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ORIGINAL PAPER

Interferon alpha-2b versus 5-fluorouracil as primary treatment modalities for ocular surface squamous neoplasia: a study of 116 eyes

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Abstract

Purpose To compare the efficacy and side-effect profile of interferon alpha-2b (IFNα2B) and topical 5-fluorouracil (5-FU) as primary treatment modalities for ocular surface squamous neoplasia (OSSN).

Methods Retrospective comparative study of 116 OSSN eyes treated with topical 1 MIU IFNα2B with/without 5 MIU/cc subconjunctival injection (group 1) or topical 1% 5-FU (group 2) in mutually exclusive time periods of treatment.

Results Of the 116 eyes with OSSN, 64 eyes belonged to group 1 and 52 eyes to group 2. The mean tumor basal conjunctival diameter for groups 1 and 2 was 10 mm (median, 10 mm; range 0–28 mm) and 5 mm (median, 4 mm; range, 0–24 mm) respectively ($p < 0.0001$). Complete tumor regression with medical management alone was achieved in 51 (80%) eyes in group 1 and 43 (83%) eyes in group 2 ($p = 0.6814$). The mean number of sessions/cycles of treatment for complete tumor regression was 3 (median, 3; range, 1–6) for group 1 versus 2 (median, 2; range, 1–6) for group 2 ($p < 0.0001$). Tumor recurrence was noted in 3 (5%) eyes in group 1 over a mean follow-up period (months) of 11 (median, 7; range, 3–41) versus 1 (2%) in group 2 ($p = 0.25$) over a mean follow-up period (months) of 6 (median, 5; range, 1–25). Side-effects included transient conjunctival hyperemia (9%), and flu-like symptoms (3%) in group 1 versus transient conjunctival hyperemia (2%), punctal stenosis (2%), and partial limbal stem cell deficiency (2%) in group 2.

Conclusion Primary treatment of OSSN with IFNα2b or 5-FU offers comparable and good tumor control with minimal side-effects.

Keywords Eye · Tumor · Conjunctiva · Ocular surface squamous neoplasia · OSSN · 5-fluorouracil · Interferon

Introduction

Ocular surface squamous neoplasia (OSSN) is one of the commonest ocular surface malignancies varying from squamous dysplasia to frank invasive squamous carcinoma [1]. The management of OSSN has undergone a paradigm shift in the past decade with majority of the cases being managed medically. Surgical management involves a standard no-touch technique with 3–4 mm margins and double freeze–thaw cryotherapy to the edges [2]. Surgery provides rapid resolution with definitive tissue diagnosis but also has chances of tumor recurrence, ocular surface disease, pseudo pterygium formation, conjunctival scarring and limbal stem cell deficiency [3–6].

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Medical management for OSSN has been well-established and gained momentum over the past decade due to ease of use, better acceptance by the patients, and fewer side-effects when compared to surgery. Topical therapy also has the ability to treat the entire ocular surface, including treatment of clinically subtle/invisible microscopic disease. However, medical management of OSSN can be associated with side-effects and requires multiple visits to the clinic spanning over several months, and thus can have compliance issues.

Various drugs have been used in the treatment of OSSN including Mitomycin C (MMC), interferon alpha-2b (IFNα-2b), 5-fluorouracil (5-FU), retinoic acid, cidofovir, and bevacizumab [3, 7]. Among these, MMC, IFNα-2b, and 5-FU are widely studied and accepted. Studies have demonstrated MMC's effectiveness, ranging from 79 to 100%, with a recurrence rate of 0–15.1% [8–11]. Despite its potency, the high rate and severity of adverse effects have reduced its popularity [9, 12–14]. IFNα-2b and 5-FU have demonstrated efficacy in the literature, but they differ significantly in terms of availability, cost-effectiveness, and storage requirements, which can greatly impact patient compliance. To the best of our knowledge, only two studies in the literature have compared the safety and efficacy of IFNα-2b and 5-FU. Llorens et al. evaluated the two treatments as secondary treatment following surgery, while Venkateswara et al. compared them as primary treatment modalities. Notably, no such studies have been conducted in the Asian Indian population. Herein, in this study, we compare these two drugs in terms of efficacy, adverse effects, and cost-effectiveness as primary treatment modalities for OSSN.

