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REVIEW ARTICLE

# Medical treatment for ocular surface squamous neoplasia

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Ocular surface squamous neoplasia (OSSN) is the most common non-melanocytic tumour of the ocular surface. Surgical excision with wide margins using the "no-touch" method was originally the most popular treatment for OSSN. However, in the past two decades, the use of topical medications for OSSN treatment has gained a reputation amongst ophthalmologists for being an effective alternative to surgical excision. Furthermore, technological advancements, such as those seen in high-resolution optical coherence tomography (HR-OCT) for the anterior segment, have facilitated the diagnosis and monitoring of OSSN. When selecting a topical agent, interferon alpha-2b (IFNα-2b) and 5-fluorouracil (5-FU) are two of the gentlest medications used for OSSN and are often considered first line therapies due to their high-resolution rates and mild side effect profiles. Mitomycin C (MMC), on the other hand, has a highly toxic profile; therefore, while effective, in our hands it is considered as a second-line treatment for OSSN if the other modalities fail. In addition, newer and less studied agents, such as immune checkpoint inhibitors, retinoic acid, aloe vera, and anti-vascular endothelial growth factor have anti-neoplastic properties and have shown potential for the treatment of OSSN. We enclose an updated literature review of medical treatments for OSSN.

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## INTRODUCTION

The term ocular surface squamous neoplasia (OSSN) encompasses several conjunctival and corneal epithelial malignancies with variable degrees of invasiveness ranging from squamous epithelial dysplasia to invasive squamous cell carcinoma (SCC) [1]. OSSN generally presents in the temporal and nasal exposure zone, at the limbus, but may appear anywhere on the bulbar surface, or less commonly, the forniceal and tarsal surfaces. Salient clinical features include a gelatinous, papillary, leukoplakic, or opalescent appearance. Hairpin neo-vascularisation and feeder vessels are also typically seen leading to the site of the tumour [2, 3]. While often diagnosed clinically, by impression cytology, or full thickness biopsy, the development of anterior-segment high-resolution optical coherence tomography (HR-OCT) technology has facilitated the process of diagnosing and monitoring OSSN. By providing high-resolution cross-section images of the cornea, OSSN can be differentiated from other ocular surface lesions rapidly and in a non-invasive manner [3–11].

Surgical excision using a "no-touch" method has been the gold standard treatment for OSSN due to its potentially rapid resolution time, ability to provide a diagnosis, and low recurrence rates when margins are negative [12–14]. However, surgical excision may be associated with several unfavourable outcomes, such as conjunctival scarring, symblepharon, and limbal stem cell deficiency with repeated excision or if the tumour is overlying several limbal clock hours [15–17]. A recent study by Bowen et al. revealed that surgical excision is associated with recurrence frequencies as high as 31% (mean follow up of 42 months) when the excised tissue is found to have positive margins and 14% when the excised tissue had negative margins [18]. Therefore, the goal of surgery is clear margins to minimise the risk of tumour persistence [13, 14, 18, 19].

Within the past 20 years, medical treatment of OSSN with topical immuno- and chemotherapy has gained popularity amongst ophthalmologists as an alternative to surgical excision as the primary treatment option, for neoadjuvant therapy, and as intra- and postoperative adjuvant therapy [12, 20]. Additionally, the neoadjuvant use of topical chemotherapy has proven to be effective in significantly reducing the size of OSSN lesions measuring 6 limbal clock hours before ultimately being surgically excised [19]. Moreover, studies have shown that the adjuvant use of postoperative immuno- or chemotherapies are helpful to reduce the frequency of recurrences in cases with positive surgical margins [14, 18].

The most popular topical treatment options include interferon alpha-2b (IFNα-2b), 5-fluorouracil (5-FU), and mitomycin C (MMC) [12, 20–22]. Other topical medications that are infrequently used in the treatment of OSSN include retinoic acid, anti-vascular endothelial growth factor (anti-VEGF), and aloe vera [23–31]. Finally, several studies support the potential of newer medications, such as antibodies against programmed death-1 (anti PD-1), to aid in the treatment of select cases of squamous cell carcinoma [32–38]. These medications have been sporadically applied to the treatment of select cases of OSSN [33, 38].

## MOST POPULAR MEDICAL THERAPIES USED FOR THE TREATMENT OF OSSN

### 5-fluorouracil

5-FU is a structural analogue of thymine that inhibits thymidylate synthase, an enzyme that catalyses the formation of

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nucleotides essential for DNA synthesis. This results in a cascade of events that ultimately inhibits the rapid proliferation of cancerous cells that rely heavily on DNA synthesis for division and growth [39]. The FDA has approved the use of 5-FU for the treatment of patients with adenocarcinoma of the breast, stomach, pancreas, colon, and rectum. The recommended administration route is via intravenous bolus or intravenous injection.

