornea, tarsal conjunctiva, palpebral conjunctiva, caruncle, and intraocular compartments [excluding the orbit]), and T4 tumor invades the orbit with or without further extension. Considering the uncertainty for distinction between the *in situ* and invasive disease based on clinical features and lack of histopathologic data, the tumors were classified either as T1, T2, or T3, and we did not include a Tis stage.[18] Slit photographs were taken at the baseline and during each visit for patients.

All patients received a 3 million IU/mL formulation of topical interferon alpha-2b (PDferon B®, 3 MIU/ml, Pooyesh Darou, Tehran, Iran) started at a dose of four times a day. Interferon vials were substituted in artificial tear bottles under sterile conditions in the local pharmacy. The patients were instructed to store the drug in a refrigerator (2°C–8°C). Patients were examined in nearly 2 weeks and then every month until resolution of tumor. In the case of inadequate response to therapy as evidenced by failure to observe regression of tumor in two subsequent visits, perilesional injections of interferon alpha-2b were added to the treatment protocol. Perilesional injections of 1 cc of 3 MIU/mL interferon alpha-2b were given under sterile conditions and topical anesthesia at multiple sites around the lesion as an outpatient procedure. Injections were continued every 2 weeks until tumor resolution. Topical interferon alpha-2b was continued until complete tumor resolution and 1 month beyond and then tapered to BID and continued for an additional 2 months. In the case that complete tumor resolution was not achieved with topical and subconjunctival injections, surgical excision was performed.

Complete tumor resolution was defined as complete regression of the tumor based on slit-lamp examination after initiation of the treatment. Treatment failure was referred to the failure of complete tumor resolution and the need for surgical excision of the tumor. Time to resolution was defined as the time required for complete tumor resolution. Patients were divided into two groups based on the time to resolution to early responder group (treatment duration ≤4 months) or late responder group (treatment duration >4 months).

Statistical analysis

Descriptive statistics were used to describe the distribution of the data. Kolmogorov–Smirnov test was used to assess the normality of the distribution of the data. Kruskal–Wallis and Chi-square tests were used for comparison of continuous and categorical variables between groups, respectively. Spearman's rank correlation test was used to analyze the correlation between the baseline parameters and complete tumor resolution and time to resolution. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using the STATA software (STATA version 15.1; StataCorp LP, College Station, TX, USA).

Results

Ninety-two OSSN tumors from 92 patients were included in the study. The demographic features and

tumor characteristics are shown in Table 1. The median age of patients at presentation was 64 years (mean: 62.28 ± 13.70, range: 26–91); 66 (71.74%) were male, and 26 (28.26%) were female. The total follow-up duration was 13.57 ± 2.14 months (median: 12, range: 3–23). A review of history for risk factors included history of chronic ultraviolet (UV) exposure (65 [70.65%]), smoking (45 [48.91%]), systemic immunosuppression and organ transplant (2 [2.17%]), and malignancy (chronic myeloid leukemia in 1 case [1.08%]). None of the patients had HIV infection, corneal transplantation, or topical steroid/immunosuppressive use. Impression cytology results were positive in 64 patients (69.5%) and showed conjunctival intraepithelial neoplasia.

Table 1: Baseline demographic data and tumor characteristics

	n (%)
Age (years)	
Mean±SD	62.28±13.70
Median (range)	64 (26-91)
Sex	
Male	66 (71.74)
Female	26 (28.26)
Number of tumors	92
Tissue involved	
Conjunctivolimbal	62 (67.39)
Corneolimbal	25 (27.17)
Corneal	5 (5.43)
Multifocality	
Single	89 (96.73)
Multiple	3 (3.27)
Location[a]	
Nasal	58 (63.04)
Temporal	19 (20.65)
Superior	6 (6.52)
Inferior	8 (8.69)
Multiple	15 (16.30)
Growth pattern	
Flat/sessile	89 (96.73)
Dome	3 (3.27)
Morphology	
Papilliform	26 (28.26)
Gelatinous	31 (33.69)
Leukoplakic	29 (31.52)
Mixed	6 (6.52)
AJCC classification[b]	
T1	57 (61.95)
T2	10 (10.86)
T3	25 (25.17)
Maximum tumor diameter (mm)	
Mean±SD	4.13±1.37
Median, range	4 (2-9)
Tumor size (mm)	
≤5	61 (66.30)
>5	31 (33.70)

[a]Tumors may involve >1 quadrant, [b]All tumors belonged to AJCC classification on cancer clinical category N0M0. SD: Standard deviation, AJCC: American Joint Committee on Cancer

