Original Article

Topical chemotherapy for giant ocular surface squamous neoplasia of the conjunctiva and cornea: Is surgery necessary?

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Purpose: The purpose of this study is to report on the efficacy and safety of topical chemotherapy alone for giant ocular surface squamous neoplasia (OSSN). **Methods:** In this retrospective, interventional series, 10 eyes with giant OSSN underwent exfoliative biopsy to confirm the diagnosis followed by application of interferon alpha 2b (IFN α2b) and/or 5 fluorouracil, 1% (5FU). Reported outcome measures were tumor response, visual acuity, recurrence, systemic metastasis, and treatment complications. **Results:** Ten patients (3 female, 7 male) had a mean age of 73 (median, 69; range 40–89) years. Mean tumor diameter was 13.1 (median, 12.3; range 8.2–19.4) mm. Five (50%) eyes were treated with IFN-α2b alone; 1 (10%) with 5-FU alone and 4 (40%) required both IFN-α2b and 5-FU. The mean duration of treatment was 3, 0.5, and 6.4 months for IFN-α2b alone, 5-FU alone, and both IFN-α2b and 5-FU respectively. Complete tumor response was observed in all 10 cases at mean follow-up of 12.8 (median, 11.5; range, 3–25) months. Complications noted were transient irritation and burning (n = 4), dry eyes (n = 2), and transient flu-like symptoms (n = 2). There was no evidence of chemotherapy-related symblepharon, stem cell deficiency, scleral thinning, or corneal opacity. There were no tumor recurrences, and no patient required surgical excision or cryotherapy. **Conclusion:** Topical chemotherapy was a safe and effective treatment, inducing complete regression in all cases of giant OSSN in this series. There were no sight-limiting complications.

Key words: Topical chemotherapy, giant **o**cular surface squamous neoplasia, interferon alpha 2b, 5-fluorouracil

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Ocular surface squamous neoplasia (OSSN) is the most common malignancy of conjunctiva and cornea.[1] Although surgical excision with adjuvant cryotherapy was the standard treatment, nonsurgical treatments involving topical or intralesional chemotherapy have increased in popularity over the last decade.[2,3] Chemotherapeutic agents for OSSN include interferon alpha-2b, (IFN-α2b), 5-fluorouracil (5-FU), and mitomycin C (MMC). Each drug has been effective as primary or adjuvant therapy.[4-8] As compared to excision and cryotherapy, primary topical chemotherapy is relatively noninvasive, treats the entire ocular surface, and avoids the risks of surgery.

The management of extensive OSSN lesions can be particularly challenging. They typically involve both palpebral and forniceal conjunctiva, cornea, and caruncle. Surgical management typically requires conjunctival and corneal excisions, occasional deep scleral/corneal resection as well as adjuvant cryotherapy. These interventions have been associated with secondary complications as eye wall thinning, symblepharon, stem cell deficiency, and corneal opacities.

The side effect profiles of topical IFN-α2b and 5-FU have also been described in literature.[4-11] With the use of 5-FU (1%), reported side effects include acute effects as conjunctival hyperemia, allergy, superficial punctate keratitis, pain, and epiphora. Long-term effects include recurrent corneal erosions, limbal stem cell deficiency, and punctal stenosis.[4,9] In contrast, photophobia, ocular discomfort, and flu-like symptoms have been reported with IFN-α2b.[7,8,10,11] The optimal approach for each case should be determined by weighing the risks and benefits of different treatment modalities.

Herein, we describe our experience utilizing intensive topical chemotherapy alone (no surgery or cryotherapy) as an alternative treatment for large or giant OSSN.

