Original Article

Recombinant interferon alpha 2b for ocular surface squamous neoplasia: An efficient and cost-effective treatment modality in Asian Indian patients

Swathi Kaliki, Swati Singh, Sadiya Iram, Dharani Tripuraneni

Purpose: The purpose was to study the efficacy of interferon alpha 2b (INF α2b) in the treatment of ocular surface squamous neoplasia (OSSN) and analyze its cost-effectiveness in India. **Study Design:** This was a retrospective study of thirty patients with OSSN treated with topical INF α2b (1 MIU/cc) ± perilesional INF α2b (5 MIU/cc). **Results:** The tumor involved cornea (*n* = 9, 30%), conjunctivo-limbal-corneal surface (*n* = 19, 63%), or bulbar conjunctiva (*n* = 2, 7%). The mean basal dimension of the tumor was 16 mm. The tumors belonged to Tis (*n* = 6, 20%) or T3 (*n* = 24, 80%) based on the American Joint Committee Classification, 7th edition. In the six patients with Tis, three cycles of topical INF α2b were used for immunoprevention. In the remaining 24 patients, INF α2b was advised for immunoreduction, but served as immunotherapy with 100% tumor regression in 22 (92%) cases, and resulted in 95% immunoreduction in 2 (6%) cases. Complete tumor regression by immunotherapy (*n* = 22) was achieved with a mean number of three topical INF α2b cycles and two perilesional injections. All these 22 patients received three additional topical INF α2b cycles after complete tumor regression. For immunoreduction (*n* = 2), both patients received six cycles of topical INF α2b which was three perilesional INF α2b injections. The mean total treatment cost per patient with INF α2b was INR 9164 ($US 137). Based on maximum basal diameter of tumor at presentation, the mean total treatment cost per patient with INF α2b was INR 4866 ($US 73) for eyes with microscopic evidence of tumor residue (*n* = 6), INR 9607 ($US 143) for tumors ≤10 mm (*n* = 13), and INR 10,985 ($US 164) for tumors >10 mm (*n* = 11), with two patients needing additional surgical excision for complete tumor control. **Conclusion:** INF α2b can be used for immunoreduction, immunotherapy, or immunoprevention of OSSN. INF α2b is a cost-effective treatment modality for OSSN at an average total treatment cost of INR 9164 ($US 137) per patient.

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Ocular surface squamous neoplasia (OSSN) includes a spectrum from mild/moderate/severe dysplasia to carcinoma *in situ* to invasive squamous cell carcinoma involving the conjunctiva and/or cornea.[1] The most widely practiced treatment strategy for OSSN includes wide excision biopsy with 3–4 mm tumor-free margin by "no-touch" technique for the conjunctival component, alcohol-treated limited superficial keratectomy for the corneal component, followed by adjunct double-freeze thaw cryotherapy to the conjunctival surgical margins and surface reconstruction.[2] In extensive invasive OSSN, plaque radiotherapy, external beam radiotherapy, extended enucleation, or anterior orbital exenteration may be needed.[3-5] Topical chemotherapy with mitomycin-C (MMC), cidofovir, 5-fluorouracil (5-FU), or immunotherapy with interferon alpha 2b (INF α2b) has been found to be effective in the treatment of noninvasive OSSN.[6-11]

OSSN most commonly arises in the limbal region,[1] sometimes involving 360° limbus. Extensive surgical excision can result in limbal stem cell loss and ocular surface morbidity. Topical agents offer the advantage of delivering treatment not only to the affected ocular surface but also to the entire ocular surface, and thus potentially eliminating subclinical OSSN, and also diminish the risk of limbal stem cell deficiency and associated ocular surface morbidity.[6-22] Although the efficacy of topical medications on OSSN is comparable (80%–100%),[6-22] MMC has the highest reported rates of side effects (76%), followed by 5-FU (42%), and INF α2b is reported to have the least rates of side effects (15%).[18,19] However, the cost of INF α2b ($US 175–225 per treatment) could limit its use in some patients.[13,14,20,21] In this study, we evaluate the efficacy of recombinant human INF α2b in the treatment of OSSN and analyze its cost-effectiveness.

