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Diagnosis and Medical Management of Ocular Surface Squamous Neoplasia

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Abstract

Introduction—Topical chemotherapy has gained popularity among clinicians for the treatment of ocular surface squamous neoplasia (OSSN). The principal topical chemotherapy agents used in the management of OSSN are interferon- α 2b, 5-fluorouracil, and mitomycin C. High-resolution optical coherence tomography (HR-OCT) is a non-invasive technique that can differentiate OSSN from other ocular surface lesions.

Areas covered—This review highlights the current regimens and diagnostic modalities used in managing OSSN. A review of the literature was performed using the keywords “conjunctival intraepithelial neoplasia”, “ocular surface squamous neoplasia”, “optical coherence tomography”, “interferon- α 2b”, “5-fluorouracil” and “mitomycin C”.

Expert commentary—Topical chemotherapy for OSSN can be used as primary therapy, for chemoreduction prior to surgical excision, and postoperatively to prevent tumor recurrence. It has the advantage of treating microscopic disease as well as large tumors. HR-OCT provides an “optical biopsy” that can assist in diagnosis and guide management of OSSN lesions.

Summary

This review discusses the current role of topical chemotherapy agents in the treatment of ocular surface squamous neoplasia and presents novel diagnostic imaging modalities for this entity.

Keywords

ocular surface squamous neoplasia; interferon- α 2b; 5-fluorouracil; mitomycin C; high resolution optical coherence tomography; topical chemotherapy; conjunctival neoplasia

1. Introduction

Ocular surface squamous neoplasia (OSSN) is a clinical term that describes a spectrum of neoplastic changes of the squamous epithelium of the cornea and conjunctiva. This name was proposed by Lee and Hirst[1] in 1995 to encompass squamous epithelial lesions of the

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Declaration of interest

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ocular surface ranging from mild dysplasia to intraepithelial neoplasia (i.e. carcinoma *in situ*) and frank squamous cell carcinoma. Similar to gynecologic intraepithelial neoplasia, OSSN is graded based upon pathologic examination depending on the degree of dysplastic involvement of the epithelium.[2] Of 771 non-melanocytic conjunctival tumors from a single ocular oncology center, OSSN was the most common non-pigmented tumor of the ocular surface; 23% (179 tumors) of the surveyed lesions were classified as OSSN.[3]

Clinically, OSSN lesions typically present as fleshy conjunctival lesions with a gelatinous, leukoplakic, or papillary appearance. They are thought to arise from the limbal stem cells. OSSN lesions are most commonly found in the interpalpebral region involving the cornea and/or bulbar conjunctiva with the tarsal conjunctiva being less frequently involved. They can be flat or raised, localized or diffuse, and they may have feeder conjunctival vessels. They can be associated with other ocular surface lesions such as pterygia,[4] and pinguecula. Flat and diffuse lesions can present similar to scleritis. Staining of devitalized squamous cells with Rose Bengal can help delineate an OSSN lesion; other stains that can be used include lissamine green and methylene blue.[5] Factors associated with high grade lesions on pathology, (i.e. increased mitotic activity, low cellular differentiation and dysplasia) include male gender, temporal location of the lesion, and multifocality.[6] Moreover, raised lesions are typically of higher grade than flat lesions.[6] Similar to squamous lesions of the skin, corneal and conjunctival squamous neoplasia is unlikely to metastasize systemically but it can extend locally.

The incidence of OSSN is higher in equatorial regions and in older white men (mean age at presentation, 56 years).[7] For example, its incidence in the United States is 0.3–8.4 per million people per year,[8,9] while in Australia it has been reported as high as 19 per million people per year,[7] and in Uganda as 12 per million people per year.[10] Putative mutagenic factors implicated in the pathogenesis of OSSN include ultraviolet radiation,[11] smoking, immunosuppression, genetics, ocular surface injury, exposure to chemicals (petroleum products, beryllium, trifluridine, arsenic), and vitamin A deficiency.[2] Though the human papilloma virus (HPV) is known to be carcinogenic in cervical and head and neck squamous cell carcinomas, definitive data regarding the role of HPV in the pathogenesis of OSSN is still lacking. The current thinking among ocular surface oncologists is that HPV may be a cofactor in the development of OSSN in already susceptible hosts,[12,13] although the presence of HPV in the tumor does not seem to be a prerequisite for response to interferon.[14] Though a disease of the elderly, when OSSN is found in younger patients, an underlying immunosuppressive condition, such as infection with the human immunodeficiency virus (HIV),[15,16] or genetic predisposition as in xeroderma pigmentosum [17] should be sought.