Methods

This study adhered to the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act of 1996. We obtained approval from the Institutional Review Board of the respective institutions to perform a retrospective chart review of cases presenting with giant OSSN managed with topical chemotherapy between 2013 and 2016. Of the 250 cases reviewed, this study includes 10 patients with large tumors who received topical chemotherapy alone for their giant OSSN. Patients requiring any form of secondary adjuvant treatment, i. e., intralesional chemotherapy, surgical excision, cryotherapy, or external beam radiation therapy were excluded from the study.[12-14]

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History and ophthalmic examination

Patient records were reviewed for demographic information (age, race, and ethnicity), systemic illness and risk factors for OSSN, skin cancer, human papillomavirus, human immunodeficiency virus, and smoking. Ophthalmological examination was inclusive of but not limited to visual acuity with the Early Treatment of Diabetic Retinopathy Study charts/rooms, slit-lamp biomicroscopy with photography, tonometry, gonioscopy, scleral transillumination, high-frequency ultrasonography (20 and 35 MHz), indirect ophthalmoscopy, and examination of regional lymph nodes by palpation. Slit-lamp biomicroscopy was utilized to document clinically evident limbal, forniceal, tarsal, and/or caruncle involvement along with the multifocality of the tumors. Tumor size was determined by direct method with slit-lamp biomicroscopy or by indirect method, using anterior segment photography. The tumor size and location provided the basis for American Joint Committee on Cancer (AJCC, 8th edition) staging of each tumor.[15]

Of these, visual acuities, slit-lamp photography, gonioscopic photography, high-frequency ultrasound imaging, ophthalmoscopy, and regional lymph node examination were performed at each subsequent visit wherever applicable.[16]

Diagnosis

Our decisions were based on the clinical diagnosis of conjunctival carcinoma. Therefore, in this series, exfoliative cytology was used for adjunctive confirmation.[17] The method of conjunctival biopsy used has been described.[17] In sum, conjunctival and/or corneal cytologic specimens were obtained in our outpatient clinics under topical anesthesia with a platinum spatula; cells and tissue were scraped from the surface of the tumors. Several passes were typically made to capture cells beneath the (often hyperkeratotic) surface for each slide. The specimens were smeared onto four glass slides. Each slide was immediately immersed in 95% ethyl alcohol (within the slide carrier) and was submitted for cytologic evaluation. Glass slides with cytologic material were subsequently stained with hematoxylin and eosin. The ophthalmic pathologist interpreted and thus we recorded each as no dysplasia, presence of dysplasia, severe dysplasia, or squamous cell carcinoma [Table 1].

Informed consent

All patients were counseled about current modalities of management including but not limited to: surgical excision with adjuvant cryotherapy followed by ocular surface reconstruction and topical chemotherapy. Informed consent involved a detailed discussion of each procedure's relative risks and potential benefits.

Topical chemotherapy

A punctal plug was placed in the lower eyelid of the affected eye before administration of topical chemotherapy. The drops were advised to be instilled in the superior fornix of the eye while the patient maintained a downgaze. After each drop was instilled, the patient was asked to stay reclined for 5 min to make sure the medication was evenly distributed.

Interferon alpha-2b

Intron A (Schering Corporation, Kenilworth, NJ, USA) powder (10 million IU) reconstituted to topical 1 million IU/cc was administered as 1 drop 4 times daily, 7 days a week for 3 months.

Table 1: Pretreatment tumor characteristics

Features	*n* (%)
Laterality	
Right	3 (30)
Left	7 (70)
Greatest basal diameter (mm)	
Median, mean, range	12.3, 13.1, 8.2-19.4
Limbal clock hours involvement	
Median, mean, range	7, 7.1, 6-10
Multifocal tumor	3 (30)
Tumor location*	
Superior	8 (80)
Temporal	3 (30)
Inferior	6 (60)
Nasal	4 (40)
Structures involved† conjunctiva	
Bulbar	10 (100)
Palpebral	3 (30)
Forniceal	0
Tarsal	0
Caruncle	0
Cornea	9 (90)
Morphologic appearance‡	
Leukoplakia	3 (30)
Papillomatous	7 (70)
Nodular	5 (50)
Gelatinous	7 (70)
AJCC stage (TNM)#	
$T1cN_0M_0$	5 (50)
$T1d\ N_0M_0$	2 (20)
$T2b\ N_0M_0$	3 (30)
Exfoliative cytology analysis##	
No dysplasia	0
Mild-to-moderate dysplasia	4 (40)
Severe dysplasia or squamous cell carcinoma	6 (60)