Since its first use in 1986, 5-FU has gained popularity amongst ophthalmologists as an effective agent for primary and adjuvant treatment for OSSN [12, 14, 21, 40–45]. In our hands, it's generally administered in cycles of four drops per day for 1 week followed by a 3-week resting period of no medication [40, 42, 44]. These cycles are repeated until complete tumour resolution is seen, which typically requires ~4 cycles (4 months) [42, 44] (Fig. 1). Other administration regimens have been studied, such as pulse dosing, where 5-FU is administered 4 times per day for 2 to 4 consecutive days per month [45]. In another study 5-FU was administered for 4 weeks continually followed by 3 months of no treatment until the next cycle [43]. The efficacy of 5-FU as a primary treatment for OSSN has been supported with several studies revealing complete tumour resolution in 82 to 100% of patients and recurrence frequencies ranging from 0 to 11% 1 year after complete resolution [42–47] (Table 1).

Compared to IFNα-2b and MMC, 5-FU is the least expensive, costing roughly US$50 per cycle. However, the cost of all compounded medications is typically not covered by insurance and should therefore be considered when choosing a treatment plan. When compared to the other topical medications, 5-FU offers an intermediate side effect profile [42, 44]. The reported side effects following treatment with topical 5-FU include pain, tearing, redness, eyelid oedema, and keratopathy. However, these side effects are usually mild, so most patients can tolerate them well and continue treatment [42–44]. Several recommendations are made to minimise the side effect profile. Manual punctal occlusion is recommended to lower the risk of developing punctal stenosis, application of petroleum jelly on the eye lids is advised to avoid developing irritation, and liberal lubrication with preservative-free artificial tears is recommended throughout the day to help alleviate discomfort that may develop.

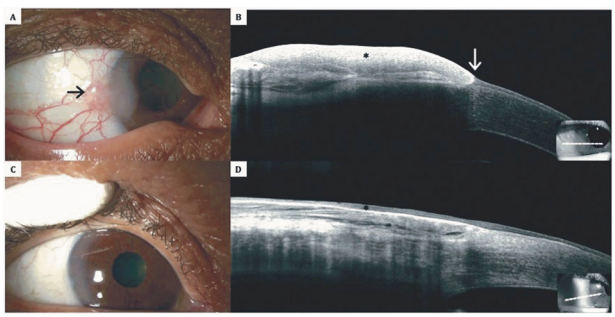


**Fig. 1 Images of an ocular surface squamous neoplasia lesion before and after medical treatment with 5-FU. A** Slit lamp photo demonstrates a gelatinous lesion with feeder vessels on the temporal limbus of the right eye consistent with OSSN (arrowhead), prior to beginning treatment with topical 1% 5-FU. **B** HR-OCT image of the temporal conjunctiva and cornea demonstrates hyper-reflectivity and thickness on the epithelium (asterisk) along with an abrupt transition between normal and abnormal epithelium (arrowhead). Inset represents anatomical location of raster. **C** Slit lamp photo of the right eye after four cycles of topical 5-FU therapy shows clinical resolution of the lesion. **D** HR-OCT image of the temporal conjunctiva and cornea demonstrates thin and normalised epithelium (asterisk) after four cycles of topical 5-FU therapy consisting of tumour resolution. Inset represents anatomical location of the raster.

## INTERFERON ALPHA-2B

IFNα-2b is a naturally occurring low molecular weight glycoprotein that exhibits anti-viral and anti-neoplastic properties. The anti-neoplastic properties of interferons include the ability to induce apoptosis, inhibit angiogenesis, and prolong cell cycle time in cancerous cells [48]. IFNs have a history of being used to treat many other diseases, including cervical intraepithelial neoplasia, actinic keratosis, and metastatic malignant melanoma [49, 50].

Since the first reported use of IFNα-2b for the treatment of OSSN in 1994, the medication gained popularity as an effective alternative to surgical excision [12, 20, 51]. IFNα-2b can be used as a primary or adjuvant therapy and can be administered via subconjunctival injection, eye drops, or using both methods [52, 53]. The most common dosage for topical IFNα-2b eye drops is 1 million IU/ml, and it is typically administered 4 times daily until complete clinical resolution is achieved, which takes ~12 weeks [52, 54–56]. Often it is used 1 or 2 months post clinical resolution as "insurance" for subclinical disease [57] (Fig. 2).

