Management of Ocular Surface Tumors: Excision vs. Topical Treatment

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Abstract

Ocular surface squamous neoplasia (OSSN) encompasses a range of corneal and conjunctival lesions from intraepithelial dysplasia to invasive squamous cell carcinoma. The mainstay of treatment for OSSN has traditionally been surgical excision with wide margins and cryotherapy. Increasing evidence on the efficacy and safety of medical therapy and the avoidance of surgical complications has made topical chemotherapy increasingly popular among corneal specialists. The most common topical agents used for the treatment of OSSN include mitomycin C, 5-fluorouracil, and interferon α2b. Herein, we review recent advances in the surgical and medical management of OSSN and discuss advantages and disadvantages of each approach. The role of ultra high-resolution optical coherence tomography in the diagnosis and treatment of primary and recurrent OSSN lesions is also discussed.

Key words: ocular surface squamous neoplasia; interferon α2b; mitomycin C; 5-fluorouracil; ultra-high-resolution optical coherence tomography.

Relevant evidence-based information

Introduction

Ocular surface squamous neoplasia (OSSN) is the most common non-pigmented tumor of the ocular surface.[1] The term "OSSN" encompasses a broad clinical and pathological spectrum of neoplastic squamous epithelial disorders ranging from intraepithelial dysplasia to conjunctival or corneal intraepithelial neoplasia (CIN) (also known as carcinoma *in situ*) to frank squamous cell carcinoma of the cornea and conjunctiva.[2,3] In a survey of 771 nonmelanocytic conjunctival tumors from a single ocular oncology center 23% (179 tumors) were classified as OSSN.[1]

Clinically, OSSN lesions can have a gelatinous, papillary, opalescent or leukoplakic appearance, they can be flat or raised, localized or diffuse, and may have a feeder conjunctival vessel.[4] OSSN is thought to arise from the limbal stem cells. Thus, it is most commonly found in the interpalpebral region involving the cornea and/or bulbar conjunctiva with the tarsal conjunctiva being less frequently involved.[5]

The incidence of OSSN is higher in equatorial regions and in older white men (mean age at presentation, 56 years).[6] For example, its incidence in the United States is 0.3-8.4 per million people per year[7,8], while in Australia it has been reported as high as 19 per million people per year[6] and in Uganda as 12 per million people per year.[9]

Putative mutagenic factors implicated in the pathogenesis of OSSN include ultraviolet radiation[10], smoking, immunosuppression, genetics, ocular surface injury, exposure to chemicals (petroleum products, beryllium, trifluridine, arsenic), and vitamin A deficiency.[11] Though the human papilloma virus (HPV) is known to be carcinogenic in cervical and head and neck squamous cell carcinomas, current data regarding HPV infection in the pathogenesis of OSSN is still unclear, but it can be a cofactor in its development in already susceptible hosts.[12] 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)[13,14], or genetic predisposition as in xeroderma pigmentosum[15], should be sought.

Surgical Excision: Goals and Limitations

Historically, the mainstay of treatment for OSSN has been surgical excision with a "no-touch" technique and additional cryotherapy.[16] The principles of this technique include obtaining wide margins (typically 4 mm) and avoiding any contact of the surgical instruments with the tumor to prevent tumor seeding. The lesion is removed *en bloc*. For tightly adherent tumors, a partial sclerectomy may be required. For tumors involving or abutting the cornea, absolute alcohol is applied first and then the devitalized epithelium is scraped again taking 3-4 mm margins. The scleral bed is cauterized to ensure hemostasis and kill any residual tumor cells and cryotherapy (via a double freeze-thaw cycle) is applied to the limbus and the conjunctival margins. For closure, we favor an amniotic membrane transplant is secured over the resultant conjunctival defect with tissue glue rather than pro-inflammatory sutures. Primary closure is an option used by others. Fresh instruments are used during this final step again as an additional measure to prevent tumor seeding.

Surgical excision with cryotherapy has been the gold standard as the initial management strategy of OSSN because it is both diagnostic and therapeutic. It quickly establishes the diagnosis, provides complete control of the disease if the margins are clear, and is covered by most insurers.

However, the track record for prevention of recurrences after surgery alone has been relatively poor. Microscopic subclinical residual disease is thought to be responsible for the reported recurrence rates of 33% with negative surgical margins[17,18] and up to 56% when margins are positive.[18] Moreover,

extensive surgical excision can lead to limbal stem cell deficiency or diplopia due to subsequent scarring and symblepharon formation. Infection, formation of pyogenic granuloma, and damage to the sclera and retina from excessive cryotherapy are less frequent complications.

