Treatment outcome with interferon alpha 2b in ocular surface squamous neoplasia: Recommendation as primary treatment by peripheral ophthalmologists

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Abstract:
BACKGROUND: To evaluate the role of interferon alpha 2b (IFNα2b) in the management of primary/recurrent cases of ocular surface squamous neoplasia (OSSN).

METHODOLOGY: Medical records of 27 OSSN cases managed with IFNα2b (topical drops and/or perilesional injection) in 1 year were retrospectively reviewed.

RESULTS: The median age of presentation was 60 years with a male: female ratio of 3.5:1. American Joint Commission on Cancer tumor grading was T1 in 1 eye (3.7%) and T3 in 26 eyes (96.3%). Eighteen cases were treated with topical drops (1 million IU/ml), 4 cases with perilesional subconjunctival injection (3–6 million IU/ml), and 5 cases with combined therapy. Overall, treatment response was seen in 88% cases. Complete regression was achieved in 80% cases. Median time to complete regression of tumor was 3 months (range 1–11 months) in cases treated with topical interferon therapy and 2.5 months (range 0.7–3 months) in cases managed with injections or a combination of the two. The mean duration of follow-up was 24 months. All cases with partial/no response showed complete regression on subsequent management with topical mitomycin C. None of the patients required surgery. Acute ocular surface congestion was seen in two patients necessitating discontinuation of therapy.

CONCLUSION: In view of excellent treatment outcome and few side-effects, interferons can be considered as a primary, safe, and cost-effective treatment option for OSSN not only in tertiary centers but also by peripheral ophthalmologists.

Keywords: Immunotherapy, interferon alpha 2b, interferon, ocular surface squamous neoplasia

Introduction
Ocular surface squamous neoplasia (OSSN) occurs commonly in countries located close to the equator. The conventional treatment of OSSN is wide surgical excision with “no-touch” technique combined with cryotherapy of conjunctival margins or margin control with frozen section. It is associated with a high risk of recurrence if tumor excision is performed without appropriate tumor handling and inadequate margin control. Topical chemotherapeutic agents (mitomycin C [MMC], 5-fluorouracil) have been employed as a nonsurgical treatment option but can cause side effects such as limbal stem cell deficiency, scleral melting, and punctal stenosis, especially in larger tumors.

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More recently, several studies have reported remarkable treatment outcome and minimal side effects with the use of interferon alpha 2b (IFNα2b) in the management of OSSN. [6-15] Most of these are from developed world. There is limited literature on the treatment outcome with interferon from Indian subcontinent, where surgical excision still remains the most common method of treating OSSN. Herein, we report an excellent treatment outcome of primary or recurrent cases of OSSN treated with IFNα2b at our center and recommend it as primary therapy for OSSN by the peripheral ophthalmologists.

**Methodology**

This was a retrospective study conducted at a tertiary eye care center. The present study was approved by the Institutional Ethics Committee of our center and followed the tenets of declaration of Helsinki. Medical records of patients clinically diagnosed with OSSN at our center, from March 2015 to March 2016, were reviewed. Treatment outcome of patients treated with IFNα2b, as eye drops and/or as perilesional injection, was analyzed.

Demographic details and clinical data including previous treatment history, risk factors or any systemic associations, best-corrected visual acuity, laterality and clinical staging of tumor (American Joint Commission on Cancer [AJCC] TNM Classification scheme cancer staging manual, 7th edition) [16] were noted. The clinical characteristics of tumor documented were tissues involved, location, size, height of tumor on ultrasound biomicroscopic examination (UBM), multiplicity, presence of feeder vessels, clinical appearance (gelatinous/papilliform/ulcerative), growth pattern (nodular/sessile), presence of leukoplakia, presence of pigmentation, intraocular involvement, and nodal and systemic metastasis. Based on the number of clock hours of limbal involvement or maximum basal diameter tumor was classified as small (≤5 mm basal diameter or ≤3 clock h of limbal involvement), large (6–15 mm in basal diameter or >3–6 clock h of limbal involvement), and diffuse (more than 15 mm in basal diameter/forniceal/eyelid involvement or >6 clock h of limbal involvement). Histopathology and/impression cytology details and imaging scans were reviewed for all cases.