*Single eye could have tumor involving more than one quadrants, †More than one structures could have been involved by the tumor, ‡More than one description could apply for single tumor, #According to the AJCC 8th edition cancer staging manual,[15] ##No dysplasia: No evidence of any dysplastic cells, Mild-to-moderate dysplasia: Few or clusters of dysplastic cells intermixed with normal cells, severe dysplasia, or squamous cell carcinoma: All visible cells show dysplasia without evidence of normal morphology. AJCC: American Joint Committee on Cancer, TNM: Tumor node metastasis

5-Fluorouracil

Topical 5-FU was used at a concentration of 1%, administered as 1 drop 4 times daily, 7 days a week for 2 weeks.

Definitions and parameters

For the purpose of this study, "giant" squamous cell carcinoma was defined as having a greatest basal diameter of >15 mm or involvement of >6 limbal clock hours. Specific characteristics of each tumor were documented including the involved eye, tumor location, tumor size (maximum basal diameter in millimeters), number of clock hours of involvement, involved ocular structures (conjunctiva [palpebral, bulbar, forniceal, tarsal],

cornea, limbus, orbit), AJCC T-size, regional lymph nodes and distal metastasis (tumor node metastasis) stage,[12] morphological findings (leukoplakic, gelatinous, papillomatous, flat, or nodular) and vascularity (feeder vessels and intrinsic vascularity) based on clinical description, and slit-lamp photographs. High-frequency ultrasound/ultrasound biomicroscopy (UBM) was performed to evaluate for intraocular tumor invasion.[16] The findings of exfoliative cytology analysis, topical chemotherapy details of drug, treatment duration, tumor response, and posttreatment follow-up were documented.

Outcome measures

The main outcome measures were tumor response, tumor recurrence, new tumor appearance, visual acuity, treatment-related complications, and metastasis (regional and systemic).

Tumor response was recorded as the time to complete resolution (clinically defined on slit-lamp examination). Recurrence was defined as reappearance at a similar location as the original tumor (after complete resolution of original tumor). New tumors were defined as those appearing at a different location from that of original tumor (after complete resolution of original tumor). Follow-up duration was defined from the time of resolution of lesion until the last visit. Complication surveys included redness, irritation, watering, flu-like symptoms, follicular hypertrophy, superficial corneal epitheliopathy, dry eyes, limbal stem cell deficiency, and infection.

Results

The general trend toward starting treatment with IFN-α2b was related to its more favorable side-effect profile.[11] However, in the United States of America, IFN-α2b is more expensive and the course is typically for 3 months. In contrast, 5-FU treatments lasted 10–14 days. Therefore, lack of insurance coverage and the patient's need for a shorter treatment course affected the choice of primary medication.

Ten patients with giant OSSN were cured without surgery for a mean follow-up of 12.8 months (median, 11.5 months; range, 3 to 25 months). In this series, 5 (50%) received only IFN-α2b monotherapy, 1 eye (10%) received 5-FU monotherapy, and 4 eyes (40%) required both topical IFN-α2b and 5-FU to reach complete response.

Pretreatment characteristics

All 10 (100%) patients presented with unilateral disease [Table 2]. The left eye was affected in 7 (70%) of patients. Of the risk factors associated with OSSN,[1] 1 (10%) patient had a history of HIV, 1 (10%) had a prior history of OSSN in the contralateral eye, while 3 (30%) had a history of smoking. The mean largest basal tumor diameter was 13.1 (median, 12.3; range 8.2–19.4) mm. The mean number of limbal clock hours involved was 7.1 (median, 7; range, 6–10). According to the AJCC 8th edition clinical staging criteria, 5 (50%) were T1c, 2 (20%) were T1d, and 3 (30%) were T2b. The details of tumor location, structures involved, and morphological appearance are described [Table 1].

High-frequency ultrasound imaging before and at last follow-up revealed no intraocular invasion (n = 0/10, 0%) [Fig. 1]. Similarly, no case showed evidence of regional lymph node or distant metastasis at presentation.