There are several studies in the literature demonstrating the efficacy of IFNα-2b as primary treatment for OSSN, with resolution and recurrence frequencies ranging from 81% to 100% and 0% to 20%, respectively [44, 52, 53, 58–61] (Table 1). In addition, IFNα-2b has been used for neoadjuvant and adjuvant therapy. In one study, 18 eyes with large OSSN lesions (measuring 6 limbal clock hours) were treated with topical IFNα-2b 4 times daily ($n = 12$) or with intralesional IFNα-2b ($n = 3$). In 7 eyes, clinical resolution was achieved within a median of 5 months, and in 5 eyes, immunoreduction was achieved before ultimately undergoing surgical excision [19]. In other studies, the use of postoperative topical IFNα-2b was found to lower the frequency of recurrence to a level near that of patients with negative surgical margins [14, 18].

Moreover, IFNα-2b eye drops offer a very minimal side effect profile and is the least toxic topical medication compared to MMC and 5-FU [55]. Some of the major disadvantages of using topical IFNα-2b eye drops to treat OSSN are that the medication requires refrigeration and is the most expensive of the three topical medications, with an approximate out-of-pocket cost of US$800 per month in the United States [3, 15, 54]. Compounded eye drops are usually initially rejected by insurers. However, subconjunctival IFNα-2b is commercially available and thus usually covered. In addition, the subconjunctival route can be an advantageous option for patients that struggle to comply with a medication regimen, who have a tumour superiorly where the drops are less likely to get to, and for those willing to commit to frequent clinic visits. The most common side effect of IFNα-2b administered via injection is the development of flu-like symptoms, which patients develop for roughly 48 h after receiving the injection [52, 62]. To help minimise the flu-like symptoms patients can be advised to take 1 g of acetaminophen every 4 h until the following day. Despite the excellent results with topical IFNα-2b for the treatment of OSSN, the future use of this medication remains unknown due to a production discontinuation of IFNα-2b.

## MITOMYCIN C

MMC is an anti-neoplastic and anti-biotic agent that is isolated from *Streptomyces caespitosus* [63]. After metabolic activation, which happens under aerobic conditions, MMC becomes an alkylating agent that forms free radicals. These free radicals then cause DNA strand breaks, impaired DNA synthesis, and a cytotoxic environment, which ultimately results in the induction of apoptosis in proliferating and non-proliferating cells [64]. Therefore, MMC has been used in other fields for the treatment of colorectal and gastric carcinoma, and bladder squamous cell carcinoma [65–67].

In ophthalmology, MMC can be used as a primary treatment medication for OSSN, intraoperatively as an adjuvant to surgical excision, or post-operatively in patients with positive margins

**Table 1.** The table compiles information on of the major efficacy studies that were referenced in the paper for topical 5-fluorouracil, interferon α-2b, and mitomycin C including dose, regimen, number of treatment cycles used, follow up time, and recurrence and response frequencies.

**5-Fluorouracil 1%**

| Studies | Population (*n*) | Regimen | Mean treatment cycles (median, range) | Mean follow up in months (median, range) | Recurrence frequencies at 1 year | Response frequency |
|---|---|---|---|---|---|---|
| Venkateswaran et al. [44] | 54 | QID × 1 weeks followed by 3 weeks of no treatment | 4.2 (4, 2–12) | 15.8 SD = 9.7 | 11.4% | 96.3% |
| Parrozzani et al. [43] | 41 | QID × 4 weeks followed by 3 months of no treatment | 1.5 (1–3) | 105 (60–171) | 9.8% | 82% |
| Joag et al. [42] | 44 | QID × 1 weeks followed by 3 weeks of no treatment | 3.8 (4, 1–3) | 10 (2–77) | 6% | 82% |
| Al-Barrag et al. [46] | 15 | QID × 4 days followed by 30 days of no treatment | 6.4 (6, 6–12) | 15 (6–30) | 6.7% | 100% |
| Yeatts et al. [45] | 7 | QID × 2–4 days followed by 30–45 days of no treatment | 3.75 (2–5) | 18.5 (7–36) | 43%[a] | 100% |
| Sun et al. [47][b] | 6 | Subconjunctival/perilesional injections (25 mg/0.5 ml) | 17 injections (15.5, 9–30) | 3 years after initiation of treatment | 0% | 100% |