Methods

This study is a retrospective study conducted at a single institution. The Institutional Review Board approval was obtained for the study. The medical records of all patients with OSSN treated with INF α2b were reviewed. The study period ranged from August 2013 to December 2015. The patients with extensive tumor (>20 mm basal dimension or >6 clock hours involvement of limbus, with flat tumor configuration), OSSN

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limited to the corneal surface, recurrent tumor postsurgical excision and/or MMC, and those with microscopic tumor residue postexcision biopsy were treated with INF α2b. Patients with OSSN treated with INF α2b with a minimal follow-up of 3 months were included in the study. The patients who were noncompliant to treatment, or those who were lost to follow-up, or have <3 months follow-up, or with ongoing/incomplete treatment were excluded from the study.

The demographic details (age, gender) were reviewed. Systemic history and past history were recorded. The recorded clinical features included tumor laterality, presenting complaints, duration of symptoms (months), tumor location and extent (conjunctiva, cornea, conjunctival-limbal-corneal surface), maximum basal tumor diameter (mm), number of limbal clock hours involved by the tumor, and tumor pattern (leukoplakic, gelatinous, nodular, papillary, placoid, pigmented). The primary tumor was classified based on the American Joint Committee Classification, 7th edition.[23] The diagnosis of OSSN was made by clinical findings. Histopathology confirmation of the diagnosis of OSSN before initiation of treatment with INF α2b was established by slide/block review in cases with a previous history of excision biopsy. Locoregional lymph node examination and medical examination to rule out locoregional or systemic metastasis of tumor were performed in all cases.

INF α2b was used for immunoreduction (to reduce the tumor size) or immunotherapy (as the sole treatment for tumor regression) or immunoprevention (to prevent tumor recurrence in those with histopathology evidence of residual tumor at margins postexcision biopsy). The patients with only corneal OSSN were advised topical INF α2b eye drops (1 MIU/cc) four times/day for immunoreduction/immunotherapy. The patients with conjunctival or conjunctivo-limbal-corneal lesions were given a combination of topical INF α2b eye drops (1 MIU/cc) four times/day and perilesional INF α2b injection (5 MIU/cc) once a month for immunoreduction/immunotherapy. Those patients with Tis, who had undergone excision biopsy of the lesion and showed carcinoma *in situ* at one or more surgical margins on histopathology review, were advised topical INF α2b eye drops (1 MIU/cc) four times/day for immunoprevention.

Recombinant human INF α2b (1 cc prefilled syringe of Intalfa 5 MIU, manufactured and marketed by Intas Pharmaceuticals Limited, India) was used in all patients. The cost of each syringe during the study period and at the time of manuscript preparation was INR 811 ($US 12). Topical drops were prepared under sterile conditions by adding 4 cc of distilled water to 1 cc of INF α2b 5 MIU, to achieve a dose of 1 MIU/cc. The medication was packed in a thermocol icebox and two bottles of 5 ml each were dispatched to the patient at each visit during the treatment period. The patient was instructed to store the drug in a refrigerator (2°C–8°C) and apply one drop four times/day. Under sterile conditions and topical anesthesia, perilesional INF α2b 5 MIU/cc was injected directly from the prefilled syringe as an outpatient procedure in suitable cases.

All patients were advised to use topical medication four times/day for 1 month. Every patient was reviewed once a month during the treatment period. Tumor details were recorded during each visit. If the patient had a residual tumor, the patient was advised to continue topical medication until complete tumor regression and 3 months beyond complete tumor regression. Topical INF α2b 1 MIU/cc drops were freshly prepared and dispatched every month as needed. The additional perilesional injection was repeated every month in suitable cases. After complete tumor regression had been achieved, topical drops were continued for another 3 months. If there were tumor residue after six cycles of topical INF α2b eye drops and three perilesional injections of INF α2b, the lesion was surgically excised. The histopathology details of excised tumor were recorded. All patients with Tis receiving INF α2b as immunoprevention were advised three cycles of topical INF α2b eye drops. After complete tumor regression had been achieved, the patients were reviewed once in 3 months in the first year and every 4 months in the second year.

The outcome was also analyzed based on maximum tumor dimension on presentation. The patients were divided into three groups; Group 1, with no clinical evidence of tumor (Tis, INF α2b used to prevent tumor recurrence in those with histopathology evidence of residual tumor at margins postexcision biopsy); Group 2, with maximum basal diameter of tumor <10 mm; Group 3, with maximum basal diameter of tumor >10 mm at presentation.

The number of cycles of INF α2b (topical drops ± perilesional injections) per patient was recorded. The total treatment cost of INF α2b per patient was recorded. The side effects of treatment and any event of tumor recurrence were noted.