Surgery has been the traditional treatment for primary OSSN,[18], but now topical chemotherapy has been gaining increasing popularity among corneal specialists. This trend is evident in the most recent survey of the “standard of care” in the management of OSSN. In 2003, surgery alone was used for primary OSSN in 66% of corneal specialists, and in 2012 this dropped to 51%, with the other half now favoring medical therapy.[18,19]

The purpose of this review is to familiarize general ophthalmologists with the various topical chemotherapy treatment protocols for OSSN and highlight the potential role of optical coherence tomography in this disease.

2. Methods

A PubMed search of all articles published in English from January 1980 to December 2015 on the diagnosis and management of OSSN was performed. Searches included a combination of the following terms: “ocular surface squamous neoplasia,” “conjunctival intraepithelial neoplasia,” “corneal intraepithelial neoplasia,” “CIN,” “OSSN,” “conjunctival squamous cell carcinoma,” “topical chemotherapy,” “mitomycin C,” “5-fluorouracil,” “interferon α 2b,” “anti-VEGF,” “anterior segment optical coherence tomography,” “high resolution optical coherence tomography.” The resulting references were then reviewed for pertinent articles.

3. Results

Prior to the development of high resolution imaging modalities for the ocular surface, histopathological examination of biopsy specimens was the only way to diagnose and grade OSSN. Thus, traditionally, treatment of OSSN has been surgical excision with wide margins and intraoperative cryotherapy.[20] However, surgery alone has proven inadequate for prevention of disease recurrence.[21] The reported recurrence rate ranges from 33% with negative surgical margins, to 56% with positive margins.[22] Extensive surgical excision can result in limbal stem cell deficiency, scarring and symblepharon formation. Other less frequent complications include damage to the sclera and retina from excessive cryotherapy, formation of pyogenic granulomas, and post-operative infections. (Table 1)

For these reasons, the use of topical chemotherapy in the management of OSSN has been steadily increasing over the past two decades.[18,19] Whether used as primary therapy, for preoperative tumor debulking (chemoreduction),[25,39] or for postoperative prevention of disease recurrence (chemopreventive), topical chemotherapy has changed the standard of care in the treatment of OSSN.[18,19] Topical chemotherapy is effective for primary lesions. It has been shown to be equally efficacious with similar recurrence rates to surgical excision of primary OSSN.[23] (Table 1) Topical chemotherapy is especially helpful in treating recurrent lesions, as well as large and multifocal disease.[24,25]

Medical therapy allows treatment of the entire ocular surface, therefore treating subclinical disease. The three most studied and used compounds are interferon- α 2b (IFN- α 2b),[23–28] 5-fluorouracil,[29–32] and mitomycin C (MMC).[33–40] (Table 2) Anti-vascular endothelial growth factor (anti-VEGF),[41–45] retinoic acid,[46,47] and aloe vera[48] have also been used but their efficacy is not well-established yet.

3.1. Interferon alpha-2b (IFN- α 2b)

Interferon alpha is an immunomodulatory cytokine produced by human leukocytes, and along with interferon beta form the group of type I interferons. Type I interferons are low molecular weight glycoproteins that, upon binding to a cell surface receptor, can activate

various signal transduction pathways that converge in altering gene expression, inducing apoptosis, and inhibiting protein synthesis.[49–51] Their effect is most pronounced in virus-infected and neoplastic cells, where they have been shown to inhibit viral replication and mitosis of cancer cells.[49] Interferon α was first cloned and produced in a recombinant form by genetically-modified *Escherichia coli* cells in 1980.[52] Since then, systemic interferon has been used for the treatment of chronic hepatitis B and C, hairy cell leukemia, Kaposi's sarcoma, metastatic malignant melanoma, cervical intraepithelial neoplasia, and cutaneous squamous cell carcinoma.[53] While possibly a causal cofactor in OSSN, the presence of HPV in the tumor does not seem to be a prerequisite for response to interferon. [14]