Topical interferon therapy was preferred in cases with large and diffuse involvement. Perilesional injections were advised in small OSSN, recurrent OSSN, and patients who could not maintain cold chain for eye drops at home. IFNα2b (1 million IU/0.5 ml) eye drops were prepared by the ocular pharmacology department of our center, by dilution of the injectable recombinant form (Reliferon, 3 million IU/0.5 ml) using preservative-free balanced salt solution. The patients were instructed to refrigerate the eye drops and use it four times a day.

For perilesional injection, the preparation (3 million IU/0.5 ml) was directly injected using a tuberculin syringe and a 30 G needle through adjacent normal conjunctiva, into the subconjunctival space with an aim to achieve ballooning of conjunctiva all around the tumor. The patients treated with eye drops were followed every 6 weekly. The injections were repeated at 1–3 weekly intervals. In case of no response to IFNα2b therapy on two consecutive follow-ups, the treatment was stopped, and alternative treatment was advised. Maintenance therapy with interferon eye drops was advised for a period of at least 1 month after complete regression of the tumor.

Complete response/regression was defined as the total disappearance of tumor. Partial response/regression was defined as the reduction in tumor size. No response was defined as no change in the size of the tumor on two consecutive visits. The response to treatment, duration for complete/partial regression of tumor, duration of total treatment, recurrence or relapse, side effects, and period of follow-up were noted. The treatment advised in cases of no response or partial response was also documented.

**Results**

A total of 27 eyes of 27 patients were managed with IFNα2b therapy during the study period at our center and were included in the study. The median age of presentation was 60 years (range 10 years–80 years). There was a male preponderance with a male: female ratio of 3.5:1. Risk factors were sunlight exposure in 70% cases (n = 19), ocular trauma in 7.4% (n = 2), ocular surgery in 7.4% cases (n = 2), cigarette smoking in 33.3% (n = 9), and immunosuppression in 3.7% (n = 1). Fifty-nine percent (n = 16) cases had a left-sided involvement. A previous treatment history was present in 57% cases (n = 12). Of 12 cases, history of surgery was present in eight cases, while the rest was treated with MMC (75%). Histopathology reports were available in 4 out of eight patients and revealed well-differentiated squamous cell carcinoma in three cases and moderately differentiated carcinoma in one case.

The mean duration of symptoms was 2 ± 4.36 years. The tumor characteristics of 27 cases at the time of presentation are summarized in Table 1. Majority of the cases had a gelatinous appearance (63%) and a sessile growth pattern (55.6%). Mean largest basal diameter was 11.9 mm (range 4 mm–28 mm). The AJCC grading of tumor was T1 in 1 eye (3.7%) and T3 in 26 eyes (96.3%). None of the cases had a regional lymph node involvement or distant metastasis at presentation. Impression cytology and UBM examination were done in all except one pediatric patient. Impression cytology showed dysplastic cells in 65% (n = 17/26) cases. Mean tumor height was 1.47 ± 1.43 mm (range 0.24 mm–5.3 mm), and there was no
Meel, et al.: Treatment outcome with IFNα2b in OSSN

Intraocular involvement in any of the cases on UBM. Associated ocular pathologies seen in the affected eye were senile ptosis \((n = 2)\) and lagophthalmos secondary to facial palsy \((n = 1)\). The systemic associations found were xeroderma pigmentosa \((n = 1)\), human immunodeficiency virus \((n = 1)\), and Berger’s disease \((n = 1)\).

Of 27 eyes, 18 eyes were treated with topical IFNα2b \((1 \text{ million IU/ml})\), 4 eyes with perilesional/sub-conjunctival IFNα2b injection \((3–6 \text{ million IU/ml})\), and 5 eyes with combined topical and subconjunctival IFNα2b. One case was lost to follow-up. Topical IFNα2b drops had to be discontinued in two patients due to intolerance secondary to severe ocular surface inflammation. In one of the two patients, despite the discontinuation of interferon drops, there was complete regression of tumor clinically and on impression cytology without any additional treatment. The other patient with intolerance to IFNα2b eye drops achieved partial tumor regression and was treated with MMC drops for residual tumor. Hence, the treatment response was evaluable in 25 out of 27 cases. Overall, 22/25 \((88\%)\) cases showed response to treatment with IFNα2b [Figure 1]. There was complete regression of tumor in 20 cases \((80\%)\), partial regression in two cases \((8\%)\), and no response in three cases \((12\%)\). All cases with partial or no response to interferon therapy belonged to T3 stage \((AJCC)\) and showed complete regression on subsequent management with topical 0.04% MMC. None of the patients required surgery. The median time to complete regression of tumor in cases treated with topical interferon therapy was 3 months \((\text{range 1–11 months})\) and in cases managed with injections or a combination of eye drops and injection was 2.5 months \((\text{range 0.7–3 months})\). The median duration of follow-up was 24 months \((\text{range 14–32 months})\).

