Treatment of Ocular Surface Squamous Neoplasia with Interferon Alpha-2b

Zahid Kamal, Farooq Ahmad, Shahid Tarar, Farah Huma, Amir Yaqoob

Purpose: To study the efficacy and safety of Interferon (IFN) alpha 2b for Ocular Surface Squamous Neoplasia (OSSN).

Study Design: Quasi experimental Study.

Place and Duration of Study: Mayo Hospital Lahore, Lahore General Hospital, Armed Forces Institute of Ophthalmology, Rawalpindi, Pakistan October 2010 to August 2016.

Material and Methods: Patients with suspected conjunctival growth underwent incisional biopsy. Ninety-one eyes of 88 patients were included in the study. The patients with suspected conjunctival growths underwent incisional or excisional Biopsy +/- cryotherapy. After confirming the diagnosis of Ocular Surface Squamous Neoplasia (OSSN), on histopathology, cases were inducted in the study. Intralesional/peri-lesional Interferon (IFN) Alpha-2b was given to the patients weekly along with interferon Alpha-2b topical drops four times daily, for three months. These patients were followed-up in respective hospitals and examined for resolution or recurrence of lesion for atleast three (03) months.

Results: Out of 88 patients, 29 were females and 59 were males. The age of the patients was between 52 to 76 years. Eighty eyes tolerated and responded well to the treatment. There was recurrence in 08 eyes, which had advanced squamous cell neoplasia. Three patients were lost to follow up. Mean resolution time of tumor was 3 months and mean follow up time was 12 months with range of 3 months to 5 years. The side effects recorded in our study were filamentary keratitis, conjunctivitis and pyogenic granuloma.

Conclusion: For the management of Ocular surface squamous Neoplasia IFN alpha 2 b is safe and effective choice with low recurrence rates.

Key Words: Conjunctival squamous cell carcinoma, Conjunctival intraepithelial neoplasia (CIN), Ocular surface squamous neoplasia (OSSN), Interferon alpha-2b.

Ocular surface squamous neoplasia encompasses a broad spectrum of neoplastic abnormalities which include squamous dysplasia, squamous cell carcinoma in situ, and invasive squamous cell carcinoma. Squamous cell carcinoma of the conjunctiva includes neoplastic abnormalities that may cause severe morbidity to the patients. It is the third most common conjunctival malignancy worldwide and is commonest in dark-skinned, Caucasians and in tropics. Its incidence is 37.3 per million eyes with ocular tumors. Thorough clinical assessment and early diagnosis is the key for preventing the visual loss and morbidity in patients. Persons in the older age group, those who have UV-light exposure and are smokers have increased risk of developing ocular surface squamous neoplasia. Recurrence rate after surgical excision within 2 years is 15-52% and associated with tissue disruption enhancing the ability of tumor cells to enter in the eye. Previously, mitomycin-C and 5-fluorouracil have been...
used with very good results but the complications associated with these drugs have alarmed the physicians\textsuperscript{5}. The complications include uveitis, epithelial erosions, ulceration, and glaucoma. Recent advances suggest use of Interferon-2b for treating these neoplasms\textsuperscript{6,7,8}. Interferons are glycoproteins that bind to cell receptors, and trigger effector proteins that inhibit viruses, activate immunocompetent cells and regulate oncogenes. Interferon $\alpha$-2b is a recombinant form that has been used for hepatitis B/C, malignant melanoma, follicular lymphoma, condyloma acuminateum, Kaposi’s sarcoma, multiple myeloma, and hairy cell leukemia. The standard dose of topical interferon $\alpha$-2B is 1M IU/ml. Median age for the complete tumor resolution was three months. Few adverse effects of interferon $\alpha$-2b are reported as photophobia, follicular conjunctivitis, conjunctival hyperemia with foreign body sensation and pyogenic granuloma. However, still it is better tolerated than the other forms of topical therapies.