Results

During the study period, 254 patients with OSSN were examined. Of these, 38 (11%) patients were treated with INF α2b. Eight patients were excluded from the study due to noncompliance to treatment (n = 2), <3 months follow-up duration (n = 2), combination treatment with perilesional INF α2b injection and topical MMC (n = 2), and ongoing treatment (n = 2). Of the thirty patients included in this study, the mean age at presentation was 55 years (median: 57 years; range: 27–80 years). There were 20 (67%) males and 10 (33%) females. History of prior intervention was present in 13 (43%) patients, including excision biopsy (n = 12; 40%) and/or MMC (n = 3; 10%). The most common presenting complaint included mass on the ocular surface (n = 18; 60%). The mean duration of symptoms was 12 months (median: 7 months; range: 1–48 months).

The tumor involved cornea (n = 9, 30%), conjunctivo-limbal-corneal surface (n = 19, 63%), or bulbar conjunctiva (n = 2, 7%). The mean basal dimension of the tumor was 16 mm (median: 20 mm; range: 4–30 mm). The mean number of limbal clock hours involved by the tumor was 6 (median: 5; range: 1–12). At the time of initiation of INF α2b, the tumors belonged to Tis (n = 6, 20%) or T3 (n = 24, 80%) [Table 1]. Histopathology confirmation of the diagnosis of OSSN was available in 12 (40%) cases before initiation of treatment with INF α2b.

Of the six patients with Tis, four patients had undergone excision biopsy of the lesion at another hospital and were referred to us with residual tumor at the surgical margins, and two patients were operated at our institute and histopathology showed positive margins. Carcinoma *in situ* at one or more surgical margins was noted on histopathology. These six patients were advised three cycles of topical INF α2b for

immunoprevention. In the remaining 24 patients, INF α2b was advised for immunoreduction but served as sole immunotherapy with 100% tumor regression in 22 (92%) cases [Table 2].

Complete tumor regression by immunotherapy (n = 22) was achieved with a mean number of topical INF α2b cycles of 3 (median: 2; range: 1–5), and perilesional INF α2b injections of 2 (median: 2; range: 2–3). All these 22 patients with immunotherapy received three additional topical INF α2b cycles after complete tumor regression [Table 3 and Figs. 1 and 2]. For immunoreduction (n = 2), the mean number of topical INF α2b cycles was 6 (median: 6; range: 5–6), and perilesional INF α2b injections were 3 (median: 3; range: 3). The residual tumor was surgically excised. On histopathology, both patients showed mild dysplasia.

The mean total treatment cost per patient (including additional three cycles of topical INF α2b after complete tumor regression) with INF α2b was INR 5001 ($US 75) (median: INR 4866 [$US 73]; range: 2433 [$US 36]–8921 [$US 133]) [Table 3]. The side effects of treatment with INF α2b included mild conjunctival hyperemia (n = 4, 13%), which was temporary and resolved after discontinuation of treatment, and flu-like syndrome (n = 1, 8%), which was present in the first 6 h of perilesional INF α2b injection, and subsided with a single dose of oral acetaminophen. No tumor recurrence was noted in any patient at a mean follow-up period of 9 months (median: 7 months; range: 3–28 months).

Table 1: Demographics and clinical features of patients with ocular surface squamous neoplasia (n=30)

Feature	n (%)
Age (years)	
Mean (median, range)	55 (57, 27-80)
Gender	
Male	20 (67)
Female	10 (33)
Prior treatment before referral	
Excision biopsy	10 (33)
Excision biopsy+mitomycin-C	2 (7)
Mitomycin-C	1 (3)
HIV infection	1 (3)
Presenting complaints	
Asymptomatic	5 (17)
Mass	18 (60)
Pain	1 (3)
Diminution of vision	3 (10)
Redness	3 (10)
Duration of symptoms (months)	
Mean (median, range)	12 (7, 1-48)
Tumor location	
Cornea	9 (30)
Conjunctivo-limbal-corneal surface	19 (63)
Bulbar conjunctiva	2 (7)
Tumor basal dimension (mm)	
Mean (median, range)	16 (20, 4-30)
Number of limbal clock hours involved	
Mean (median, range)	6 (6, 1-12)
Tumor pattern (n=26)*	
Leukoplakic	2 (8)
Gelatinous	11 (42)
Nodular	3 (12)
Papillary	1 (4)
Placoid	8 (31)
Pigmented	1 (4)
T at the time of initiation of INF α2b (based on AJCC, 7th edition)	
Tis	6 (20)
T3	24 (80)