**Interferon α-2b**

| Studies | Population (*n*) | Regimen | Mean treatment duration in months (median, range) | Mean follow up time in months (median, range) | Recurrence frequencies at 1 year | Response frequency |
|---|---|---|---|---|---|---|
| Shields et al. [61] | 64 | QID until complete tumour resolution (1 MIU/cc) | 5.8 (5, 0.5–13) | 23.0 (14.4, 1.3–114.6) | 3% | 95% |
| Venkateswaran et al. [44] | 48 | QID until complete tumour resolution (1 MIU/cc) | 4.2 (4, 2–8) | 20.9 SD = 13.3 | 4.5% | 81.3% |
| Kusumesh et al. [60] | 24 | QID until complete tumour resolution (1 MIU/cc) | (3.25, 2–4) | 18.81 (14–22) SD = 3.81 | 0%[c] | 91.6% |
| Shah et al. [59] | 20 | QID until complete tumour resolution (1 MIU/cc) | 7 (6, 1–12) | 7, (6, 1–12) | 4%[c] | 83% |
| Karp et al. [53] | 15 | Subconjunctival/perilesional injection (IFN 3 MIU in 0.5 ml) and 10/15 with adjuvant topical (1 million IU/ml) QID until complete tumour resolution | 6.13 injections (6, 2–11) | 66.3% (55, 4.4–144) | 7%[c] | 87% |
| Karp et al. [58] | 5 | Topical IFN (1 million IU/ml) QID until complete tumour resolution | 11.6 (10, 4–22) | 17.6 (10, 7–28) | 20%[c] | 100% |
| Vann et al. [52] | 6 | Combination of subconjunctival/perilesional injection (IFN 3 MIU in 0.5 ml) and topical interferon drops (1 MIU/ml) QID until complete tumour resolution | 4.5 weeks (4.5, 3–6) | 7.2 (2–11) | 0%[c] | 100% |

**Mitomycin C**

| Studies | Population (*n*) | Regimen | Mean treatment cycles/ duration (median, range) | Mean follow up time in months (median, range) | Recurrence frequency | Response frequency |
|---|---|---|---|---|---|---|
| Besley et al. [105] | 93 | Topical MMC (0.4 mg/ml) QID × 1 week followed by 3 weeks of no treatment (cycles) | 3.3 cycles (2–6) | 23 | 15.1% | 79.1% |
| Ballalai et al. [73] | 23 | Topical MMC 0.02% QID × 4 weeks | 4 weeks | 44.4 | 4.3%[c] | 100% |
| Hirst [70] | 26 | Topical MMC (0.4 mg/ml) QID × 3 weeks, with crossover of drops if there was no regression within 6 to 8 weeks | Not evaluated | (1 week–1 year) | Not evaluated | 92% |

**Table 1.** continued

| Studies | Population (*n*) | Regimen | Mean treatment cycles/ duration (median, range) | Mean follow up time in months (median, range) | Recurrence frequency | Response frequency |
|---|---|---|---|---|---|---|
| **Mitomycin C** | | | | | | |
| Prabhasawat et al. [69] | 7 | Topical MMC 0.002% QID until complete tumour resolution | 5.2 weeks (2–14) | 30.7 (2–52) | 14.3% | 100% |
| Wilson et al. [71] | 7 | Topical MMC 0.04% QID × 1 week in alternate weeks | 20 days (21, 4–35) | 9 (9, 2–16) | 0% | 86% |
| Frucht-Pery et al. [68][d] | 17 | Topical MMC 0.02%–0.04% QID for 7 to 28 days with retreatment in cases of regrowth | 4.8 weeks (4, 1–12) | 25.4 (24, 12–40) | 6% | 100%[e] |
| Frucht-Pery et al. [75][d] | 3 | Topical MMC 0.02% QID for 10 to 22 days | 15 days (14, 10–22) | 10.7 (12, 4–16) | 0% | 100% |

This table demonstrates data from the efficacy studies referenced in this review paper for the use of medical treatment for ocular surface squamous neoplasia only. Single case reports were excluded.
*MMC* mitomycin C, *IFN* interferon α-2b, *QID* four times daily, *MIU* million international units.
[a]The data represent recurrence frequency after completion of the initial treatment. These patients were treated with additional (3–6) cycles and complete resolution was achieved in the three patients.
[b]To our knowledge, there is only a single study of six patients supporting the use of subconjunctival/perilesional 5-fluorouracil for the treatment of ocular surface squamous neoplasia. Further study is needed to evaluate this modality.
[c]One year recurrence frequency not evaluated.
[d]Patients were treated on a case-by-case basis with variable medication regimen.
[e]Decreased lesion size was noted in all 17 patients, but complete resolution of the tumour was seen in ten patients after initial treatment. The remaining seven patients received additional treatment.