Methods

Electronic medical records (EMR) database of the Operation Eyesight Universal Institute for Eye Cancer, LV Prasad Eye Institute, Hyderabad, India, was used to identify all patients of OSSN during the time period 2015–2021. Those treated with either IFNα-2b or 5-FU as the primary agents were included in the study. Patients with inadequate data, and patients with xeroderma pigmentosum were excluded from the study. The diagnosis of OSSN was established based on slit-lamp examination and anterior segment optical coherence tomography (AS-OCT) findings. Characteristic AS-OCT features for diagnosing OSSN included a thickened, hyper-reflective epithelium with an abrupt transition from normal to abnormal epithelium. Those with inconclusive clinical diagnosis were not included in this study.

Retrospective chart review was conducted for all patients included in this study. Prior to COVID-19, IFNα-2b was the primary topical treatment modality at our Ocular Oncology Services. Post-COVID, with decreasing availability of IFNα-2b and challenges of prolonged treatment, topical 5-FU became our primary topical treatment modality. Thus, all OSSN patients receiving topical treatment with/without subconjunctival IFNα-2b as primary treatment between the time periods 2015–2018 were considered as group 1 and all OSSN patients receiving topical 5-FU as primary treatment between the time periods 2020 to 2021 were considered as group 2. In group 1, all patients with conjunctival component of OSSN received a combination of topical treatment with subconjunctival IFNα-2b and patients with isolated corneal or limbal OSSN received only topical IFNα-2b. One session of IFNα-2b treatment constituted topical IFNα-2b 1MIU/cc 4 times/day for a month with/without single dose of 5 MIU/cc IFNα-2b perilesional subconjunctival injection. All patients were instructed to store IFNα-2b in a refrigerator at 2–6 °C during topical treatment. After complete tumor regression, patients were continued on topical IFNα-2b 4 times/day for 3 months. One cycle of 5-FU constituted topical 1% 5-FU 4 times/day for a week followed by 3 weeks drug holiday. Along with topical 5-FU, patients were also prescribed topical lubricants 4 times/day till next visit. After complete tumor regression, patients were given one extra cycle of topical 5-FU and were continued on topical lubricants for at least 3 months.

All patients were reviewed once a month till completion of medical treatment, and periodically thereafter. All patients (groups 1 and 2) underwent slit-lamp examination and the tumors were documented with clinical drawings, external photographs, slit-lamp photographs, and AS-OCT, during each visit.

Data extracted from the EMR included demographics (age, sex, laterality), risk factors (immune status), tumor details, treatment details, and outcomes. Tumor characteristics included tumor dimensions, location, morphological type, and associated

features including presence of keratin, feeder vessels, intrinsic vascularity. Treatment details included type of drug, dosage, frequency, and length of treatment.

The primary outcome measure was the response to medical treatment. The number of sessions/cycles of medical treatment and time to tumor resolution were noted. Tumor resolution was documented by clinical photographs and disappearance of lesion on AS-OCT. Tumor response to medical treatment was classified as complete response (100% tumor resolution), partial response (tumor size reduction with medical treatment but with residual tumor) or no response (no change in tumor size with atleast 3 months of medical treatment). Other outcome measures included side-effects to medical treatment and tumor recurrence. Tumor recurrence was defined as reappearance of lesion in the same location after complete resolution of tumor. Any event of locoregional/systemic metastasis and death during the follow-up period were also recorded.

Statistical analysis

Data was entered in Microsoft Excel for Mac ®, and statistical analysis was performed using IBM SPSS Statistics, version 29.0.2.0 (20). Demographics, clinical features, management, and outcomes were compared between two groups. Continuous data was expressed as mean, median, and range and compared using the Student-t-test. Categorical data was expressed as proportions, and compared using the Chi-square test. p-value ≤ 0.005 was considered as statistically significant.