Two formulations of IFN- α 2b are used in the management of OSSN: a topical drop or a subconjunctival perilesional injection. Both can be used for primary or adjunctive treatment in the management of OSSN. For the topical drops, the typical regimen is 1 million IU/ml four times daily until resolution, usually followed by one or two more months after resolution. (Figure 1A, 1B) The mean time to resolution is about 4 months and side effects are limited to mild irritation and follicular conjunctivitis. The 1 million IU/ml dose seems as effective as the higher dose of 3 million IU/ml with less side effects.[54] A compounding pharmacy is required to make these formulations, since the drops are not commercially available. The cost in the United States may range from \$240–300/month for self-pay patients. Cost may differ depending on insurance coverage and government subsidy policies. This cost may also vary in other countries based on the pharmaceutical market and availability.

Subconjunctival perilesional IFN- α 2b injections are generally administered at a dose of 3 million IU/0.5 ml weekly until clinical resolution, which usually takes 4–5 injections. [55] Doses as high as 10 million IU given once a month[56] and weekly pegylated IFN- α 2b injections (80 μ g/ 0.5 ml/injection) have also been successful at controlling the disease[57]. Compared to topical drops, interferon injections help OSSN lesions resolve faster, clinical response is not affected by patient compliance, and no compounding is necessary as the injections are commercially available. IFN- α 2b is commercially available in a number of options, including powder or injection-ready solution. We favor the 18 million IU multidose vial which provides multiple doses (e.g. 6 injections of 3 million IU each) and thus usually enough for complete treatment of most tumors. IFN- α 2b injections, in contrast to topical drops give a “flu-like” syndrome that ensues after each injection. An oral anti-pyretic (e.g. acetaminophen, ibuprofen) is usually effective in alleviating such post-injection symptoms. [55] We give 1000 mg of acetaminophen at the time of injection and then every 4–6 hours as needed.

As primary therapy, IFN- α 2b (topical or subconjunctival) has an overall success rate of 76–100%. Most recurrences can be successfully re-treated with IFN- α 2b.[27,28,54,55,57–64] In addition to its role as a primary treatment for OSSN, IFN- α 2b can also be used post-excision for positive margins. When used as an adjunct to surgical excision with positive margins, it reduces the recurrence rate from 13% to 4%.[65] In this scenario, topical interferon 1 million IU/ml is used four times daily for 2 months.[65]

3.2. 5-Fluorouracil (5-FU)

5-FU is a pyrimidine analog of the purine base uracil that inhibits the enzyme thymidine synthase, and thus impairs DNA and RNA synthesis.[66] Inhibition of DNA synthesis puts a halt on the rapid proliferation of cancer cells. Several regimens exist for its administration in OSSN, but our favored protocol includes 1% 5-FU drops four times daily for 1 week, followed by 3 weeks off. (Figure 1C, 1D) We generally use 1% 5-FU drops for a total of 4 cycles. Other reported regimens vary widely with it being used as frequently as four weeks per cycle or as scarcely as 2–4 days per month in a pulse-dose fashion.[30],[67–69] A recent large study using 5-FU as primary therapy for OSSN showed efficacy of 85%, which is similar to the other available agents. In this study, 1% 5-FU was used for four weekly cycles four times daily with a 3 week drug holiday between each cycle.[32] Published tumor recurrence rates range from 1.1%[70] to 43%[30] depending on the study design and the length of follow up. Long-term efficacy of 5-FU is not established, especially for invasive squamous cell carcinoma.