**Fig. 2 Images of an ocular surface squamous neoplasia lesion before and after medical treatment with IFNα-2b. A** Slit lamp photo demonstrates an opalescent lesion on the temporal conjunctiva and limbus of the right eye consistent with OSSN (arrowheads), prior to beginning treatment with topical IFNα-2b. Note leukoplakia, gelatinous features, and feeder vessels. **B** HR-OCT image of the inferior-temporal conjunctiva and cornea demonstrates hyper-reflectivity and thickness on the epithelium (asterisk) along with an abrupt transition between normal and abnormal epithelium (arrowhead). Inset represents anatomical location of raster. **C** Slit lamp photo of the right eye demonstrates clinical resolution of the lesion after completing seven cycles of topical IFNα-2b therapy. **D** HR-OCT image of the inferior-temporal conjunctiva and cornea demonstrates thin and normalised epithelium (asterisk) after seven cycles of topical IFNα-2b therapy consistent of tumour resolution. Inset represents anatomical location of raster.



**Fig. 3 Images of an ocular surface squamous neoplasia lesion before and after medical treatment with MMC. A** Slit lamp photo demonstrates a papilliform lesion on the nasal conjunctiva and cornea of the right eye consisting with OSSN (arrowhead) prior to beginning treatment with 0.04% MMC. Note papillary and leukoplakic features of this elevated tumour. **B** HR-OCT image of the nasal conjunctiva and cornea demonstrates hyper-reflectivity and thickness on the epithelium (asterisk) along with an abrupt transition between normal and abnormal epithelium (arrowhead). Inset represents anatomical location of the raster. **C** Slit lamp photo of the right eye after five cycles of topical MMC therapy shows clinical resolution of the lesion and reveals an underlying pinguecula. **D** HR-OCT image of the nasal conjunctiva and cornea demonstrates thin and normalised epithelium (asterisk) after five cycles of topical MMC therapy consisting of tumour resolution. A subepithelial hyper-reflectivity is consistent with a pinguecula. Inset represents anatomical location of the raster.

[68–71]. Topical MMC eye drops are usually compounded at a concentration of 0.02 to 0.04% [70, 72–74]. However, several administration regimens have been described in the literature, even using super low concentrations of 0.002% [69]. We typically administer MMC 4 times daily for 1 week followed by a 3-week resting period where no medication is administered. The cycles are generally repeated until complete tumour resolution is achieved (Fig. 3). The effectiveness of topical MMC is supported by several studies that demonstrate resolution frequencies ranging from 79 to 100% and recurrence frequencies ranging from 0% to 15.1% [68–73, 75, 76] (Table 1).

In the United States the cost of a bottle of topical MMC can range between US$100 and US$400 and similarly to the other topical medications, it is not typically covered by insurance [15]. The biggest downside of treatment of OSSN with topical MMC is that patients generally exhibit more severe adverse side effects. Pain, redness, tearing, corneal erosion, hyperaemia, punctate staining of the cornea, punctal stenosis and limbal stem cell deficiency have all been reported in patients undergoing treatment with topical MMC [21, 41, 72, 73, 76, 77]. Prior to beginning treatment, punctal plugs are placed to prevent punctal stenosis and application of petroleum jelly on lower eyelid skin is recommended to minimise the risk of irritation. While undergoing treatment, liberal lubrication with preservative-free artificial tears is recommended to help alleviate discomfort.

## LIMITATIONS OF TOPICAL MEDICATIONS FOR THE TREATMENT OF OSSN

In cases where the tumour has invaded the sclera, or extended through Bowman's layer, surgical excision will be required. Clinically the tumour is immobile, and adherent to the sclera, and ultrasound biomicrospcopy may also suggest invasion. Whether clinically suspected or pathologically confirmed with map biopsies, topical medications in these scenarios may be used as a neoadjuvant or chemoreduction before ultimately undergoing surgery. In such cases, the topical medications can shrink the tumour, and then 2–4 mm wide margin surgical excision using a "no touch" technique with adjuvant cryotherapy using a double freeze slow thaw method is recommended [13, 14, 18]. In the case of positive conjunctival margins, the patient can be treated with adjuvant topical therapy to reduce the chances of recurrence [14, 18]. In contrast, positive deep margins would require further excision with sclerectomy and cryotherapy or a plaque brachytherapy (Fig. 4).

## SYSTEMIC THERAPY AS A POTENTIAL TREATMENT FOR OSSN

### Programmed cell death-1 inhibitors

Programmed death-1 (PD-1) is an inhibitory receptor that is expressed on the cell surface of T cells. PD-1 activation is most notably associated with T-cell suppression, and thus suppression of anti-neoplastic activities associated with T cells. Activation of PD-1 occurs upon engagement with the inhibitory ligand, PD-L1, which is expressed by several cell types, including cancer cells [78–80]. In ophthalmology, the level of expression of PD-L1 in neoplastic cells has been corelated with the degree of OSSN tumour invasion [29, 81]. Additionally, upregulation of PD-L1 has been associated with cancerous cells treated with chemotherapy [82]. Therefore, the use of anti-PD-1 and anti-PD-L1 monoclonal antibodies have been studied to avoid developing antineoplastic immunity and aid in cancer treatment [37, 83–87].