Results

Of the 116 eyes included in this study, 64 belonged to group 1 and 52 to group 2. The mean age at diagnosis of OSSN in group 1 was 58 years (median, 59 years; range, 21–83 years) and in group 2 was 52 years (median, 52 years; range, 22–87 years) (Table 1). Four (6%) patients in group 1 and 2 (4%) patients in group 2 were HIV positive. Three (5%) lesions in group 1 were recurrent OSSN at the time of initiation of topical treatment. None of the lesions in group 2 were recurrent. Mean tumor basal diameter in groups 1 and 2 was 10 mm (median, 10 mm; range < 1–28 mm) versus 5 mm (median, 4 mm; range, 0–24 mm), respectively ($p = < 0.0001$). Mean tumor thickness was 2 mm (median, 1 mm; range, < 1–6 mm) in both the groups ($p = 1$). Complete tumor regression with respective medical monotherapy was achieved in 51 (80%) eyes in group 1 versus 43 (83%) eyes in group 2 ($p = 0.68$) (Fig. 1). Mean number of sessions of topical IFNα-2b in group 1 for complete tumor control was 3 (median, 3; range 1–6) and the mean number of cycles of topical 5-FU in group 2 for complete tumor control was 2 (median, 2; range, 1–6) ($p < 0.0001$). In group 1, 51(80%) patients were administered a combination of topical and subconjunctival IFNα-2b, whereas 13 (20%) were administered only topical IFNα-2b.

Over a mean follow-up period of 11 months (median, 7 months, range, 3–41 months), tumor recurrence was noted in 3 (5%) eyes in group 1. There was no statistically significant difference between cases with tumor recurrence versus those without based on baseline tumor size (12.6 mm versus 9.3 mm; $p = 0.3746$) or treatment duration (5 months versus 5 months; $p = 0.65$). The mean interval between complete tumor regression and tumor recurrence was 13 months (median, 13 months; range 8–18 months). These recurrences were managed with topical IFNα-2b (n = 2) or surgical excision (n = 1). Over a mean follow-up period of 6 months (median, 5 months; range, 1–25 months) in group 2, tumor recurrence was noted 1 (2%) eye, 4 months after complete tumor regression, which was managed with restarting topical 5-FU. The average cost of treatment in INR for complete tumor regression in group 1 was INR 9763 ($117) (median, INR 9100; range, INR 3900–20800) versus 12 ($ < 1) (median, 12; range, 6–36) in group 2.

Globe salvage was achieved in 63 (98%) patients in group 1 and 49 (94%) patients in group 2. Side-effects included transient conjunctival hyperemia (n = 6), and flu-like symptoms (n = 2) in group 1 versus transient conjunctival hyperemia (n = 1), punctal stenosis (n = 1), and partial limbal stem cell deficiency (n = 1) in group 2 (Fig. 2). There was no event of locoregional/systemic metastasis or death in any patient during the study period (Table 2).

Discussion

Interferon alpha-2b, a naturally occurring low molecular weight glycoprotein, is known for its antiviral

Table 1 Demographic details and tumor characteristics of ocular surface squamous neoplasia

Features	Group 1 n = 64 n (%)	Group 2 n = 52 n (%)	*p*-value
Age at diagnosis (years) Mean (median, range)	58 (59, 21–83)	52 (52, 22–87)	0.0224
Gender			
Male	46 (72)	36 (69)	0.8795
Female	18 (28)	16 (31)	
Basal tumor dimensions (mm) Mean (median, range)	10 (10, < 1–28)	5 (4, < 1–24)	< 0.001
Tumor thickness (mm) mean (median, range)	2 (1, < 1–6)	2 (1, < 1–6)	1.0000
Corneal involvement	59 (92)	37 (71)	0.0029
Tumor staging (AJCC 8th edition)			
Tis	1 (2)	0 (0)	0.3699
T1	2 (3)	28 (54)	< 0.0001
T2	0 0)	14 (27)	< 0.0001
T3	61 (95)	10 (19)	< 0.0001
Tumor morphology			
Leukoplakia	10 (16)	3 (6)	0.0942
Nodular	7 (11)	17 (33)	0.0040
Papillomatous	26 (41)	10 (19)	0.0133
Placoid	8 (13)	10 (19)	0.3194
Gelatinous	14 (22)	12 (23)	0.8773
Keratin	29 (45)	34 (65)	0.0309
Feeder vessel	55 (86)	32 (61)	0.0025
Tumor epicentre			
Conjunctiva	8 (12.5)	25 (48)	< 0.0001
Cornea	8 (12.5)	11 (21)	0.2104
Limbus	48 (75)	16 (31)	< 0.0001