Topical treatment: primary and adjunct role

The aforementioned limitations led to the development of alternative and complimentary medical therapies to surgical excision over the last couple of decades. The three most effective compounds are mitomycin C (MMC)[19-26], 5-fluorouracil (5-FU)[27-29], and interferon α2b (IFN-α2b).[30-32] Other topical agents with less established efficacy include anti-vascular endothelial growth factor (anti-VEGF)(33, 34) and retinoic acid.[35,36]

Mitomycin C is an alkylating agent that inhibits cell division by causing DNA cross-linking. The two most common dosing regimens for the treatment of OSSN are either 0.02% or 0.04% topical drops. The 0.02% formulation is gentler to the corneal epithelium and can has been given four times daily continuously for 28 days or until the lesion resolves.[20] Treatment with the 0.02% topical drops for 2 weeks or less is associated with a recurrence rate of 35%.[20] The 0.04% formulation causes greater epithelial toxicity and is, thus, typically used four times daily in week on-week off cycles until clinical resolution.[37]

Reported rates for resolution of OSSN with topical MMC range from 75-100%. Recurrences were seen in 0-35% of treated cases; most of them were successfully re-retreated with MMC. It has also been used intra-operatively (0.02% on the scleral bed for 5 minutes) as an adjunct to surgical excision and pre-operatively as chemoreduction.[19-25] The efficacy of topical MMC for the treatment of OSSN was confirmed by a randomized placebo-controlled study with 24 out of 26 MMC-treated OSSN lesions resolving clinically, whereas none of 20 placebo-treated OSSN lesions responded to therapy.[26]

The major limitation of topical MMC is the pain and corneal epitheliopathy that it induces. Administration in alternate weeks with a topical steroid and frequent lubrication reduces discomfort and enhances patient compliance.[37] Long-term complications of topical MMC include punctal stenosis and limbal stem cell deficiency. The use of punctal plugs is, thus, indicated as a preventative measure since, at least in one study, 14% of treated patients developed epiphora from punctal stenosis.[38] Recurrent corneal erosion and limbal stem cell deficiency have been reported in about 17% of patients that received MMC for OSSN lesions.[39,40] Other limitations for the use of topical MMC include its cost at about $250/cycle at the time of this writing, the requirement of a compounding pharmacy and its instability at room temperature.[41]

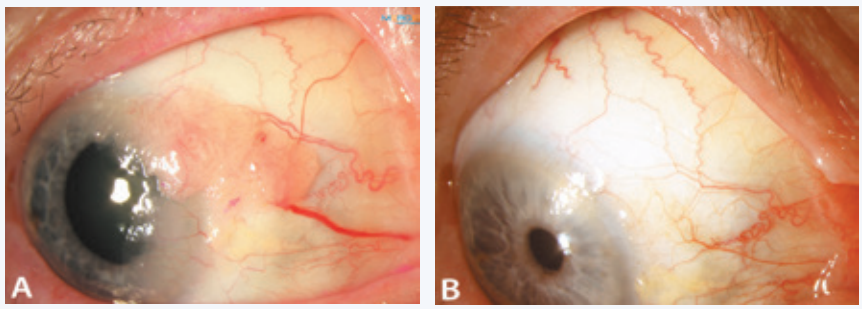

Figure 1. Slit lamp photograph of an ocular surface squamous neoplasia with gelatinous and papillary features before (A) and after (B) treatment with 2 one week-on, three weeks-off cycles of topical 5-fluorouracil 1% four times daily. The lesion resolved completely after a total of 4 cycles of treatment.

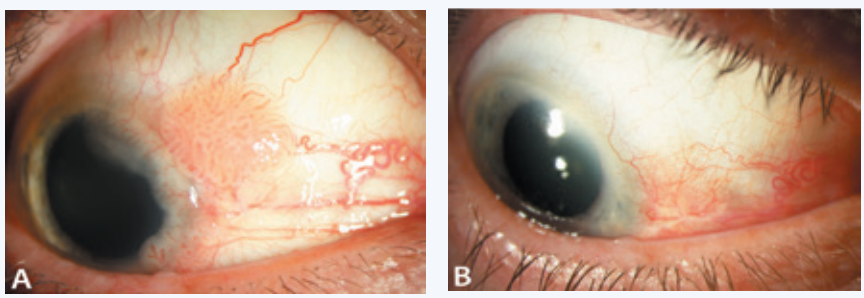

Figure 2. Slit lamp photograph of a papillary ocular surface squamous neoplasia with feeder vessels before (A) and 4 months after (B) treatment with topical interferon α2b 1 million IU/ml drops four times daily.