5-FU is associated with more side effects compared to interferon, as it also affects the proliferation of normal rapidly dividing epithelial cells and fibroblasts. These side effects include transient lid edema, conjunctival hyperemia, superficial keratitis, filamentary keratitis and on rare occasion, superficial stromal melting.[25,67] Concurrent use of topical steroids and lubricating drops can alleviate most symptoms of ocular surface dryness. Systemic 5-FU treatment for other cancers can lead to punctal and canalicular stenosis. This has not been reported with topical 5-FU.[68,71] 5-FU is less expensive than interferon and is compounded at around \$75 per bottle in the United States, which typically lasts for two cycles. While it does require compounding, no refrigeration is needed.

3.3. Mitomycin C (MMC)

MMC is an antimetabolite isolated from *Streptococcus caespitosus*, which acts as a DNA alkylating agent, thus inhibiting mitosis. Different concentrations of MMC have been used for the treatment of OSSN with higher concentrations causing greater degrees of epithelial toxicity. Although a concentration as low as 0.002% has been reported in one series,[72] the most common regimens are 0.02% or 0.04% drops.[38,39],[73–75] Our preferred protocol is to use MMC 0.04% 4 times daily for a week, then two to three weeks off until the eye is quiet and then repeat. In general, patients may need a total of 3 cycles for the tumor to resolve.[38,39],[73–75] As primary therapy for non-invasive OSSN, MMC has a relative resolution rate of 40.87 compared to placebo.[40] Recurrences can be re-treated with MMC with successful outcomes.[38] (Figure 1E, 1F)

As described above for interferon, MMC may also be given post-operatively for positive margins. As an adjuvant post-operative therapy, MMC has been reported to decrease the incidence of recurrence from 66.7% to 5.9%.[76] It can also be used pre-operatively for chemoreduction [25][39] and intra-operatively as an adjunct to surgical excision.[77] The problem with MMC is its toxicity to the epithelial surface and topical preservative free tears and steroid drops are often needed to alleviate this toxicity.[25][36,78,79] Other side effects include limbal stem cell deficiency in about 12% of treated patients, and punctal stenosis in 14% of patients.[73,74,78–81] The use of punctal plugs and topical steroids may be

indicated in patients that receive topical MMC.[25][36,78,79] Another disadvantage of MMC compared to 5-FU is its cost at about \$200/bottle in the United States, its need for refrigeration, and compounding at a pharmacy.

Other experimental agents tried:

3.4. Anti-vascular endothelial growth factors (anti-VEGF)

Anti-VEGF agents such as bevacizumab or ranibizumab are monoclonal antibodies against VEGF that can inhibit angiogenesis. The expression of VEGF has been detected in conjunctival squamous cell carcinoma,[82] but its clinical utility is controversial. Published case reports and case series have exhibited variable results for intralesional bevacizumab or ranibizumab injections; their efficacy is still unclear. Some have suggested better efficacy for treating conjunctival rather than corneal lesions.[43] One study showed success in treating recurrences refractory to therapy with other topical agents.[41] There is also some very limited evidence that anti-VEGF agents may have a role in the treatment of extensive squamous cell carcinoma. Three out of five patients with diffuse invasive squamous cell carcinoma of the conjunctiva that received a median of 22 ranibizumab injections experienced complete regression of their disease.[41] Another study showed complete resolution in only 2 out of 6 patients, with a total reduction in tumor size ranging between 42–100% among all 6 patients.[42] No local or systemic side effects have been reported with the use of anti-VEGF agents for OSSN, but the cost can be quite limiting. Several other studies have not found these agents to be effective in the treatment of OSSN,[43–45] so recommendation for their use remains unclear.

3.5. Retinoic acid

Retinoic acid, a synthetic analogue of vitamin A, plays a role in cellular growth and differentiation of epithelial cells. It has also been used alone or in combination with interferon for the treatment of OSSN lesions [46]. In a series of 89 patients that received combination therapy with interferon and retinoic acid, complete tumor resolution was achieved in 98% of them with a recurrence rate of 2.3% after a mean follow up of more than four years.[46,47]

3.6. Aloe Vera

The use of aloe vera in the form of eye drops has been reported in one case,[48] with resolution after 3 months of continuous use 3 times per day. However, the lesion was not biopsy-proven OSSN at diagnosis due to patient refusal. Further research is required to assess the putative mechanism of action of aloe vera in OSSN and whether it can be considered as a method of treatment.