No side effects were reported in 16 out of 18 cases treated with topical therapy. Acute ocular surface congestion and foreign-body sensation, necessitating discontinuation of interferon eye drops, were noted in two patients [Figure 2]. Patients receiving perilesional injection complained of local pain at the site of injection and fever/chills that were controlled with medications.

Spearman’s correlation coefficient was calculated between the duration of treatment and various parameters such as age \((P = 0.21)\), duration of complaints \((P = -0.16)\), extent of limbal involvement \((P = 0.29)\), extent of conjunctival involvement \((P = 0.35)\), and tumor staging \((P = 0.34)\). No significant correlation was noted between these parameters.

### Discussion

In this retrospective study, we analyzed the treatment outcome in cases of primary and recurrent, grade T1–T3 OSSN who were treated with IFNα2b eye drops or/and perilesional injections.

In developing countries, wide local excision still remains the most common method for treating OSSN. In the current study, 56\% \((12/27)\) cases were recurrent and 75\% \((8/12)\) of these had undergone previous surgical excision. Tumor excision unless done with proper technique leads to the high rate of recurrence. Recurrences may be

| Table 1: Clinical features of 27 cases of ocular surface squamous neoplasia |
|---------------------------------|------------------|
| Clinical characteristics        | Number of cases  |
| Primary/recurrent               | Number (%) \(n=27\) |
| Primary                         | 19 (70.4)        |
| Recurrent                       | 8 (29.6)         |
| Clinical appearance             |                 |
| Gelatinous                      | 17 (63)          |
| Papilliform                     | 9 (33.3)         |
| Ulcerative                      | 1 (3.7)          |
| Fungating                       | 0 (0)            |
| Growth pattern                  |                 |
| Nodular                         | 12 (44.4)        |
| Sessile                         | 15 (55.6)        |
| Multiplicity                    |                 |
| Single                          | 25 (92.6)        |
| Multiple                        | 2 (7.4)          |
| Structures involved             |                 |
| Limbus                          | 26 (96.2)        |
| Bulbar conjunctiva              | 25 (92.5)        |
| Tarsal conjunctiva              | 2 (7.4)          |
| Fornices                        | 3 (11.1)         |
| Cornea                          | 25 (92.6)        |
| Lid                             | 2 (7.4)          |
| Feeder vessels                  |                 |
| Present                         | 27 (100)         |
| Absent                          | 0 (0)            |
| Leukoplakia                     |                 |
| Present                         | 7 (25)           |
| Absent                          | 20 (75)          |
| Pigmentation                    |                 |
| Present                         | 6 (22.2)         |
| Absent                          | 21 (77.7)        |
| Impression cytology             |                 |
| Positive                        | 17 (65.4)        |
| Negative                        | 9 (34.6)         |
| Tumor as classified in the current study |         |
| Small                           | 8 (29.6)         |
| Large                           | 7 (26)           |
| Diffuse                         | 12 (44.4)        |
| AJCC grading                    |                 |
| T1                              | 1 (3.7)          |
| T2                              | 0 (0)            |
| T3                              | 26 (96.3)        |

AJCC: American Joint Commission on Cancer

Oman Journal of Ophthalmology - Volume 14, Issue 1, January-April 2021
more aggressive and difficult to treat. In our study, with the available surgical notes, it was not clear whether tumor excision in recurrent cases who were operated from outside was supplemented with frozen section or cryotherapy for edge control. According to a recent study from Asia, OSSN is currently the most common cause of orbital exenteration. Although treatment with interferon use has been reported with remarkable outcomes from developed countries, it has not been adopted by peripheral ophthalmologists in developing world primarily because of the cost, and secondly, because they may not have a pharmacy facility for dispensing eye drops.

In the current study, the average cost of treatment was 40 USD for eye drops and 68 USD for the combinations of eye drops and injections. The cost-effectiveness of this treatment in comparison to surgical excision has also been reported in another study from the subcontinent.