Group 1 = Patients treated with topical with or without subconjunctival interferon α2b; Group 2 = patients treated with topical 5-fluorouracil; AJCC: American joint committee on cancer classification

and antineoplastic properties, and has been shown to be effective in the treatment of OSSN. Its antineoplastic effects include inducing apoptosis, inhibiting angiogenesis, and extending the cell cycle duration in cancer cells [15]. The drug, IFNα-2b is available in concentrations of 1 MIU, 3 MIU, 5 MIU, and 5 MIU. A study comparing different concentrations of IFNα-2b found no statistically significant difference in the efficacy or treatment duration between the various drug concentrations [16]. There is no difference in efficacy of IFNα-2b based on tumor configuration (flat or dome-shaped) [17]. A study of 98 eyes by Nanji ete al. compared topical IFNα2b to surgical excision, and showed similar tumor recurrence rates between the groups: 3% in the IFNα-2b group and 5% in the surgery group, with comparable side effect rates [5]. In our previous study on use of INFα2b in 30 eyes with OSSN, the tumor recurrence rate was 0% and side-effects were noted in 5% patients [18]. In the current study, the tumor recurrence rate with INFα2b was 5% and side-effects were noted in 13% patients. We also analysed the cost-effectiveness of INFα2b for the treatment of OSSN in our previous study and showed that the mean cost for treatment of tumors < 5 mm was INR 9607 ($143) and for tumors > 5 mm was INR 10985 ($164) [18]. In our current study including tumors with a mean tumor diameter of 10 mm, the average cost for complete tumor regression with INFα2b was INR 9763 ($ 117).

A pyrimidine analogue, 5-FU is another effective agent for OSSN. It inhibits thymidylate formation from uracil, leading to the inhibition of DNA and