Rationale of the study was to analyze non-surgical treatment of OSSN. Topical interferon alpha-2b therapy can be used to treat OSSN (Immuno-therapy) as well as to reduce the size of OSSN (Immuno-reduction) prior to excision. It may avoid the morbidity of excision that includes loss of limbal stem cells or scarring of ocular surface. The purpose of the study was to find the efficacy and safety of topical and intra-lesional Interferon (IFN) $\alpha$-2b for Ocular Surface Squamous Neoplasia (OSSN) in Pakistani population.

MATERIAL & METHODS
This was a Quasi experimental study, which was conducted in Mayo hospital/KEMU Lahore, Armed Forces Institute of Ophthalmology, Rawalpindi and Lahore General Hospital, Pakistan from October 2010 to August 2016. Total Sample size of 90 patients was estimated by using 95\% confidence level, 10\% absolute precision with expected percentage of Ocular surface squamous neoplasia as 91.6\%.

\[ n = \left(\frac{Z_{1-\alpha/2}}{d}\right)^2 \times P \times q / d^2 \]

\[ Z_{1-\alpha/2} = \text{Confidence level 95\% = 1.96} \]

\[ P = \text{Prevalence 91.6\%} \]

\[ q = 1-P \]

\[ d = \text{Absolute precision 10\%} \]

Non-probability purposive sampling was done. The patients with suspected conjunctival growths underwent incisional or excisional Biopsy +/- cryotherapy. After histological confirmation of Ocular Surface Squamous Neoplasia (OSSN) the case was included in the study. Patients with all other forms of growths and patients with previous history of OSSN were excluded from the study. All the pre- and post-operative data was recorded on a Proforma. Intra-lesional/peri-lesional IFN $\alpha$-2b was injected weekly with a dose of 3 million IU along with interferon $\alpha$-2b topical drops qid (1 MIU) until the resolution of tumor. The drug was aspirated using a sterile syringe and transferred into an emptied bottle of the artificial tears. The bottle was kept refrigerated until used.

Only those cases that completed at least 3 months follow-up after the resolution or recurrence of lesion were included. Descriptive statistical results like frequency and percentage was calculated by using SPSS Version 21.

RESULTS
Ninety-one eyes of 88 patients were included in study. Out of these, 29 were females and 59 were males. The age of the patients was 52-76 years (Mean 64years). Eighty eyes tolerated and responded well to the treatment and got cured. There was recurrence in 08 eyes (9.2\%), all of which had advanced squamous cell neoplasia. Three patients were lost to follow up. Mean resolution time of tumor was 3 months and mean follow up time was 12 months with range of 3 months to 5 years.

The resolution time is shown in Fig-1. The side

\[ \text{Fig. 1: Resolution Rate.} \]
DISCUSSION

Ocular surface squamous neoplasia is the most common malignancy in elderly patients, resulting in severe ocular damage and visual impairment. We note that mean age of our study population was a bit younger than those of Caucasian population.

Any lesion that is epithelial in origin mostly grows at the limbus, because normal epithelial cellular activity is maximum at limbus due to the presence of Limbal Stem Cells.

The squamous cell carcinoma incidence varies from 0.02 to 3.5 per 100,000. In Conjunctival intra-epithelial neoplasia (CIN/Bowen’s disease), basement membrane is not breached and lesion is involving epithelial membrane only. If the tumor cells invade the basement membrane and involve the sub-epithelial tissues, it is called Squamous cell neoplasia.

Histological spectrum of squamous cell carcinoma includes; micro-invasive, invasive, poorly differentiated and spindle cell. Conjunctival and corneal surface can be involved with tumor, showing dysplastic changes in epithelium from mild to moderate grade, and also of infiltrative variety.

Previously, tumor was treated with excision leaving 2-3 mm tumor free margins, and cryotherapy was applied for the prevention of recurrence. Still, patients showed recurrence rate of 6-30% with negative margins and up to 55% with positive margins. A study from Victoria (Australia) reported death of 8% cases due to metastasis, despite orbital exenteration for invasive OSSN. In 18 patients reported from Pakistan, 42% needed exenteration even after aggressive treatment of this tumor. Therapy with antimetabolite agents like Mitomycin C, 5-Flourouracil has been effective in treating the small lesion and can be given as adjunctive therapy following excision but have higher rate of recurrence.