The use of anti-PD1 therapy has been studied for various forms of cancer and in several different locations throughout the body [33, 35–38, 88]. The anti-PD1 therapy, nivolumab, has shown some potential as a therapy for squamous cell carcinoma in the head, neck, oesophagus, and anal canal [35–37, 88]. According to the FDA, 240 mg should be administered through intravenous infusion every 2 weeks or 480 mg every 4 weeks. Similarly, the anti-PD-1 agent, pembrolizumab, has been approved by the FDA to treat select cases of oesophageal cancer, melanoma, and squamous cell carcinoma in the head, neck, and skin. Lastly, the anti-PD1 agent, cemiplimab, has been approved for the treatment of select cases of basal and cutaneous squamous cell carcinoma [89].

Some studies have analysed the efficacy of checkpoint inhibitors as a therapeutic option for OSSN. In one study, 5 individuals with advanced conjunctival squamous cell carcinoma with orbital extension were treated with systemic pembrolizumab or cemiplimab after declining orbital exenteration. Four had complete tumour resolution and did not experience a recurrence 2 to 11 months after tumour resolution; however, one patient

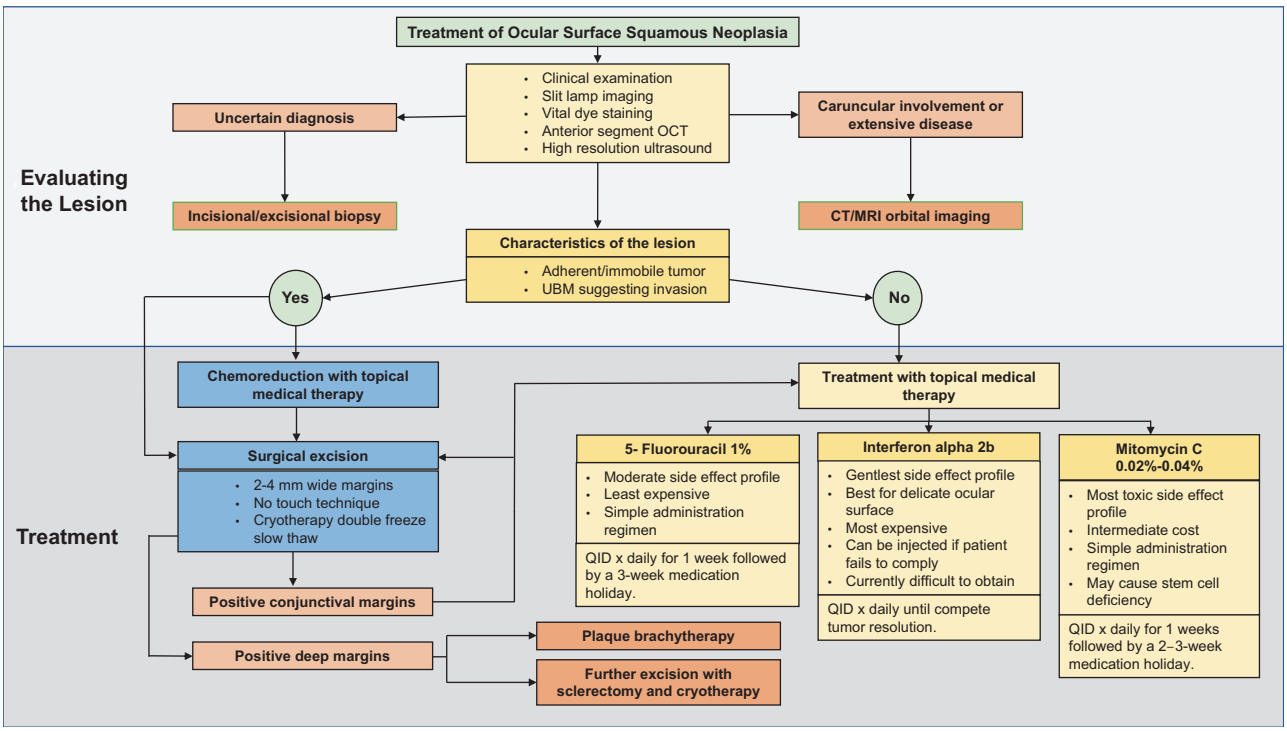


**Fig. 4 Algorithm for ocular surface squamous neoplasia treatment including decision making for primary medical treatment and surgical excision.** Key indications for the use of primary immuno- and chemotherapeutic agents are described as well as treatment for lesions with extension to sclera. QID four times daily, OCT optical coherence tomography, MIU million international units, MRI magnetic resonance imaging, CT computerised tomography, UBM ultrasound biomicroscopy.

showed progressive disease despite completing 3 cycles of pembrolizumab combined with 5-FU and carboplatin. The patient ultimately underwent wide resection and radiotherapy [33].