*No information available in four patients since they had undergone excision biopsy of the lesion at another hospital and were referred to us with microscopic residual tumor at the surgical margins; T: Primary tumor, AJCC: American Joint Committee Classification, INF α2b: Interferon alpha 2b, HIV: Human immunodeficiency virus

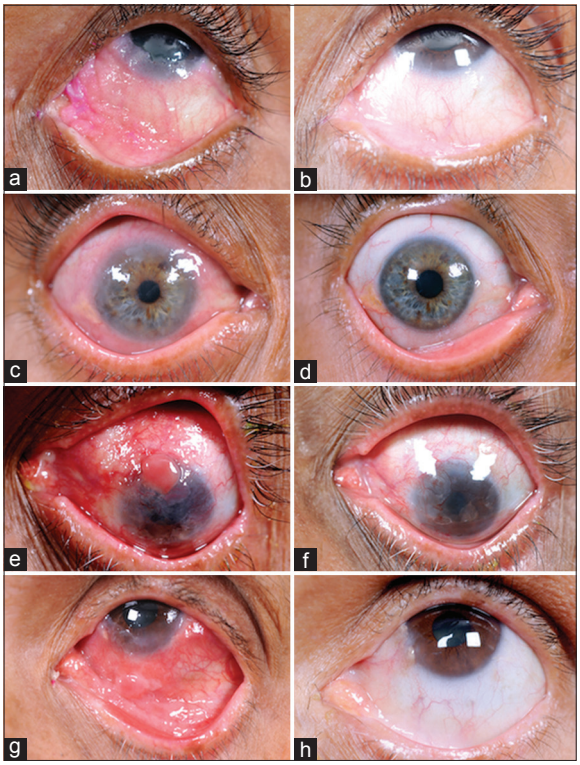

Figure 1: Interferon alpha 2b as immunotherapy for extensive ocular surface squamous neoplasia. (a) A 58-year-old female with recurrent/residual ocular surface squamous neoplasia status post seven cycles of mitomycin-C (b) showed complete tumor regression with three cycles of topical and perilesional interferon alpha 2b injections. (c) A 45-year-old female with diffuse ocular surface squamous neoplasia (d) showed complete tumor regression with five cycles of topical interferon alpha 2b and three perilesional interferon alpha 2b injections. (e) A 62-year-old male patient with recurrent/residual ocular surface squamous neoplasia status postexcision biopsy 2 and two cycles of mitomycin-C (f) showed complete tumor regression with two cycles of topical and perilesional interferon alpha 2b injections. Tumor regression was confirmed by map biopsy from 17 sites of the ocular surface. (g) A 53-year-old one-eyed patient with diffuse ocular surface squamous neoplasia (h) showed complete tumor regression with three cycles of topical and perilesional interferon alpha 2b injections