On the other hand, recurrence rates after topical or injected interferon alpha-2b are between 1% and 28%. with follow-ups ranging from 2 to 28 months, which is much lower. Our study also showed a similar recurrence rate (8.7%). Interferon alpha-2B has proven beneficial in small sized localized lesions, large diffuse lesions and partially excised ocular surface neoplasia, as well as in recurrent disease (Immunotherapy). Analysis of 36 studies were published by Siedlecki et al and they concluded that excision of OSSN with positive margins followed by topical Interferon alpha-2B is the best strategy to reduce recurrence or persistent disease. In diseases that include extensive involvement of ocular tissues, interferon alpha-2B can be used to reduce the size of the tumor (Immuno-reduction) so that after excision there is less bare surface and lesser complications.

Mitomycin-C, can result in corneal epitheliopathy, corneal ulceration, dry-eye, uveitis and glaucoma. It has to be used as a tedious “on and off” regimen, to prevent the complications associated with its continuous use.

With the use of topical Interferon alpha-2b we came across very few side effects as compared to other agents. The side effects we came across in our study were filamentary keratitis, conjunctivitis and pyogenic granuloma formation, which were managed effectively. Most of the time these resolved with lubricants, though pyogenic granuloma needed excision. The major benefit of Interferon topical therapy is, that it obviates the need of wide surgical excision. A study comparing the quality of life in excision versus Interferon alpha-2b resulted in similar outcomes.

This topical medication is not available commercially in Pakistan hence, the drops had to be dispensed in a sterile eye drops bottle. Patients should be counseled about refrigeration and compliance of the therapy. The limitation in our study was a smaller population.

CONCLUSION

Intra-lesional and perilesional Interferon alpha-2b along with topical drops is a better option for the treatment of ocular surface squamous neoplasia (OSSN) in our population. Future studies are needed to determine the long-term effects.

ACKNOWLEDGEMENT

We want to acknowledge Hafiza Ummara Rasheed COAVS Lahore for assistance in statistical analysis.

REFERENCE

1. Kaines A, Davis G, Selva D, Leibovitch I, Dodd T, Malhotra R. Conjunctival squamous cell carcinoma
TREATMENT OF OCULAR SURFACE SQUAMOUS NEOPLASIA WITH INTERFERON ALPHA-2B

with perineural invasion resulting in death. Ophthalmic Surg Lasers Imaging, 2005; 36 (3): 249-51.

2. Basti S & Macsai MS. Ocular Surface Squamous Neoplasia: A Review. Cornea. 2003; 22 (7): 687-704.

3. Ng J, Coroneo MT, Wakefield D, Di Girolamo N. Ultraviolet radiation and the role of matrix metalloproteinases in the pathogenesis of ocular surface squamous neoplasia. Invest Ophthalmol Vis Sci. 2008 Dec; 49 (12): 5295-306.

4. Sen S, Sharma A, Panda A. Immuno-histochemical localization of human papilloma virus in conjunctival neoplasias: a retrospective study. Indian J Ophthalmol. 2007; 55 (5): 361-3.

5. C Chen, D Louis, T Dodd, J Muecke. Mitomycin C as an adjunct in the treatment of localised ocular surface squamous neoplasia. Br J Ophthalmol. 2004; 88 (1): 17-18.

6. Di Pascaule, Mario A, Espana, Edgar M, Tseng, Scheffer C.A. Case of Conjunctiva-Cornea Intraepithelial Neoplasia Successfully Treated with Topical Mitomycin C and Interferon Alfa-2b in Cycles; Cornea. 2004: 23 (1): 89-92.

7. Karp CL, Galor A, Chhabra S, Barnes SD, Alfonso EC. Subconjunctival/perilesional recombinant interferon α-2b for ocular surface squamous neoplasia: a 10-year review. Ophthalmology, 2010; 117 (12): 2241-6.