Table 2: Demographic features

Features	*n* (%)
Age (years)	
Median, mean, range	73, 69, 40-89
Race	
Caucasian	3 (30)
Hispanic	5 (50)
African-American	2 (20)
Sex	
Male	7 (70)
Female	3 (30)
Associated comorbidities	
Hypertension	2 (20)
Diabetes mellitus	1 (10)
Cardiac illness	2 (20)
Skin cancer	0
Other systemic malignancies	1 (10)
Risk factors for OSSN	
HPV	0
HIV	1 (10)
Smoking	3 (30)
History of OSSN	1 (10)

OSSN: Ocular surface squamous neoplasia, HPV: Human papillomavirus, HIV: Human immunodeficiency virus

Local tumor control

Topical IFN-α2b monotherapy was curative in 5 or 50% (n = 10) of patients in this group with the mean and median duration of treatment of 3 months. Complete resolution (100%) was noted at that 3 months' visit in all 5 cases. With longer follow-up (mean, 8.8 months), there was no evidence of recurrence [Figs. 2a, b and 3c, d].

In this series, one OSSN was treated with topical 5-FU monotherapy. It showed complete resolution with treatment duration of 0.5 month (2 weeks) and was followed for 18 months without recurrence.

Four lesions (40%) required both topical 5-FU and IFN-α2b. These tumors showed complete resolution (100%) with a mean treatment duration of 6.4 months. In this group, there was no evidence of tumor recurrence over a mean follow-up of 16.5 months [Table 3, Figs. 2c, d and 3a, b].

Visual acuity

At presentation, four (40%) patients demonstrated best-corrected visual acuity of 20/16–20/40 while 6 (60%) had visual acuity of 20/40–20/200. The causes of low visual acuity at presentation included preexisting cataract (n = 2), corneal opacity (n = 1), and tumor-induced astigmatism (n = 3).

No loss of vision was associated with the treatment. At the last follow-up, the best-corrected visual acuity was 20/16–20/40 in 8 (80%) and 20/40–20/200 in 2 (20%) cases. Eight (80%) cases were within 2 Snellen lines or equal to their pretreatment visual acuity while 2 (20%) showed improvement of more than 2 lines at a mean follow duration of 12.8 months [Fig. 4].

Table 3: Giant ocular surface squamous neoplasia managed with topical chemotherapy in 10 patients: Treatment and outcome

Features	Topical IFN-α2b (*n*=5), *n* (%)	Topical 5-FU (*n*=1), *n* (%)	Both topical IFN-α2b and 5-FU (*n*=4), *n* (%)
Total months of treatment; mean, median	3, 3	0.5, 0.5	6.4, 6.5
Tumor control			
Complete resolution (100% response)	6 (100)	1 (100)	3 (100)
Partial response	0	0	0
Failure	0	0	0
Time to tumor resolution (months); mean, median, range	3, 3	1, 1	6.4, 6.5, 3.5-9
Tumor recurrence	0	0	0
New tumor	0	0	0
Follow-up (months); mean, median, range	8.8, 7, 3-20	18, 18, NA	16.5, 15, 8-25