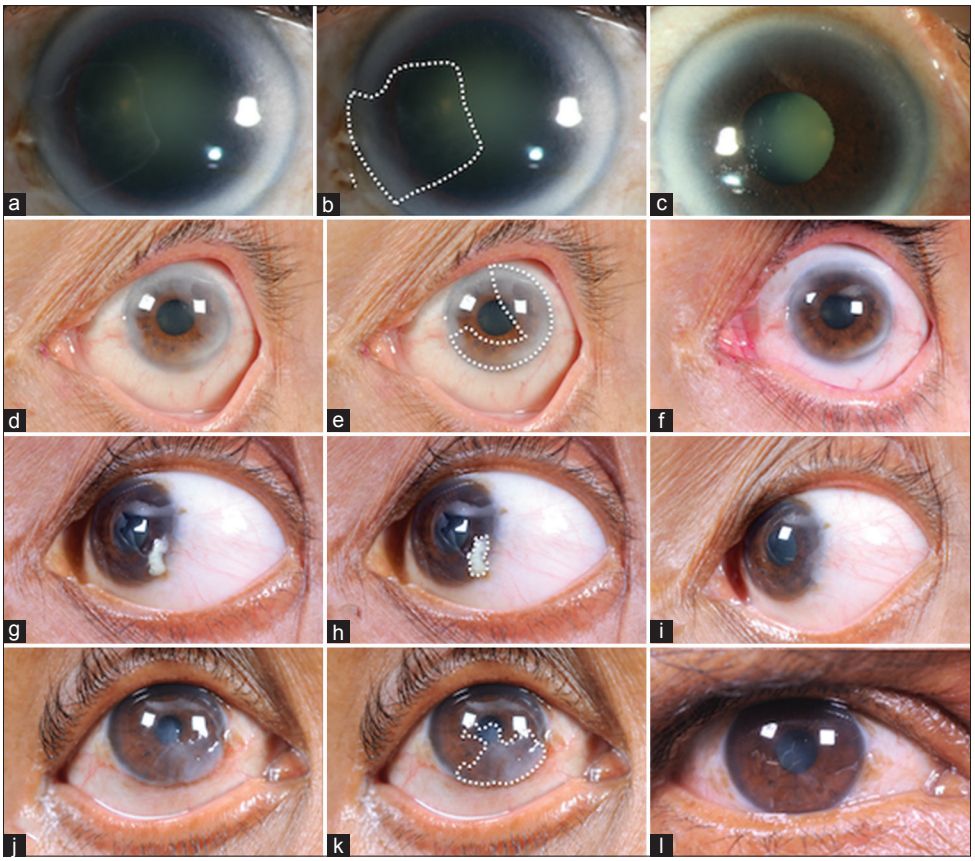

Figure 2: Interferon alpha 2b as immunotherapy for corneal ocular surface squamous neoplasia. (a and b) A 50-year-old female patient with corneal ocular surface squamous neoplasia (white outline) (c) showed complete tumor regression with two cycles of topical interferon alpha 2b. (d and e) A 42-year-old patient with a history of excision biopsy and two cycles of mitomycin-C developed recurrent corneal ocular surface squamous neoplasia (white outline). (f) Complete tumor regression was achieved with two cycles of topical interferon alpha 2b. (g and h) A 60-year-old male patient with a history of prior excision biopsy presented with recurrent corneal ocular surface squamous neoplasia (white outline). (i) Complete tumor regression was achieved with two cycles of topical interferon alpha 2b. (j and k) A 57-year-old female patient with corneal ocular surface squamous neoplasia (white outline) (l) showed complete tumor regression with four cycles of topical interferon alpha 2b

Based on maximum tumor dimension at presentation [Table 4], the mean number of topical and injection INF α2b cycles was 3 and 0 for Group 1, 5 and 2 for Group 2, and 6 and 3 for Group 3, respectively. The mean total treatment cost per patient (including additional three cycles of topical INF α2b after complete tumor regression) with INF α2b was INR 4866 ($US 73) for Group 1, INR 9607 ($US 143) for Group 2, and INR 10,985 ($US 164) for Group 3. Two patients had minimal tumor residue (5% residual tumor) with INF α2b and underwent surgical excision of the residual tumor.

Discussion

INF α2b is a Type 1 INF consisting of 165 amino acid residues with arginine in position 23. This glycoprotein is produced by recombinant DNA technology and resembles INF secreted by leukocytes.[18,19] It exhibits antineoplastic and antiviral effects.[18,19] In solid tumors, INF α causes prolongation of the cell cycle time of malignant cells, inhibits biosynthetic enzymes and apoptosis, interacts with other cytokines, and increases the immunomodulatory and antiangiogenic effects.[24] In cutaneous basal and squamous cell carcinomas, INF α causes tumor regression by concomitant upregulation of interleukin (IL)-2 and downregulation of IL-10 messenger RNA expression in the lesions, thus increasing immunomodulatory effects by improving the T-cell mediated immune response.[25] The mechanism of action of INF α2b in OSSN is unclear but may include inhibition of angiogenesis and/or inhibition of human papillomavirus replication.[26,27] However, recent studies have shown that the presence of human papillomavirus is not required for a favorable response with INF α2b.[28]

The US Food and Drug Administration has approved INF α2b for the treatment of AIDS-related Kaposi sarcoma, hairy cell leukemia, malignant melanoma, aggressive follicular non-Hodgkin's lymphoma, chronic hepatitis B and C, and condyloma acuminata. INF α2b has been used off-label in the treatment of OSSN since the first publication in 1994.[22] Good response to treatment with complete tumor regression is achieved in 85%–100% OSSN cases with INF α2b.[12-22]

In a study of 22 cases of OSSN treated with INF α2b monotherapy, complete tumor regression was achieved in 75% Tis (three of four patients), 100% T1 (all eight patients), and 70% T3 (seven of ten patients).[14] In our study, complete tumor regression was achieved in 100% Tis (all six patients) and 92% T3 (22 of 24 patients). INF α2b with/without surgery achieved complete tumor regression in 100% cases. Complete tumor control was achieved with topical INF α2b monotherapy

Table 2: Treatment details and outcome of patients with ocular surface squamous neoplasia (*n*=30)