5. Diagnostic modalities

Histopathological examination following an excisional or incisional biopsy provides a definitive diagnosis (Figure 2). Less invasive methods that can aid in diagnosis of OSSN are exfoliative cytology, *in vivo* confocal microscopy, and high resolution spectral domain optical coherence tomography. The use of exfoliative cytology is limited to identifying

superficial dysplastic lesions. By definition, it cannot assist in the grading of epithelial dysplasia or exclude microinvasive growth, which requires a full thickness assessment of the involved tissue. Careful preparation and immediate analysis after tissue sampling are crucial for obtaining reliable results.[83] *In vivo* confocal microscopy[84,85] is another way to morphologically assess individual cells for dysplasia or neoplasia, but its use requires substantial technical expertise. The efficacy of confocal microscopy in the diagnosis of OSSN has been variable, and discerning neoplasia on confocal microscopy is challenging.[86]

While most often OSSN can be diagnosed clinically, sometimes this is difficult, especially in the setting of other ocular surface disease or inflammation. A novel way to diagnose subtle or suspicious lesions is by performing an “optical biopsy” with the use of high resolution (5–10µm) or ultra high resolution (3–5µm) spectral domain optical coherence tomography (HR OCT). High resolution OCT is particularly useful at detecting epithelial thickening and differentiating epithelial lesions from subepithelial lesions of the conjunctiva and cornea.[87,88] It is non-invasive, non-contact and can be used for the initial diagnosis of OSSN, the detection of OSSN in the presence of concomitant ocular surface disease, and during the follow up of patients on topical treatments for OSSN.[89]

There are some classic findings on HR OCT for OSSN:

- a. Epithelial thickening. By definition, OSSN is an epithelial neoplasia. Thus, the first thing to look for is a thickened epithelial layer that acquires a hyper-reflective character on HR OCT (Figure 3).
- b. Abrupt transition from normal epithelium. Similar to histopathologic examination of OSSN lesions, an abrupt transition from healthy to diseased epithelium is evident on HR OCT (Figure 3).
- c. In non-invasive lesions, often a distinct plane between the lesion and underlying tissue can be seen. When the lesion is thin, this is easily seen. In thicker lesions, shadowing may occur and the underlying plane may not be as evident (Figure 3). This device is also useful in monitoring response to treatment, so that topical chemotherapy is stopped only after complete resolution of the neoplastic lesion. (Figure 3C, 2D)

4. Expert Commentary

When a patient presents with an OSSN lesion, both surgical and medical approaches to resolution should be considered. As discussed above, medical therapy has gained increasing popularity[18] and is advantageous in that it treats the whole ocular surface, treating subclinical and microscopic disease. Topical therapy can be used for small primary disease (Figure 2), but is especially helpful in large, annular, or multifocal disease in which surgical excision could induce symblephara or limbal stem cell deficiency (Figure 1).[24,25]

In terms of which medication to use, this is determined by patient preferences, ability to tolerate surface pain, and compliance. Our favored treatment is with topical interferon eye drops as they are well tolerated and gentle to the ocular surface. We use 1 MIU/ml four

times daily until the lesion resolves, which is usually 4 months[54] (Figure 1A, 1B). The downside of interferon is that it is used daily, is costly, and requires refrigeration. Our second favorite chemotherapy drop is 5-FU. This drop is cycled, and we do four times a day for a week and then off for 3 weeks. In general, we do 4 cycles, which means that it generally takes four months for the OSSN lesion to resolve (Figure 1C, 1D). 5-FU does cause epitheliopathy and pain. Although the disadvantage is pain, 5-FU is inexpensive, and requires no refrigeration. Many patients find the one-week cycle easy to handle in terms of compliance. The most painful medication is MMC. It can be extremely epithelial toxic. This is cycled just like the 5-FU, using it four times daily for a week in concentration of 0.02% or 0.04% and then off until the eye is quiet, usually 2 or 3 weeks. This medication is not kind to the ocular surface, requires aggressive topical lubrication and steroids to control pain, and a punctal plug to avoid punctal stenosis and nasal mucosal irritation. While effective (Figure 1E,1F), it is our least favorite. All of the topical medications above represent off label use of approved medications, and patients need to be aware of this as well as that compounded medications are often not covered by insurers; most of the time they are initially denied, but will be covered when the patient appeals.