IFN-α2b: Interferon alpha-2b, 5-FU: 5-fluorouracil, NA: Not available

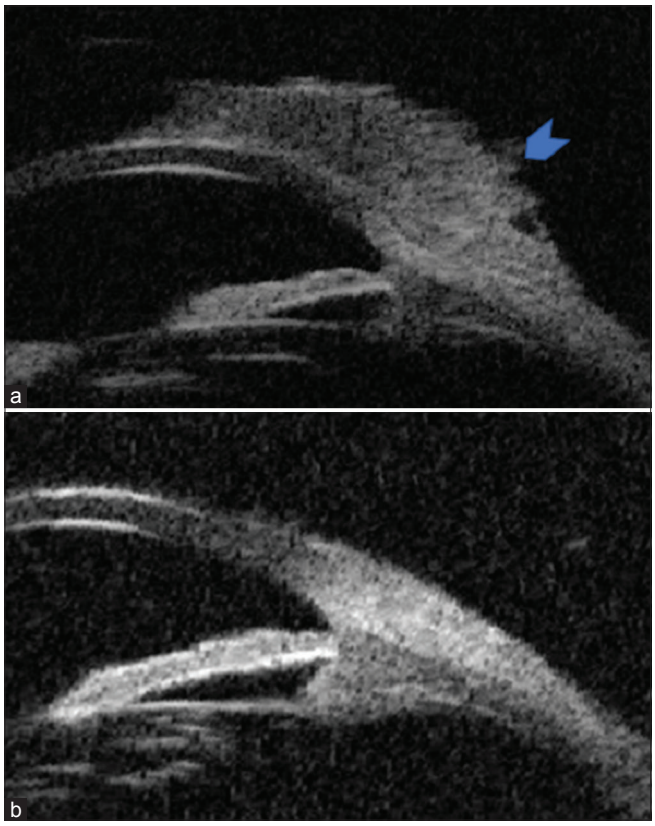

Figure 1: High-frequency (35 MHz) ultrasound image (longitudinal section) of giant ocular surface squamous neoplasm. Pretreatment (a) (blue arrow shows the epibulbar tumor) before treatment. (b) Posttopical chemotherapy showing resolution of the tumor along with absence of scleral or intraocular invasion (e.g., angle blunting or uveal thickening)

Side effects and complications

Six patients (60%) experienced treatment-related side effects. The most common complication [Table 4] was irritation and burning sensation (*n* = 4), followed by symptoms of dry eye (*n* = 2) and transient flu-like symptoms (*n* = 2). There was no evidence of recurrent corneal erosions, limbal stem deficiency, symblepharon formation, corneal opacity, or scleral thinning (*n* = 0, 0%) noted in our series [Figs. 2 and 3].

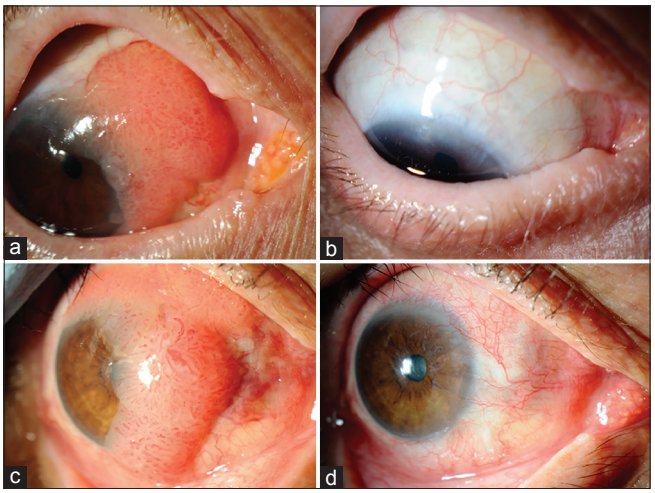

Figure 2: Slit-lamp photograph of a giant ocular surface squamous neoplasm with extensive bulbar conjunctival, limbal, and corneal involvement. Pretreatment (a) and (b) showing complete resolution of tumor utilizing topical interferon alpha-2b (3 months) at 12 months of follow-up. Pretreatment (c) multifocal lesion and (d) showing complete resolution utilizing topical interferon alpha-2b (3 months) and 5-fluorouracil (2 weeks) at 15 months. Note the absence of symblepharon, corneal or scleral thinning

Intraocular invasion, regional and systemic metastasis

No case demonstrated intraocular, regional lymphatic, or distant metastatic spread (*n* = 0, 0%) at the mean follow-up of 12.8 months.