Feature	*n* (%)
Purpose of starting INF α2b	
Immunoreduction/ immunotherapy	24 (80)
Immunoprevention	6 (20)
Response achieved with INF α2b	
Immunoreduction (100% tumor regression)	22 (92)
Immunotherapy (reduction in tumor size)	2 (6)
Immunoprevention (prevent tumor recurrence)	6 (100)
Total treatment cost with INF α2b (INR), mean (median, range)	9164 (9732, 4866-15,409)
Total treatment cost with INF α2b ($), mean (median, range)	137 (145, 73-230)
Side effects	
Conjunctival hyperemia	4 (13)
Flu-like symptoms*	1 (8)
Tumor recurrence	0

*Noted in 1 of the 13 patients who received perilesional INF α2b injection.
INF α2b: Interferon alpha 2b

in 15 (50%) cases, a combination of topical and perilesional injection INF α2b in 13 (43%), and a combination of surgery and INF α2b in 2 (7%) cases.

INF α2b can be used for immunoreduction in extensive lesions (tumor basal diameter of 20 mm or >6 clock-hours),[13,17,20,29] as immunotherapy in corneal lesions or smaller conjunctival or conjunctivo-corneal lesions (tumor basal diameter <20 mm and <6 clock-hours),[21,30,31] and for immunoprevention in patients with histopathology evidence of residual tumor.[14] In a study of 18 patients with extensive OSSN by Kim *et al*., INF α2b served as immunotherapy achieving complete tumor regression in 13 (72%) patients and achieved immunoreduction in 28% cases by a median duration of 6 months.[20] In a study of five patients by Karp *et al*., two patients had corneal OSSN and both showed complete tumor regression with topical INF α2b as immunotherapy by a median duration of 2 months.[16] In our study, there were 15 (50%) patients with extensive lesions, 9 (30%) with corneal lesions, and 6 (20%) patients with a residual tumor on histopathology. Of the 15 patients with extensive lesions, INF α2b served as immunotherapy achieving complete tumor regression in 13 (87%) patients at a median duration of 3 months and achieved 95% immunoreduction in 2 (13%) patients at a median duration of 6 months. Of the nine patients with corneal OSSN, topical INF α2b as immunotherapy achieved complete tumor regression in 100% cases at a median duration of 2 months. Similar to prior studies, we found that corneal OSSN responded earlier to treatment with INF α2b.[16,21] The earlier response could be attributed to placoid nature of corneal tumor with minimal tumor thickness.

As per published literature, topical INF α2b is effective at a dose of 1 MIU/cc four to six times/day.[14-22,29-32] A comparison of effectiveness and side effect profile of two doses of topical INF α2b (1 MIU/cc vs. 3 MIU/cc) in the treatment of OSSN showed no significant difference between the two doses.[33] However, there is no consensus on the dose and dosage of perilesional INF. Some authors use 3 MIU/0.5 cc one to three times a week until clinical resolution[13,17,32] while others use 10 MIU/cc once a month until clinical resolution.[14,20,29] In our study, the dose and dosage of topical INF α2b was 1 MIU/cc four times a day until clinical resolution, and the dose of perilesional INF α2b was 5 MIU/cc once a month until clinical resolution of conjunctival component of the tumor. Furthermore, there is a lack of consensus on the duration of continuation of topical INF α2b after tumor resolution and ranges from 1 to 4 months.[14-16,30,31,33] In our study, all patients were advised to continue topical INF α2b for 3 months beyond clinical tumor resolution.

The cost of treatment with INF α2b is three times more than 5-FU and two times more than MMC.[34] The cost of each 10 MIU/cc vial of INF α2b is $US 179 (Jefferson Pharmacy; Philadelphia, PA, USA),[20,21] and it can be used to prepare 10 cc of 1 MIU/cc topical INF α2b drops for 1 month. The cost for 6 months would be $US 1074. The cost of 5 ml of 1 MIU is $US 120 (Leiter's Pharmacy, San Jose, CA, USA),[33] thus costing $US 240 for 10 cc of 1 MIU/cc topical INF α2b drops for 1 month. The cost for 6 months would be $US 1440. For perilesional injection, the patient has to bear an additional cost of $179 to $US 225 (Leiter's Pharmacy, San Jose, CA, USA) per injection, thus further increasing the total treatment cost.[13] In our study, each syringe of Intalfa 5 MIU/cc costs INR 811 ($US 12). An average six cycles of topical INF α2b (with 10 cc of 1 MIU/cc dispatched each month) costs INR 9732 ($US 144), with an additional cost of INR 811 ($US 12) per perilesional injection. In our study, the average total treatment cost per patient with INF α2b (topical with/without perilesional injection) was INR 9164 ($US 137), thus making it cost-effective for our patients. Two patients had to undergo surgical excision of the residual tumor, thus resulting in additional costs.