When compliance is an issue, we favor injections of interferon, and this is given subconjunctivally. We give weekly 3 MIU/0.5 mL, but, as mentioned above, others have used even higher doses in a monthly fashion.[55,56] IFN- α 2b comes in an injection-ready solution or powder. We like the 18 million multidose vial; it requires no compounding as it is commercially available. The injections do cause a “flu” like syndrome which generally lasts 6 hours after the injection. This is treated with acetaminophen at the time of injection and 4 hours later. The number of injections needed depends on the tumor size/volume. Most lesions resolve with 4 to 5 injections.

6. Conclusion

Topical chemotherapy has proven itself a viable option in the treatment of OSSN either as a primary treatment, as chemoreduction, or as a post-operative adjunct when margins are positive. Interferon- α 2b, 5-fluorouracil, and mitomycin C are particularly helpful especially in cases of large, annular, or recurrent lesions. These agents have proven their efficacy with the average time to resolution from initiation of treatment being 4 months. Topical chemotherapy is an important tool within the treatment repertoires for the management of ocular surface squamous neoplasia. Its role in invasive squamous cell carcinoma remains uncertain.

7. Five year view

Recent surveys among cornea specialists as to the standard of care for the treatment of OSSN[18] have shown a rise in the use of topical chemotherapy agents. We believe that this trend will continue. The advent of HR-OCT for diagnosis of even subtle OSSN lesions and its use to guide management – especially in the setting of complex ocular surface disease – has resulted in a paradigm shift in recent years with more ocular surface specialists choosing topical chemotherapy as a primary treatment for OSSN.

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Key issues

- Ocular surface squamous neoplasia commonly presents as a non-pigmented lesion of the conjunctiva near the limbus.
- OSSN lesions can be diagnosed clinically by their gelatinous, papillary or leukoplakic appearance. They often extend as a cellular growth on the cornea (it appears like frosting) and stain with rose bengal.
- Diagnosis is confirmed by biopsy; other methods to aid in diagnosis include confocal microscopy, exfoliative cytology, and high resolution OCT.
- High-resolution OCT presents a novel diagnostic method in delineating epithelial neoplasms from subepithelial lesions with similar clinical presentation.
- Topical chemotherapy is becoming the favored approach in the treatment of OSSN, especially for diffuse, annular or multifocal lesions.
- Topical treatments include interferon $\alpha 2b$, 5-fluorouracil and mitomycin C, with interferon being the most gentle on the ocular surface and mitomycin being the most toxic.
- Choice of which agent to use should be tailored to patient factors such as compliance, the ocular surface, logistic of treatment schedules, access to a compounding pharmacy and cost.
- Other topical medical treatments that are yet to be fully evaluated include anti-VEGF agents, retinoic acid, and aloe vera.

Figure 1.

A: Slit-lamp photograph of a large OSSN with papillary appearance that involves at least 5 clock hours of the limbus in a 94 year-old woman. **B:** Slit-lamp photograph after 6 months of topical interferon treatment, at a dose of 1 MIU/ml four times daily. **C:** Slit-lamp photograph of an elevated OSSN lesion in a 70 year-old male, which recurred after 3 excisions. **D:** Slit-lamp photograph after 4 one week cycles of treatment with topical 1% 5-FU drops with complete resolution of the lesion (1 week on, 3 weeks off). Residual haze at the site of the lesion. **E:** Slit-lamp photograph of a fungating OSSN lesion in a 65 year-old

female. **F:** Slit-lamp photograph showing resolution of the lesion after 4 weekly cycles of MMC. (1 week on, 2–3 weeks off)

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Figure 2.