Discussion

This study demonstrates the efficacy of topical chemotherapy alone for giant OSSN (greatest basal diameter of >15 mm or involvement of >6 limbal clock hours).The mean largest tumor diameter was 13.1 (range 8.2–19.4) mm, and there was no evidence of intraocular invasion at presentation. Five eyes (50%) were cured with 3 months of topical IFN-α2b (1 MIU/ml), 1 (10%) with 5-FU (1%) monotherapy for 2 weeks, and 4 (40%) eyes required both 5-FU (1%) and IFN-α2b (1 MIU/ml) drops for mean treatment duration of 6.4 months. Complete resolution of lesion was achieved in 100% cases and will likely be curative (with a mean follow-up 12.8 months).[18] Side effects observed were irritation

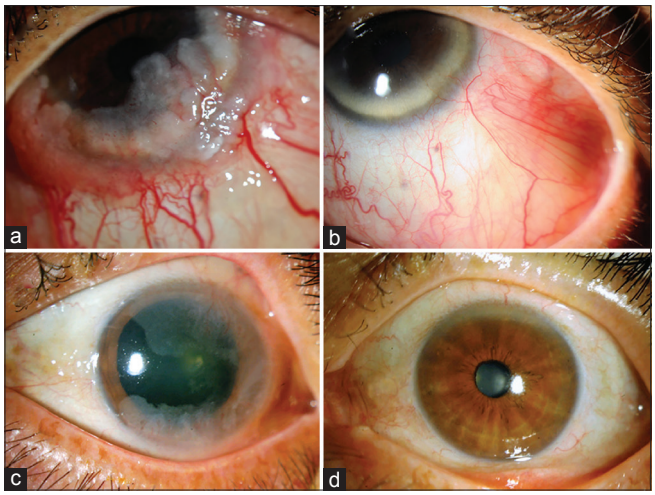

Figure 3: Slit-lamp photographs of a giant ocular surface squamous neoplasia with extensive limbal and corneal involvement. (a) Pretreatment and (b) posttreatment showing complete tumor regression after topical interferon alpha-2b (3 months) and 5-fluorouracil (2 weeks) after a follow-up of 17 months. Note the absence of pannus, corneal opacities, limbal stem cell deficiency, corneal or scleral thinning. (c) Slit-lamp photograph of ocular surface squamous neoplasia with predominantly corneal involvement. Pretreatment (c and d) after complete tumor resolution posttopical interferon alpha-2b (3 months) at 9 months follow-up. Note no evidence of corneal haze or opacity

and burning (40%), dry eye (20%), and transient flu-like symptoms (20%).

There was not one case of primary tumor recurrence, new tumor, or metastasis (0%). Further, this evidence suggests that given a clinical diagnosis (supported by exfoliative biopsy) with no evidence of scleral or intraocular invasion (UBM), surgical excision with cryotherapy may be unnecessary. As this strategy was successful for patients with large-sized conjunctival and corneal tumors, it can be used for smaller tumors.

Topical MMC, 5-FU, and IFN-α2b have been used as curative therapy or for tumor reduction with reported response rates ranging from 40% to 80%.[4-8] However, in the review of the literature, it appears that most centers selectively treat large (>8 mm in diameter) tumors with surgery and adjuvant cryotherapy.[10,11,19] When treated with primary chemotherapy, it has been delivered through intralesional or perilesional injections with or without synchronous topical therapy.

Massive and invasive AJCC-T4 lesions are typically treated by extensive surgical excision or exenteration.[20,21] In contrast, Kim *et al*. described a series of 18 cases of giant OSSN treated with topical and/or intralesional IFN-α2b where they achieved complete control in 72% and reduction in size (immunoreduction) in 28%.[10] Gupta and Muecke described the use of topical MMC as primary therapy in 91 eyes, 10 of which were "diffuse" (>5 clock hours) carcinoma *in situ* lesions. They reported partial response in 10% and recurrence rate of 20%.[22] Individual case reports have reported complete resolution of lesions with topical IFN-α2b with a treatment duration ranging from 3 to 8 months.[23-25] Recently, Joag *et al*. described 44 OSSN lesions managed with topical 5-FU as primary therapy. Of the 44, 36 (82%) lesions showed complete resolution and 4 (11%) eyes had tumor recurrence with a