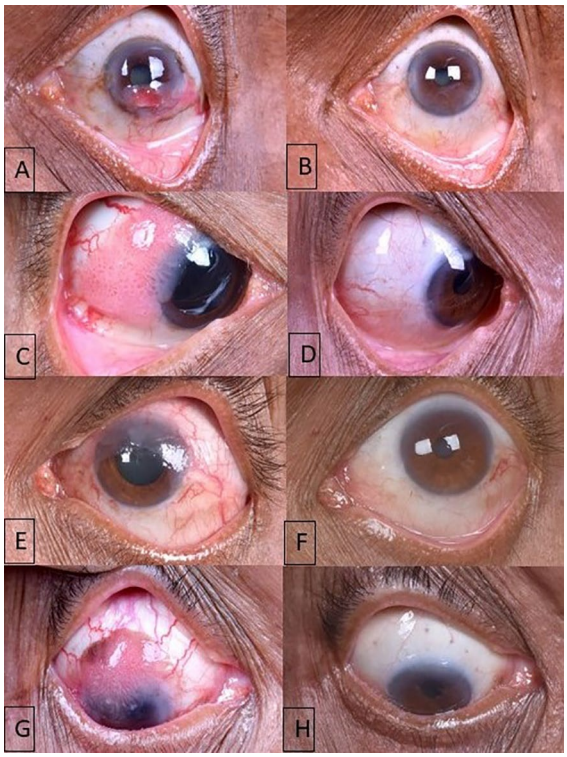

Fig. 1 Ocular surface squamous neoplasia managed with medical monotherapy. **A** A 62-year-old male with left eye gelatinous ocular surface squamous neoplasia (OSSN) was treated with topical and subconjunctival injection of interferon α2b (INFα2b). **B** Complete resolution of tumor was noted with 2 sessions of topical INFα2b and 2 subconjunctival INFα2b injections. **C** A 51-year-old female with large papillary OSSN involving more than 2 quadrants of ocular surface was treated with topical and subconjunctival injection of INFα2b. **D** Tumor completely resolved with 2 sessions of topical INFα2b and 2 subconjunctival INFα2b injections. **E** A 57-year-old male with left eye diffuse placoid OSSN mainly involving the cornea was treated with topical 1% 5-fluorouracil (5-FU). **F** Complete tumor resolution was noted with 3 cycles of topical 5-FU. **G** A 68-year-old male with right eye papillary OSSN was treated with topical 1% 5-FU. **H** Complete tumor resolution was noted with 2 cycles of topical 5-FU

RNA synthesis and cell death. It is typically administered as a 1% solution [19]. Various regimens are described, including 4 times/day for one week followed by three weeks of a drug-free interval, continuous administration three to four times a day for four weeks, or administration for two to four days followed by a 30 to 45-day drug-free period [20]. The efficacy of 5-FU ranges from 40 to 100% in the literature [21, 22], with a tumor recurrence rate of 7.3% to 10% within three months of treatment discontinuation [19, 23]. In our study, tumor recurrence rate after discontinuation of 5-FU for OSSN was noted in 2% eyes. A vial of 5% 5-FU costs 29 INR, which can be diluted to prepare five vials of 1% drug, offering the advantage of stability at room temperature, eliminating the need for refrigeration [6]. In our study, the average cost of treatment per patient for complete resolution of tumor was INR 12 ($\$ < 1$). In comparison to INFα2b, topical 5-FU is an inexpensive treatment option for OSSN and does not require special storage precautions.

In our study, the mean age at diagnosis of OSSN was 58 years in the IFNα2b group and 52 years in the 5-FU group, consistent with the reported mean age of 56 years in the literature [24], with a male predominance. The mean conjunctival basal diameter in the IFNα2b group (10 mm) was significantly larger than in the 5-FU group (5 mm), explained by the evolving criteria for the management of OSSN at our institute. Previously, smaller tumors were being managed by surgical excision and medical treatment was offered to placoid diffuse tumors. Currently, medical treatment is offered to patients with smaller tumors as well. In this study, the number of sessions/cycles for achieving complete tumor control was higher in IFNα2b group at 3 versus 2 cycles in the 5-FU group. This could be related to larger tumors in the IFNα2b group compared to 5-FU group. Also, it is reported that the treatment response is quicker with topical 5-FU compared to IFNα2b [18–23].

A comparative study of 48 eyes with OSSN primarily treated with IFNα2b monotherapy versus 54 eyes treated with topical 5-FU by Venkateswaran et al., revealed a statistically significant difference in the tumor resolution rate between 5-FU (96.3%) and IFNα2b (81.3%) ($p = 0.01$) on univariate analysis, though no difference was found on multivariate analysis, with ethnicity being the only confounding factor [25]. Another study compared the outcomes of adjuvant INFα2b versus 5-FU post-surgical excision of OSSN, and showed that there was no statistical difference between the rates of tumor resolution (94.11% versus 94.6%, respectively) [26]. In our study, complete tumor resolution was noted in 80% OSSN eyes treated with IFNα2b versus 83% treated with topical 5-FU, with no statistical difference in the outcomes.