The median largest basal tumor diameter on slit-lamp photography images was 4 mm (mean: 4.13, range: 2–9 mm). The tumor quadrant was nasal (58 [63.04%]), temporal (19 [21.34%]), superior (6 [6.52%]), inferior (8 [8.69%]), and multiple (15 [16.30%]). Tumor involvement site was conjunctival or conjunctivolimbal in 62 (67.39%), corneolimbal in 25 (27.17%) cases, and exclusive corneal involvement was noticed in 5 (5.43%) patients. There were no cases of forniceal, tarsal conjunctiva, or caruncle involvement. The tumor growth pattern was sessile in 89 (96.73%) and nodular in 3 (3.27%) cases. The morphologic features were gelatinous (29 [31.52%]), papilliform (26 [28.26%]), leukoplakic (29 [31.52%]), and mixed (6 [6.52%]). The clinical AJCC staging was T1 (57 [61.95%]), T2 (10 [10.86]), and T3 (25 [27.17%]).

After initiation of interferon alpha-2b therapy, complete tumor resolution was achieved in 89 out of 92 tumors (96.73%). The mean time to resolution was 4.64 ± 1.92 months (median: 5, range: 1–10), and the total treatment duration was 8.80 ± 3.09 months (median: 8; range: 3–14). Complete tumor resolution was 57 of 57 in T1 (100%), 8 of 9 in T2 (88.88%), and 21 of 23 in T3 (91.30%). There was a statistically significant correlation between AJCC classification and complete tumor resolution ($r = -0.22$, $P = 0.03$). There were no statistically significant correlations between age, sex, history of UV exposure and smoking, involved quadrant, morphology, and corneal involvement, and complete tumor resolution [Table 2]. There were no recurrences during the study follow-up period.

Complete tumor resolution was achieved in <4 months (early responder group) in 40 (44.47%) patients, while tumor resolution time was longer than 4 months (late responder group) in 49 (55.53%) cases. Figure 1 shows the time to resolution of tumors. There was a statistically significant correlation between the maximal basal tumor diameter and the time to resolution (Spearman's $r = 0.35$, $P = 0.001$). The median maximal basal tumor diameter was 3.5 (mean, standard deviation [SD]: 3.63 ± 1.12) and 4 mm (mean, SD: 4.42 ± 1.32) in the early and late responder groups, respectively ($P = 0.006$). There were no statistically significant correlations between age, sex, history of UV exposure, and smoking, involved quadrant, morphology, corneal involvement, and AJCC staging, and the response time (early or late responder group) [Table 2].

Eight patients required perilesional injections of interferon alpha-2b. Resolution in the subconjunctival injection group occurred in five patients after a median period of 4 months (mean: 4.20 ± 1.25, range: 2–6) since the first injection. Three (3.26%) patients did not respond to 3–4 injections of interferon alpha-2b. They required surgery to achieve complete resolution.

Adverse effects of treatment occurred in 8 (8.69%) patients. The side effects included conjunctival hyperemia 4 (4.34%),

Table 2: Treatment outcomes and time to response based on baseline characteristics