Another report describes the case of a patient with recurrent conjunctival squamous cell carcinoma that continued to progress despite receiving repeated radiotherapy. Subsequently, the patient was started on intravenous cemiplimab 3 mg/kg every 2 weeks after refusing orbital exenteration. After 19 months of continuous cemiplimab therapy, orbital magnetic resonance imaging revealed that the tumour was no longer progressing and had stabilised [38]. It is not yet known if topical PD-1 inhibitors will have a beneficial effect on less invasive OSSN.

Generally, treatment with checkpoint inhibitors tends to be very expensive in the United States, creating a barrier for physicians who wish to treat their patients with these drugs, raising questions about cost-effectiveness, and contributing to increasing health disparities [90]. The list price for each indicated dose of pembrolizumab is ~US$10,269 when given every 3 weeks and US$20,537 when given every 6 weeks. However, administration, disease management, subsequent care, and adverse events may add to the regimen-related costs listed above. Although anti-PD1 therapy may be very expensive in the United States, in many cases the cost may be covered by insurance companies. Moreover, programs from federal and state governments, manufacturers, non-profits, and other organisations exist and may help lower the cost.

## ALTERNATIVE TOPICAL THERAPIES FOR THE TREATMENT OF OSSN

### Retinoic acid

Retinoic acid is a metabolite of vitamin A that plays an important role in cell growth and differentiation [23, 91]. Retinoids also have potent growth-restricting capabilities in normal, premalignant, and malignant cells, giving retinoic acid anti-neoplastic properties [92]. Topical retinoic acid is primarily used in the field of dermatology for the treatment of acne and psoriasis, and it has been administered systemically to treat acute promyelocytic leukaemia [93, 94].

In most studies, retinoic acid is used in conjunction with IFNα-2b to treat OSSN, therefore the efficacy of retinoic acid as a sole treatment for OSSN is not well elucidated. In one study, 89 eyes with pathologically confirmed OSSN were treated with topical IFNα-2b 1 million IU/ml eye drops 4 times daily and retinoic acid 0.01% once every 2 days. Complete clinical resolution was observed at a frequency of 98% ($n = 87$) after an average of 1.69 months and partial response was seen at a frequency of 2% ($n = 2$) [26].

Retinoic acid 0.01% is moderately priced at about US$75 per 5 ml of medication. Additionally, the reported side effect profile is generally mild and well tolerated. These include allergic papillary conjunctivitis, epithelial microcysts, marginal keratitis, and eye lid irritation [23, 26].

## ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR

Anti-VEGF agents are monoclonal antibodies that block the activity of VEGF, a strong angiogenic factor that is upregulated by neoplastic cells to increase neovascularization and meet their increased metabolic demand [95]. Anti-VEGF agents, such as bevacizumab and ranibizumab, have been studied as potential topical medications for OSSN. In one study of 6 eyes with primary OSSN, treatment with topical 5 mg/ml bevacizumab 4 times daily for 8 weeks led to complete tumour resolution in 2 patients. The other 4 patients where non-responders and were ultimately treated with surgical excision [28]. In another study, 5 patients with biopsy proven conjunctival or corneal squamous cell carcinoma were treated with 0.05 mg of 10 mg/ml subconjunctival ranibizumab one or two times per month. After a median of 22 injections given over an average of 19 months, 3 patients had complete clinical resolution of the tumour and the 2 remaining patients ultimately failed treatment after experiencing an initial partial response [30]. While there have been some successes, others have found minimal or no response the anti-VEGF treatments [24, 25].

To our knowledge, there are no significant side effects associated with the use of topical anti-VEGF agents for ocular surface lesions reported in the literature [28, 30]. However, bevacizumab may exhibit inhibitory effects that result in delayed corneal healing in eyes with epithelial defects [28, 96].

## ALOE VERA

Aloe vera has been used for several centuries due to medical benefits that are observed after ingesting the plant or topical application. Several studies have demonstrated that Aloe vera contains immunomodulatory, anti-inflammatory, antiparasitic, UV protective, antioxidant, antiviral, antidiabetic, and antineoplastic properties [97, 98]. In one case report, a 64-year-old woman with OSSN had complete resolution 3 months after applying concentrated topical aloe vera eye drops 3 times daily as recommended by her friend. In addition, there was no tumour recurrence for 6 years [31]. The cost of aloe vera oil is about US$25 making it relatively inexpensive and widely available. To our knowledge, there is only one case report in the literature where topical aloe vera eye drops is used to treat OSSN, therefore further research must support its efficacy prior to using it as a primary treatment for OSSN.