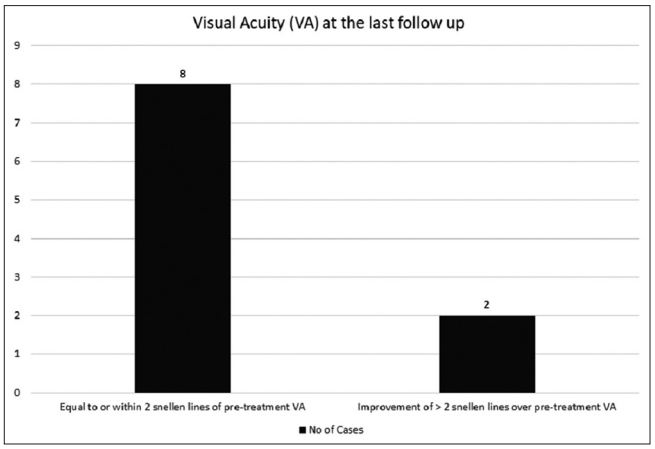

Figure 4: Bar diagram comparing the visual acuity, pretreatment and at the last follow-up. There was no loss of vision associated with the treatment

Table 4: Side effects and complication of topical chemotherapy for ocular surface squamous neoplasia

Features*	While on topical IFN-α2b, *n* (%)	While on topical 5-FU, *n* (%)	Total number, *n* (%)
Symptoms			
Pain	0	0	0
Irritation and burning	1 (10)	3 (30)	4 (40)
Photophobia	0	0	0
Transient flu-like symptoms	2 (20)	0	2 (20)
Signs eyelid			
Edema	0	0	0
Erythema	0	0	0
Blepharospasm	0	0	0
Punctal stenosis	0	0	0
Conjunctiva			
Conjunctival hyperemia	0	1 (10)	1 (10)
Conjunctival follicles	0	0	0
Pseudomembrane formation	0	0	0
Symblepharon	0	0	0
Cornea and sclera			
Dry eye	1 (10)	1 (10)	2 (20)
Pannus	0	1 (10)	1 (10)
Superficial punctate keratitis	0	0	0
Epithelial defect	0	0	0
Recurrent epithelial erosion	0	0	0
Limbal stem cell deficiency	0	0	0
Corneal opacity	0	0	0
Scleral thinning	0	0	0
Lens			
New onset or progression of cataract	0	1 (10)	1 (10)

*One or more side effects could have been experienced by a single case.
IFN-α2b: Interferon alpha-2b, 5-FU: 5-fluorouracil

median follow-up of 10 months. This series included 40 (91%) of T3 lesions according to the 7th edition AJCC staging.[9]

Here, we describe a retrospective interventional case series of large squamous tumors, which showed complete tumor resolution (100%) with the use of single or sequential topical chemotherapy alone. In addition, we found that topical chemotherapy alleviated the need for secondary surgical excision or cryotherapy in all cases. The most common side effects in our series were transient irritation and burning sensation (40%). It is important to note that we had no cases of recurrent corneal erosions, limbal stem deficiency, symblepharon formation, corneal opacity, or scleral thinning in this series.

Our study's limitations include its retrospective nature, limited number of cases, and relatively short follow-up. However, the work of Yousef and Finger with a mean follow-up of 22 months suggests that T1 and T2 tumors (without signs of intraocular invasion at presentation) are highly unlikely to recur after 12 months of posttreatment follow-up.[18] We also acknowledge that primary topical chemotherapy eliminates the possibility of surgically proven deep margins. It relies on high-frequency ultrasound imaging and gonioscopy to evaluate for scleral and intraocular invasion. Finally, there is a need for refrigeration of the medication, long treatment duration, and thus dependence on long-term patient compliance.

Conclusion

However, we report excellent tumor control with no recurrence using one or two sequential topical agents for giant AJCC-T1 and T2 tumors. We found that topical therapy treated the entire ocular surface and avoided surgical intervention. We also observed that topical chemotherapy resulted in less scarring and stem cell loss compared to our experience with surgery with cryotherapy.[18] Clearly, larger tumors than widely expected can be controlled with topical chemotherapy alone. A future analysis with large number of patients and additional tumor-staged analysis is recommended to support the use of topical chemotherapy as primary and monotherapy for giant OSSN.

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Conflicts of interest

There are no conflicts of interest.

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