	Complete tumor resolution, *n* (%)	Treatment failure, *n* (%)	r^a (*P*)	Complete tumor resolution ≤4 months, *n* (%)	Complete tumor resolution >4 months, *n* (%)	r^a (*P*)
Number	89	3		40	49	
Age (years)						
Median (range)	63 (26-91)	74 (64-80)	−0.14 (0.15)	63 (26-91)	64 (31-87)	−0.007 (0.94)
Mean±SD	61.93±13.74	72.66±8.08		61.72±14.87	61.10±19.90	
Sex						
Male	63 (70.79)	3 (100)	0.11 (0.27)	28 (70)	35 (71.43)	−0.01 (0.88)
Female	26 (29.21)	0		12 (30)	14 (28.57)	
Tissue involved						
Conjunctivolimbal	61 (68.54)	1 (33.33)	−0.11 (0.26)	26 (65)	35 (71.43)	−0.06 (0.57)
Corneolimbal	23 (25.84)	2 (66.67)		12 (30)	11 (22.45)	
Corneal	5 (5.62)	0		2 (5)	3 (6.12)	
Location[b]						
Nasal	55 (61.80)	3 (100)	−0.11 (0.26)	24 (60)	31 (63.27)	−0.00 (0.95)
Temporal	19 (21.35)	0	0.11 (0.27)	9 (22.50)	10 (20.41)	−0.01 (0.88)
Superior	6	0	0.04 (0.64)	2	4	0.06 (0.55)
Inferior	8	0	0.05 (0.59)	5	3	−0.11 (0.30)
Multiple	15 (16.85)	0	0.08 (0.44)	4 (10)	6 (12.24)	−0.01 (0.88)
Morphology[c]	0	0				
Papilliform	26 (29.21)	0	−0.15 (0.12)	10 (25)	16 (32.65)	−0.11 (0.28)
Gelatinous	30 (33.71)	1 (33.33)		13 (32.50)	17 (34.69)	
Leukoplakic	28 (31.46)	1 (33.33)		14 (35)	14 (28.57)	
Mixed	5 (5.62)	1 (33.33)		3 (7.50)	2 (4.08)	
AJCC classification[c]						
T1	57 (64.04)	0	−0.22 (0.03)	26 (65)	31 (63.27)	−0.01 (0.89)
T2	9 (10.11)	1 (33.33)		2 (5)	7 (14.29)	
T3	23 (25.84)	2 (66.67)		12 (30)	11 (22.45)	
Maximum tumor diameter (mm)						
Median (range)	4 (2-9)	7 (3-8)	−0.13 (0.18)	3.50 (2-6)	4.00 (2-9)	0.28 (0.005)
Mean±SD	4.07±1.29	6±2.64		3.63±1.12	4.42±1.32	
Tumor size ≤5 mm	60 (67.42)	1 (33.33)	−0.12 (0.22)	32 (80)	28 (57.14)	0.24 (0.02)
Tumor size >5 mm	29 (32.58)	2 (66.67)		8 (20)	21 (42.86)	

[a]Spearman's rank correlation coefficient, [b]Tumors may involve >1 quadrant, [c]AJCC classification of ocular surface squamous cell carcinoma. AJCC: American Joint Committee on Cancer, SD: Standard deviation

follicular reaction (2.17%), punctate epithelial erosions 1 (1.08%), and chemosis 1 (1.08%). The side effects were mild and did not require cessation of treatment. All these complications resolved 1 month after discontinuation of therapy.

Discussion

Our study results demonstrated the efficacy and safety of interferon alpha-2b as primary treatment for OSSN in our study population, with 96.73% of tumors responding completely to therapy. These results are in concordance with other studies demonstrating the high efficacy of interferon alpha-2b with a reported success rate of 81%–100% in treating OSSN.[5,11-16]

Interferon alpha-2b is a glycopeptide with 166 amino acids with O-glycosylated threonine at position 106 which exerts antiproliferative, immunomodulatory, antiviral, and antineoplastic properties. Interferon alpha-2b effects on tumor cells consist of direct and indirect effects. The direct effects include regulation of protein synthesis, cytotoxic effects on tumor cells, apoptosis, and differentiation. The indirect effects include immunomodulation, through activation of T-cells and natural killer cells, and antiangiogenesis effects.[19] An impact on human papillomavirus (HPV) has also been postulated.[20] However, a study found an equivalent efficacy of interferon in the treatment of OSSN, irrespective of its association with HPV.[21]

Different concentrations of topical interferon alpha-2b have been used for the treatment of OSSN. In this study, a concentration of 3 MIU/cc was used for topical treatment. A dose comparison study of interferon alpha-2b (1 MIU/cc vs. 3 MIU/cc) found no significant difference between the two doses in terms of treatment efficacy, indicating the efficacy of interferon alpha-2b in lower dosage for treatment of OSSN. However, a more rapid response was noticed with the higher concentration.[22]

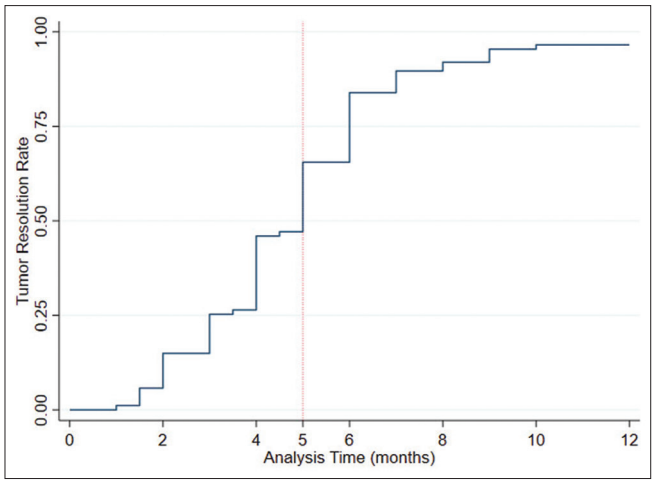

Figure 1: Tumor resolution after initiation of interferon therapy. The red dotted line displays the median time to tumor resolution