## HIGH-RESOLUTION OCT FOR OSSN

In addition to the increased use of medical therapies for OSSN, advances in non-invasive diagnostic imaging modalities, such as HR-OCT, ultrasound biomicroscopy (UBM), and in-vivo confocal microscopy (IVCM), have helped ophthalmologists shift towards non-invasive diagnosis, treatment, and vigilance [5, 99, 100]. The gold standard method to diagnose of OSSN has been excisional or incisional biopsy with subsequent histopathological examination. However, excisional biopsy may increase the risk of developing unfavourable sequelae, such as symblepharon, limbal stem cell deficiency, and scarring.

HR-OCT is capable of quickly producing high-resolution, in-vivo, cross-sectional images of the cornea and conjunctiva allowing clinicians to non-invasively evaluate pathologies of the anterior segment, make diagnoses, and monitor patients as they undergo treatment [4, 5, 7–10, 101, 102]. The diagnostic hallmarks of OSSN on HR-OCT include a hyperreflective and thickened epithelium with an abrupt transition between the diseased and normal epithelium [7, 9, 101, 102]. In addition to the morphological findings, epithelial thickness of over 140 um can also be a helpful indicator of potential neoplasia. In a study of 34 eyes with biopsy proven OSSN ($n = 17$) and pterygium ($n = 17$), a custom built, high speed, ultra-high-resolution (UHR) spectral-domain OCT device had 94% sensitivity and 100% specificity of differentiating between the two pathologies, when a cut off of 142 microns was used [8]. In another study, the HR-OCT (RTVue, Optovue, Fremont, CA) findings of 21 eyes with OSSN lesions and 24 eyes with pterygia or pinguecula were compared. When using a cutoff of 120 µm, the sensitivity and specificity frequencies for differentiating between the two groups were 100% for both [7]. In another study with 22 patients with OSSN or pterygium, AS-OCT (Spectralis SD-OCT, Heidelberg Engineering, Heidelberg, Germany) was able to differentiate between the two pathologies with a sensitivity and specificity frequency of 100% with a thickness of 141 um ($p < 0.002$) [103].

Additionally, HR-OCT may assist the surgeon in surgical planning by identifying tumour margins and subclinical disease [57, 104]. In a study of 95 patients with clinically resolved OSSN, HR-OCT detected evidence of sub-clinical disease at frequency of 17% ($n = 16$ patients). The 16 patients with subclinical disease required further

treatment but had a recurrence frequency of 0% compared to recurrence frequency of 12 % in those whose clinical resolution correlated with the HR-OCT findings [57]. Furthermore, a future HR-OCT integrated into a surgical microscope holds potential for visualisation of tumour margins and an "optical Mohs" [104].

## CONCLUSION

Management of OSSN has evolved over the years and topical medications have become excellent alternatives to surgical excision. The decision algorithm is based on tumour characteristics as well as patient factors and physician preferences (Fig. 4). Some advantages of using topical agents are their ability to treat large and multifocal lesions, the ease of use, and patients can avoid the adverse effects associated with a surgical procedure. 5-FU, IFNα-2b, and MMC are the most popular topical agents as they have demonstrated high-resolution rates, with the preferred option mainly based on side effect profile and affordability. Although 5-FU and IFNα-2b exhibit a similar efficacy profile, individuals who use 5-FU more often report mild side effects. 5-FU is preferred in our practice due to lower costs and ease of accessibility. IFNα-2b has become very scarce due to dwindling production in the US. Due to its deleterious side effects profile and higher cost compared to 5-FU, MMC is typically used for OSSN when resolution is not achieved with other options. Additional agents such as retinoic acid, aloe vera, anti-VEGF and potentially anti-PD-1 need further study to evaluate their role in OSSN.

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## AUTHOR CONTRIBUTIONS

DM was responsible for designing the review protocol, writing the protocol and report, conducting the search, screening potentially eligible studies, extracting and analysing data, interpreting results, updating reference lists, and creating the table and figure. AS was responsible for designing the review protocol and screening potentially eligible studies. He contributed to writing the report, choosing the images, extracting and analysing data, and interpreting results. AG and CLK contributed to conception, design, and writing/revision of the report.

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## COMPETING INTERESTS

CLK and AG have a pending PCT/US2022/029842 with the University of Miami, CLK is on the medical advisory board for Interfeen Biologics. All work on this study was performed prior to the MAB position. All other authors have no disclosures.

## ADDITIONAL INFORMATION

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