Venkateswaran et al. found more adverse effects with topical 5-FU compared to INFα2b, such as eyelid edema and pain [25]. San Román Llorens et al. also found a significant difference between the

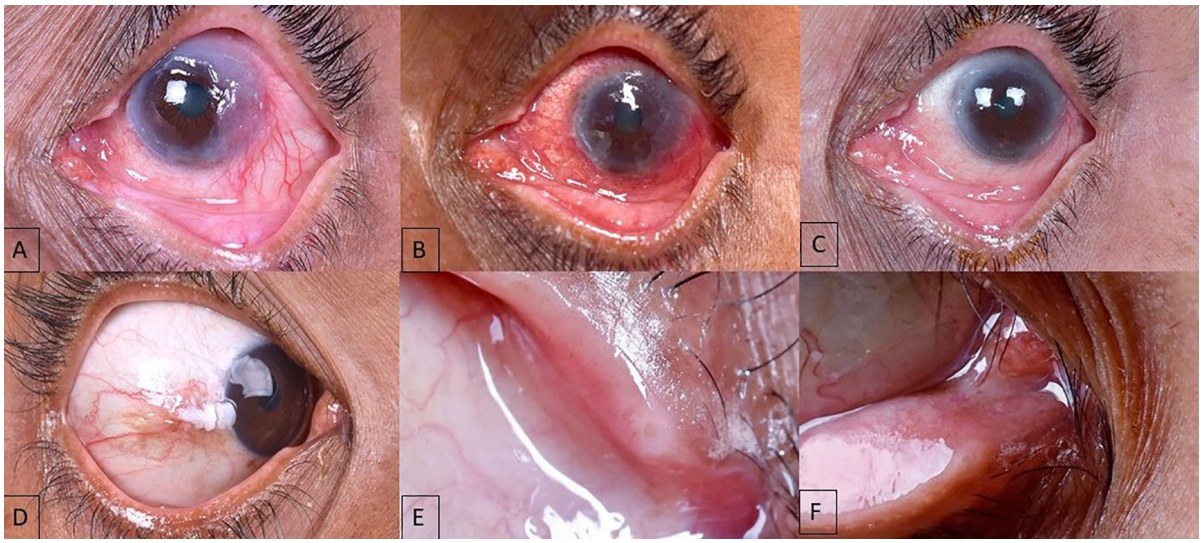

Fig. 2 Complications with medical management of ocular surface squamous neoplasia. **A** A 70-year-old female with diffuse OSSN was treated with topical and subconjunctival injection of interferon alpha 2b (INFα2b). **B** Transient follicular conjunctivitis was noted after 2 sessions of treatment. She was started on topical lubricants and INFα2b was continued. **C** Complete tumor resolution was achieved with 3 sessions of topical and subconjunctival INFα2b. The conjunctivitis also resolved with copious lubricants. **D** A 43-year-old female with nodular OSSN was being treated with topical 1% 5-fluorouracil (5-FU). **E** She developed upper and **F** lower punctal stenosis post 2 cycles of topical 5-FU

side effect profiles between INFα2b and 5-FU (19% versus 59%, $p=0.015$) [26]. Most studies report predominantly mild side-effects associated with 5-FU 1% treatment. Joag et al. observed side effects in 61% of patients, primarily pain (39%) and tearing (23%), with one case of infection [19]. Parrozzani et al. documented mild to moderate side-effects in 48% of patients with 5-FU, with no severe adverse events or treatment discontinuation [23]. Wylegala et al. noted mild hyperemia (26%) and pain (23%) as the most common side-effects, while sight-threatening complications, such as limbal stem cell deficiency, occurred in only 3% of cases [27]. In contrast, in our study, the side-effects with INFα2b was 13% and 5-FU group displayed side-effects in 6%. However, more serious complications like limbal stem cell deficiency and punctal stenosis were noted only in the 5-FU group which correlates with the existing literature. The lower side-effect profile in the topical 5-FU group in our study could be related to the judicious instillation of topical lubricants during and after use of topical 5-FU. Higher incidence of adverse effects (flu-like symptoms and hyperemia) in INFα2b group can also be attributed to administration of subconjunctival injections in 80% patients as compared to only topical therapy in 5-FU group.

Comparing the cost of the two treatments, there is a significant difference between the average cost of treatment of OSSN with INFα2b versus topical 5-FU. Treatment with INFα2b costed 813 times more than 5-FU therapy. Lower cost and lack of necessity for refrigeration makes topical 5-FU a more affordable and convenient modality of treatment for OSSN, especially in developing countries.