In this study, we used topical interferon alpha-2b as the initial treatment and reserved the perilesional injections when the response rate to topical therapy deemed inadequate based on clinical response. In five out of eight patients, complete tumor resolution was achieved with perilesional injections. Subconjunctival injections of interferon alpha-2b have been administered with a dosage of 3 MIU/0.5 cc to 10 MIU/cc and a frequency of 2–3 injections per week to monthly injections.[12,13,15,23] Compared to topical treatment, subconjunctival injection has the potential to induce more rapid tumor regression, possibly due to the higher dosage and bioavailability of the drug. Therefore, it could be considered an alternative in cases with more extensive tumor involvement, noncompliance to topical therapy, or immunoreduction before surgical excision.

Except for the modest correlation between AJCC grading, there were no significant correlations between the other baseline factors such as gender, location, morphology, and corneal involvement with the response to therapy. The response rate was the highest for the T1 (100%) and 88.88% and 90.30% for the T2 and T3 groups, respectively. Shields *et al*. reported a tumor regression rate of 75% Tis, 100% T1, and 70% T3 in 22 eyes treated with interferon alpha-2b monotherapy.[13] Kaliki *et al*. reported complete tumor regression in 100% Tis (all six patients) and 92% T3 (22 of 24 patients),[15] which are quite similar to our results in T3 tumors. Despite the modest correlation, there are limitations to the AJCC classification as a prognostic factor for the response. Lack of discrimination between different types of invasive disease, i.e., corneal involvement which in most cases is limited to epithelial involvement compared to other types of involvement of adjacent structures such as scleral or eyelid invasion which represent a more aggressive course, is a limitation of this classification. The distinction between the *in situ* and invasive disease is also not straightforward based on clinical examination when immunotherapy is used as the initial therapy.[18] Therefore, this classification is not commonly used in OSSN, especially when chemotherapy is the first treatment modality. Proposed modifications in AJCC may make it more applicable in OSSN patients.[24]

Male gender and tumors in the superior conjunctiva were associated with a higher risk of failure after interferon alpha-2b treatment in previous studies.[21] Another study found male gender, temporal and superior location, papillomatous and nodular appearance, and lack of corneal involvement to be associated with higher grades of OSSN.[25] Although all the treatment failures in our study were observed only in the male group, the association was not statistically significant. There was also not a significant correlation between tumor location, nodular appearance, and morphologic pattern, and the response to treatment.

Immunosuppression is proposed as another risk factor associated with unfavorable outcomes.[26] None of the failures in our study were observed in immunosuppressed patients. However, considering the limited number of cases (3 patients), further studies are needed to elucidate the role of immune status on treatment outcomes. Our study did not include patients with recurrent tumor, which is also associated with the risk of treatment failure.[22]

The mean time to tumor resolution was 4.64 ± 1.92 months in our study. These results are in agreement with some other studies, reporting a mean time to tumor resolution of around 5 months with interferon alpha-2b treatment.[14,22,27,28] In our study, there was a significant correlation between the tumor size and the time to tumor resolution, and comparing the groups based on time to response, larger tumor size and proportion of tumors >5 mm were demonstrated in the late responder group.

Mild complications, including conjunctival hyperemia, follicular reaction, punctate epithelial erosions, and chemosis, occurred in 8.86% of our patients. These complications did not necessitate discontinuation of treatment and resolved after 1 month of cessation of treatment. These results are in agreement with the other studies in terms of safety of topical interferon alpha-2b for treatment of OSSN, with mild irritation and follicular conjunctivitis as the main side effects.[29] Other complications such as corneal epithelial defect, conjunctival hyperemia, and epithelial microcyst formation have been reported in other studies.[30,31]

There are limitations to our study. Although no cases of tumor recurrence were observed in our study, long-term follow-up is required to address the rate of tumor recurrence. As our diagnosis of OSSN was a clinical-based diagnosis, the absence of histologic diagnosis and their correlation with response to treatment is another limitation of our study. Patients presenting with signs of scleral invasion, eyelid, or orbital invasion were excluded from this study. Therefore, the results of this study could not be applied to these circumstances. On the other hand, to the best of our knowledge, this study represents the largest sample size in our population and among the studies published on the effect of local interferon alpha-2b therapy for OSSN.

In conclusion, the results of this study in our population are consistent with the previously published studies on the efficacy and safety of topical and local interferon alpha-2b for treatment of OSSN. Topical and local interferon alpha-2 could be considered the primary treatment for OSSN.

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Conflicts of interest
There are no conflicts of interest.

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