8. Kobayashi A, Yoshita T, Uchiyama K, Shirao Y, Kitagawa K, Fujisawa A, Tseng SC. Successful management of conjunctival intraepithelial neoplasia by interferon alpha-2b. Jpn J Ophthalmol. 2002; 46 (2): 215-7.

9. Lee GA, Hirst LW. Ocular surface squamous neoplasia. Surv Ophthalmol. 1995; 39 (6): 429-450.

10. Yang J, Foster CS. Squamous cell carcinoma of the conjunctiva. Int Ophthalmol Clin. 1997; 37 (4): 73-84.

11. Fraunfelder FT, Wingfield D. Management of intraepithelial conjunctival tumors and squamous cell carcinomas. Am J Ophthalmol. 1983; 95 (3): 359-63.

12. Daniell M, Maini R, Tole D. Use of mitomycin C in the treatment of corneal conjunctival intraepithelial neoplasia. Clin Experiment Ophthalmol. 2002; 30 (2): 94-8.

13. McKelvie PA, Daniell M, McNab A, Loughnan M, Santamaria JD. Squamous cell carcinoma of the conjunctiva: a series of 26 cases. Br J Ophthalmol. 2002; 86 (2): 168-173.

14. Siddiqui ZK, Mahmood K, Lateef Q, Haider WA. Management of ocular surface squamous cell carcinoma at Lahore General Hospital, Pakistan. Pak PG Med Jr. 2009; 20 (1): 30-31.

15. Boehm MD, Huang AJ. Treatment of recurrent corneal and conjunctival intraepithelial neoplasia with topical interferon alfa-2b. Ophthalmology, 2004; 111 (9): 1755-61.

16. Siedlecki AN, Tapp S, Tosteson AN, Larson RJ, Karp CL, Lietman T, Zegan ME. Surgery versus interferon Alpha-2b treatment strategies for ocular surface squamous neoplasia: a literature-based decision analysis. Cornea, 2016; 35 (5): 613-618.

17. Kim HJ, Shields CL, Shah SU, Kaliki S, Lally SE. Giant ocular surface squamous neoplasia managed with interferon alpha-2b as immunotherapy or immunoreduction. Ophthalmology, 2012; 119 (5): 938-44.

18. Galor A, Karp CL, Chhabra S, Barnes S, Alfonso EC. Topical interferon alpha 2b eye-drops for treatment of ocular surface squamous neoplasia: A dose comparison study. Br J Ophthalmol. 2010; 94 (5): 551-4.

19. Mercado CL, Pole C, Wong J, Battle JE, Roque F, Shaikh N, et al. Surgical versus medical treatment for ocular surface squamous neoplasia: A quality of life comparison. The ocular Surface, 2019; 17 (1): 60-63.

20. McClellan AJ, McClellan AL, Pezon CF, Karp CL, Feuer W, Galor A. The epidemiology of ocular surface squamous neoplasia in a Veterans Affairs population. Cornea, 2013; 32 (10): 1354.

Author’s Affiliation

Prof. Zahid Kamal Siddiqui
Eye Unit -1, Mayo Hospital King Edward Medical college, Lahore.

Dr. Farooq Ahmad
Eye Unit -3, Mayo Hospital King Edward Medical college, Lahore.

Dr. Shahid Tarar
Armed Forces Institute of Ophthalmology (AFIO) Rawalpindi.

Dr. Farah Huma
Eye Unit -1, Mayo Hospital King Edward Medical college, Lahore.

Prof. Amer Yaqoob
Armed Forces Institute of Ophthalmology (AFIO) Rawalpindi.

Author’s Contribution

Prof. Zahid Kamal Siddiqui
Study design, surgical procedures, Data Collection, Manuscript writing.

Dr. Farooq Ahmad
Data Collection, Manuscript writing.

Dr. Shahid Tarar
Data Collection, Manuscript writing and final manuscript review.
Dr. Farah Huma
Data Collection, Biostatistics, final Manuscript review.

Prof. Amer Yaqoob
Conceiving the idea, Study design, surgical procedures, Performed procedures, final Manuscript review.