The limitations of our study include its retrospective nature, shorter follow-up, and differences in the tumor morphology and staging between the groups. Though the tumor dimensions were different in the two groups, there were comparable outcomes in both groups, indicating the effectiveness of both treatment modalities. Although no clear guidelines exist on the indications for these medications, this study provides perspective on selecting suitable treatment for patients. Especially, with the recent limited availability of IFNα2b, this study highlights the comparable efficacy and safety of topical 5-FU, which is easily available. Future prospective studies with comparable tumor dimensions in the two groups and larger sample size can help us to understand the efficacy and

Table 2 Treatment and outcomes of ocular surface squamous neoplasia

Feature	Group 1 n = 64 n (%)	Group 2 n = 52 n (%)	*p*-value
Number of sessions/cycles of topical treatment mean (median, range)	5 (5, 1–9)	2 (2, 1–6)	< 0.0001
Number of sessions/cycles for complete tumor regression (topical) mean (median, range)	3 (3, 1–6)	2 (2, 1–6)	< 0.0001
Number of monthly injections for complete tumor regression mean (median, range)	2 (2, 0–6)	na	–
Cost of treatment for complete tumor regression (INR) mean (median, range)	9763 (9100, 3900–20,800)	12 (12, 6–36)	< 0.0001
Reduction in tumor size (%) Mean (median, range)	86 (100, 0–100)	84 (100, 0–100)	0.7422
Tumor response with topical therapy			
Complete regression	51 (80)	43 (83)	0.6814
Partial regression	9 (14)	2 (4)	0.0618
No response	4 (6)	7 (13)	0.1874
Additional treatment for complete tumor control			
Excisional biopsy	11 (17)	5 (10)	0.2417
Change of medical drug	1 (2)	1 (2)	0.7417
Extended enucleation	1 (2)	1 (2)	0.7417
Change of medical drug followed by excision	1 (2)	0 (0)	0.4123
Change of medical drug followed by extended enucleation	0 (0)	1 (2)	0.2022
Excision followed by extended enucleation	0 (0)	1 (2)	0.2022
Outcomes			
Tumor recurrence	3 (5)	1 (2)	0.4171
Interval between medical treatment and tumor recurrence (months) mean (median, range)	13 (13, 8–18)	4 (4)	–
Globe salvage	63 (98)	49 (94)	0.2169
Locoregional/systemic Metastasis or death	0 (0)	0 (0)	–
Side-effects	8 (13)	3 (6)	0.2185
Transient conjunctival congestion	6 (9)	1 (2)	0.0937
Punctal stenosis	0 (0)	1 (2)	0.2049
LSCD	0 (0)	1 (2)	0.2049
Flu-like symptoms	2 (3)	0	0.2028

Group 1 = Patients treated with topical with or without subconjunctival interferon α2b; Group 2 = patients treated with topical 1% 5-fluorouracil

na, not applicable; LSCD, imbal stem cell deficiency

effectiveness of the two topical drugs, INFα2b and 5-FU. Moreover, prospective study will also ensure standardized protocol for treatment in the two groups.

In conclusion, both IFNα2b and topical 5-FU are effective, non-invasive treatments for OSSN, exhibiting comparable side-effect profiles. If IFNα2b is readily available and the patient is likely to be complaint to the treatment and its storage specifications, IFNα2b is a good treatment modality for OSSN. However, topical 5-FU aligns well with the healthcare infrastructure and economic constraints commonly found in developing countries, offering a practical solution for managing OSSN, without compromising on quality of patient care.

Author contribution Swathi Kaliki contributed to the study conception and design. Material preparation, data collection and analysis were performed by Komal Bakal and Adit Gupta. The first draft of the manuscript was written by Komal Bakal and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent to publish The authors affirm that human research participants provided informed consent for publication of the images in Figs. 1 and 2.

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of LV Prasad Eye Institute.

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