In patients who can afford the cost, we would like to encourage the peripheral ophthalmologists to use interferon for the primary treatment of OSSN. If there is no pharmacy facility available and there is lack of frozen section facility or cryotherapy to allow margin control at the time of surgery, the ophthalmologist must use interferon injections for treatment.

At our center, the administration of IFNα2b, either as eye drops (1 million IU/ml) or as perilesional injection, is based on tumor characteristics and patient profile.
Topical drops are prescribed for large/diffuse OSSN in patients who understand the importance of compliance and have a refrigerator, as reconstituted drops need refrigeration. Perilesional injections are preferred in patients with a questionable compliance to topical therapy and in recurrent cases.

Majority (96.3%) of the tumors in our study were of T3 category, similar to that reported in literature.[12,13,20] Among these, 44% (12/27) were diffuse (more than 15 mm in basal diameter or having fornicalis/eyelid involvement or with >6 clock h of limbal involvement). Overall, complete regression of tumor was seen in 80% cases in our study, which is comparable to studies reported in literature.[7‑10,12,21] Tumor response to interferon was unrelated to the size or thickness of the tumor. Average height and basal diameter of the tumors that did not respond to treatment was 1.46 mm and 11.6 mm, respectively, whereas thicker (thickest tumor −5.3 mm) and larger (largest basal diameter −28 mm) tumors completely vanished with immunotherapy. Average height of tumor that responded to treatment was 1.95 mm.

In a retrospective case series by Shields et al., where 22 patients were treated with immunotherapy, complete regression was achieved in 70% of T3 tumors.[10] In our study, 87.5% (21/24) cases of T3 OSSN achieved complete regression with immunotherapy alone. In another study by the same group involving “giant OSSN” (defined as more than 180 degrees of limbal involvement/more than 15 mm basal diameter), 72.2% cases achieved complete regression, and those with residual tumor were managed with surgical excision.[14] In our study, (12/27) 44% of the cases had diffuse tumors comparable with the definition of giant OSSN; among these 10/12 (83%) cases showed a complete response.

It is notable that none of the patients in our study required surgical excision. All the patients who did not regress or partially regressed with interferons completely regressed with subsequent topical MMC. It has been documented that interferons improve the effectiveness of chemotherapy in systemic malignancies such as colonic and hepatocellular cancer. The fact that in our study all cases that failed with immunotherapy could be managed successfully with subsequent topical chemotherapy supports the same.[22,23] Thus, we recommend a trial of topical chemotherapy in cases of OSSN that show no/partial regression with primary immunotherapy, before harping on surgical excision.

Reported median time to clinical resolution of OSSN with interferons ranges from 2 months to 9 months, depending upon the mode of administration and tumor grade.[6‑15,21,24] In our study, it was 2.5 months for injections and 3 months for topical therapy.

IFNα2b is extremely well tolerated with few reported side effects such as ocular irritation, photophobia, follicular conjunctivitis, punctate keratitis, and corneal epithelial defects.[6,12‑14,19,21,24,25] Flu-like symptoms are often reported in patients receiving perilesional IFNα2b, as also seen in our patients.[7,13] Two patients developed severe acute ocular surface congestion of the eye within 1 week of commencement of topical IFNα2b eye drops, for which the IFNα2b therapy had to be discontinued. This has probably not been reported before. However, it is interesting that one of these patients showed a dramatic resolution of tumor with just 3 weeks of immunotherapy. Both these patients showed a very rapid response to immunotherapy (although one case required MMC for residual tumor), and also both had some pre-existing inflammation to begin with [Figure 2]. We wonder if this acute inflammatory response/a pre-existing inflammation may predict a good/faster resolution of tumors with interferons.

We could not evaluate the clinical variables that may affect the treatment response to interferons, as the number of cases with poor/no response was few. No significant correlation was found between the duration of treatment and parameters such as age, duration of complaints, extent of limbal and conjunctival involvement, and tumor staging. The limitation of our study is the retrospective nature and a short follow-up.

Conclusion

To conclude, treatment outcome results with IFNα2b were comparable to that reported in literature and must encourage the peripheral practitioner to adopt this treatment safely as a primary modality for the management of OSSN in routine practice. With subsequent use of MMC complete regression may be achieved conservatively in majority of cases. Nonresponsive or partially regressed cases should be referred to higher centers for surgical excision with proper technique.

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Conflicts of interest
There are no conflicts of interest.

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