There is no difference in the recurrence rate of OSSN at 1-year between surgical excision (5%) and medical treatment with INF α2b (3%).[15] In our study, no tumor recurrence was noted in any patient at a mean follow-up period of 9 months (median: 7 months; range: 3–28 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%).[14] Systemic side effects include postinjection flu-like syndrome for 1 day (9%).[14] In our study, the side effects included transient conjunctival hyperemia (13%) and flu-like syndrome (8%), which were comparable with other studies.[13,14,33]

The limitations of the study include retrospective nature of the study, lack of histopathologic documentation of diagnosis in all cases, smaller patient cohort, and shorter duration of follow-up. The cost-effectiveness of treatment has been calculated by taking into account only the cost of INF α2b syringe. However, the patient has additional costs of frequent follow-up visits since topical INF α2b drops needs to be freshly reconstituted each month and stored at appropriate temperature in a refrigerator. The number of follow-up visits with INF α2b medical treatment is more

Table 3: Clinical features and treatment details of patients with ocular surface squamous neoplasia based on the response to treatment with interferon alpha 2b

Feature	Immunoreduction (*n*=2), *n* (%)	Immunotherapy (*n*=22), *n* (%)	Immunoprevention (*n*=6), *n* (%)
Tumor location			
Cornea	0	9 (41)	0
Conjunctivo-limbal-corneal surface	2 (100)	13 (59)	4 (67)
Bulbar conjunctiva	0	0	2 (33)
Tumor basal dimension (mm), mean (median, range)	22 (22, 20-24)	16 (19, 4-30)	NA
Number of limbal clock hours involved, mean (median, range)	9 (9, 6-12)	6 (5, 1-12)	NA
Tumor pattern (*n*=26)*			
Leukoplakic	0	2 (9)	NA
Gelatinous	1 (50)	10 (45)	NA
Nodular	0	2 (9)	1 (17)
Papillary	1 (50)	0	NA
Placoid	0	8 (36)	NA
Pigmented	0	0	1 (17)
T at the time of initiation of INF α2b (based on AJCC, 7th edition)			
Tis	0	0	6 (100)
T3	2 (100)	22 (100)	0
Number of cycles of INF α2b for complete tumor regression, mean (median, range)			
Topical (1 MIU/cc)	NA	3 (2, 1-5)	NA
Perilesional injection (5 MIU/cc)	NA	2 (2, 2-3)	NA
Combined topical+injection	NA	4 (4, 1-8)	NA
Total number of cycles of INF α2b (including three additional cycles after complete tumor regression), mean (median, range)			
Topical (1 MIU/cc)	6 (6, 6)	6 (5, 4-8)	3 (3, 3)
Perilesional injection (5 MIU/cc)	3 (3, 3)	2 (2, 2-3)	0
Combined topical+injection	9 (9, 9)	7 (7, 4-11)	NA
Total cost of treatment with INF α2b (INR) (including three additional cycles after complete tumor regression), mean (median, range)			
Topical (1 MIU/cc)	9732 (9732, 9732)	9068 (8110, 6488-12,976)	4866 (4866, 4866)
Perilesional injection (5 MIU/cc)	2433 (2433, 2433)	1991 (1622, 1622-2433)	NA
Combined topical+injection	12,165 (12,165, 12,165)	10,064 (9732, 6488-15,409)	NA
Total cost of treatment with INF α2b ($) (including three additional cycles after complete tumor regression), mean (median, range)			
Topical (1 MIU/cc)	145 (145, 145)	135 (121, 97-194)	73 (73, 73)
Perilesional injection (5 MIU/cc)	36 (36, 36)	30 (24, 24-36)	NA
Combined topical+injection	182 (182, 182)	150 (145, 97-230)	NA

*No information available in four patients since they had undergone excision biopsy of the lesion at another hospital and were referred to us with microscopic residual tumor at the surgical margins. Two patients underwent excision at our institute and had microscopic residual tumor at the surgical margins;
AJCC: American Joint Committee Classification, INF α2b: Interferon alpha 2b, NA: Not applicable, T: Primary tumor

compared to primary surgery. However, the total cost of treatment with INF α2b medical treatment is less compared to the surgical group.[35] In addition, medical treatment also avoids additional surgeries for limbal stem cell deficiency resulting from extensive surgical excision and cryotherapy for large lesions.