Histopathological examination of an excised specimen discloses mucosal epithelium that displays faulty epithelial maturational sequencing extending up to full thickness, with no invasion of the underlying tissue. Diagnosis is conjunctival intraepithelial neoplasia, in situ. (stain, hematoxylin–eosin; original magnification, X20).

Figure 3.

A: Slit lamp photograph of a raised leukoplakic lesion that stains with Rose Bengal. **B:** HR OCT shows thickened hyper-reflective epithelium (asterisk) with an abrupt transition (circle) from the adjacent normal epithelium (white arrow). Dashed line at base of epithelium **C:** Slit lamp photograph showing resolution of the lesion in A after 4 cycles (1 week on, 3 weeks off) of 5-fluorouracil 1% drops. **D:** HR OCT after 4 months of treatment with 5-FU confirms resolution of the OSSN lesion and restoration of normal thin epithelium in the same location. Dashed line at base of epithelium.

Table 1

Primary ocular surface squamous neoplasia: Side effects and recurrence rates after surgery or topical chemotherapy* .

Modality	Author/year	Population/n	Response Rate	Follow up (months)	Recurrence Rate	Side Effects
Surgery	Galor et al / 2012 [65]	389	N/A	23.4 (mean)	11.3% (44/389)	Not reported
	Tabin et al / 1997 [22]	79	N/A	54 (mean)	39% (31/79)	Not reported
	Maudgil et al / 2013 [91]	60	N/A	32 (mean)	12.8% (8/60)	Not reported
IFN	Shields et al / 2013 [56]	81	95% (77/81)	11 (median)	5% (4/81)	Irritation (4%) Conjunctival redness (5%) Superficial punctate keratitis (4%) Conjunctival follicles (1%)
	Nanji et al / 2014 [23]	49	100% (49/49)	21 (median)	3% (2/49)	Pain (27%) Irritation (53%) Itching (12%) Conjunctival redness (29%)
	Schechter et al / 2008 [61]	28	96.4% (27/28)	42.4 (median)	3.7% (1/27)	Conjunctival hyperemia & follicles (12%)
5-FU	Joag et al / 2016 [32]	44	82% (36/44)	10 (median)	11.1% (4/36)	Pain (39%) Tearing (23%) Photophobia (14%) Itching (9%) Swelling (5%) Infection (2%)
	Parrozzani et al / 2011 [68]	41	100% (41/41)	90 (mean)	7.3% (3/41)	Not reported
	Al-Barag et al / 2010 [69]	15	100% (15/15)	14.5 (mean)	6.7% (1/15)	Eyelid skin irritation Conjunctival redness
MMC	Besley et al / 2014 [90]	93	79.1% (73/93)	23 (mean)	15.1% (14/93)	Irritation (48.8%) Swelling (9.3%) Corneal erosion (0.8%)
	Ballalai et al / 2009 [73]	23	100% (23/23)	50 (mean)	4.3% (1/23)	Corneal erosion (17.4%)
	Hirst / 2007 [40]	26	92% (24/26)	3 (mean)	0%	Irritation Conjunctival redness

N/A, not applicable

* 3 largest studies for each category selected

Table 2

Treatment regimens of the principal topical medications used for ocular surface squamous neoplasia.

	Interferon alpha-2b	5-Fluorouracil	Mitomycin C
Regimens	Drops: 1 million IU/mL QID until resolution (mean, 4 months) (also 1–3MIU/ml used) [23,58–61] Injections: 3 million IU/.5cc injection/1–3×week (mean, 4–5 weeks) or 10 million IU/month [55] [56]	Drops: 1% QID for 1 week followed by 3 weeks off medication [32](mean, 4 cycles) 1% QID for 2–4 days followed by 30 days off medication [30,69](mean, 6 cycles) 1% QID for 4 weeks continuously with 3 months between courses. [68]	Drops: 0.04%, QID for 1 week followed by 3 weeks off medication(mean, 4 cycles) [90]. 0.04% QID 1 week on 1 week off [38,39],[74](reported range 2 to 6 cycles) 0.02% QID for 2–4 weeks [73] 0.002% 4 times daily until resolution [72]

QID= 4 times a day, **IU**= International units