Conclusion

INF α2b is an effective alternative to surgery in suitable cases and can be used for immunoreduction, immunotherapy, or immunoprevention of OSSN. While surgical tumor excision is still the most commonly used treatment modality at our

Table 4: Clinical features and treatment details of patients with ocular surface squamous neoplasia based on the response to treatment with interferon alpha 2b

Feature	Group 1 (no clinical evidence of tumor), *n*=6, *n* (%)	Group 2 (maximum tumor base ≤10 mm), *n*=13, *n* (%)	Group 3 (maximum tumor base >10 mm), *n*=11, *n* (%)
Tumor location			
Cornea	0	6 (46)	3 (27)
Conjunctivo-limbal-corneal surface	4 (67)	4 (31)	5 (45)
Bulbar conjunctiva	2 (33)	3 (10)	3 (27)
Tumor basal dimension (mm), mean (median, range)	NA	5 (5, 2-10)	20 (20, 12-30)
Number of limbal clock hours involved, mean (median, range)	NA	4 (5, 1-7)	9 (8, 5-12)
Tumor pattern (*n*=26)*			
Leukoplakic	NA	1 (8)	1 (9)
Gelatinous	NA	5 (38)	6 (55)
Nodular	1 (17)	1 (8)	1 (9)
Papillary	NA	0	1 (9)
Placoid	NA	6 (46)	2 (18)
Pigmented	1 (17)	0	0
T at the time of initiation of INF α2b (based on AJCC, 7th edition)			
Tis	6 (100)	0	0
T3	0	13 (100)	11 (100)
Tumor response to INF α2b			
Complete tumor regression	6 (100)	13 (100)	9 (82)
Residual tumor needing additional surgical excision	0	0	2 (18)
Number of cycles of INF α2b for complete tumor regression, mean (median, range)			
Topical (1 MIU/cc)	NA	2 (2, 1-4)	3 (2, 2-5)
Perilesional injection (5 MIU/cc)	NA	2 (2, 2-3)	3 (3, 2-3)
Combined topical+injection	NA	4 (4, 3-7)	6 (5, 4-8)
Total number of cycles of INF α2b (including three additional cycles after complete tumor regression), mean (median, range)			
Topical (1 MIU/cc)	3 (3, 3)	5 (5, 4-7)	6 (5, 5-8)
Perilesional injection (5 MIU/cc)	0	2 (2, 2-3)	3 (3, 2-3)
Combined topical+injection	NA	6 (6, 4-9)	8 (7, 5-11)
Total cost of treatment with INF α2b (INR) (including three additional cycles after complete tumor regression), mean (median, range)			
Topical (1 MIU/cc)	4866 (4866, 4866)	8859 (8110, 6488-11,354)	9437 (9732, 8110-12,976)
Perilesional injection (5 MIU/cc)	NA	1946 (1622, 1622-2433)	2129 (2433, 1622-2433)
Combined topical+injection	NA	9607 (9732, 6488-12,165)	10,985 (9732, 8110-15,409)
Total cost of treatment with INF α2b ($), (including three additional cycles after complete tumor regression), mean (median, range)			
Topical (1 MIU/cc)	73 (73, 73)	132 (121, 97-169)	141 (145, 121-194)
Perilesional injection (5 MIU/cc)	NA	29 (24, 24-36)	32 (36, 24-36)
Combined topical+injection	NA	143 (145, 97-182)	164 (145, 121-230)

*No information available in four patients since they had undergone excision biopsy of the lesion at another hospital and were referred to us with microscopic residual tumor at the surgical margins. Two patients underwent excision at our institute and had microscopic residual tumor at the surgical margins;
AJCC: American Joint Committee Classification, INF α2b: Interferon alpha 2b, NA: Not applicable, T: Primary tumor

center, INF α2b is reserved for patients with extensive tumor (>20 mm basal dimension or >6 clock hours involvement of limbus with flat tumor configuration), OSSN limited to the corneal surface, recurrent tumor postsurgical excision and/or MMC, and those with microscopic tumor residue postexcision biopsy. In our study, INF α2b was a cost-effective treatment modality for OSSN at an average total treatment cost of INR 9164 ($US 137) per patient.

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Conflicts of interest

There are no conflicts of interest.

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