5-Fluorouracil is a pyrimidine analogue that inhibits the enzyme responsible for the synthesis of the DNA base thymidine. Thus, rapidly dividing tumor cells that rely on DNA synthesis for proliferation are preferentially affected. The most common protocol for its administration is 1% 5-FU drops four times daily for 7 days, followed by 30 days off. Similar to MMC, 5-FU can be used as primary treatment for OSSN lesions or as an adjunct to surgical excision (Figure 1). Clinical resolution with topical 5-FU has been reported in about 85% of cases with recurrence rates ranging from 12.5 to 43%.[27-29] However, its efficacy for the treatment of invasive OSSN (i.e. squamous cell carcinoma) remains controversial.

Though not as painful as MMC, 5-FU also causes significant corneal toxicity that can partly be alleviated with the concurrent use of topical steroids and lubricating drops. It is less expensive ($75/cycle) and more stable than MMC, but it does require a compounding pharmacy. The main complication of 5-FU is transient conjunctival hyperemia.[42] Although systemic administration of 5-FU is known to cause punctal and canalicular stenosis,[43] these complications have not yet been reported with topical ocular use.

Interferons are low molecular weight glycoproteins produced by human leukocytes. They act as immunomodulators with anti-viral and anti-neoplastic properties. They have been shown to inhibit viral multiplication, halt cancer cell proliferation, and activate killer leukocytes. Interferon α was first cloned and produced in a recombinant form by genetically-modified *Escherichia coli* cells in 1980.[44] 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 among others.[45]

Interferon α2b can be used for the treatment of OSSN either as a topical

drop or as a subconjunctival perilesional injection.[31,32,46-55] For the topical drops, treatment doses of 1-3 million international units (IU)/ml lead to clinical response. The efficacy of 1 million IU/ml is similar to the higher dose of 3 million IU/ml, albeit with less side effects.[48] Thus, the most common treatment regimen is 1 million IU/ml four times daily until resolution, followed by two additional months after resolution (Figure 2). The average time to resolution is about 12 weeks. The drops are very well tolerated with minimal side effects, such as mild irritation and/or follicular conjunctivitis. Similar to MMC and 5-FU, compounding is required. The cost is about $250/month.

Subconjunctival perilesional IFN-α2b injections have similar efficacy to topical drops. They are generally given at a dose of 3 million IU/0.5 ml weekly until clinical resolution. The average time to resolution is 4-5 injections.[46] Others have used doses of 10 MIU given monthly.[56] Pegylated IFN-α2b injections at a dose of 80 μg/ 0.5 ml have also been used successfully in a small number of patients with the goal of prolonging the effect of the drug.[47] In contrast to all other topical drop therapies, no compounding is required as IFN-α2b is commercially available in 18 million IU multidose vial. Other advantages include the rapid resolution of the lesion and ensured patient compliance. The main disadvantage over the topical drops is a "flu-like" syndrome after each injection that can be controlled with oral acetaminophen.[46]

The overall success rate with topical or subconjunctival IFN-α2b is 76-100%, with a recurrence rate of 0-20%. Most recurrences are successfully retreated with interferon α2b.[31,32,46-55] Finally, topical interferon drops have been used successfully in patients with positive margins after primary surgical excision of OSSN. Use of topical IFN-α2b drops for a mean of 2 months after surgical excision with positive margins resulted in 4% recurrence rate. This is similar to the recurrence rate after surgical excision with negative margins and is much lower than the 13% recurrence rate that was observed after surgical excision with positive margins and no post-operative interferon use.[57] There is some very limited evidence that anti-VEGF agents may have a role in the treatment of extensive squamous cell carcinoma. Out of five patients with diffuse invasive squamous cell carcinoma that received a median of 22 ranibizumab injections, three experienced complete regression of their disease.[34] In contrast, no clinical response was noted after a single injection of bevacizumab in a recalcitrant OSSN lesion that had already been treated with topical (MMC and 5-FU) and intra-lesional (IFN-α2b) chemotherapy.[33]

Retinoic acid, a synthetic analogue of vitamin A, has also been used alone[33] or in combination with interferon[36] for the treatment of OSSN lesions. In a series of 89 patients that received combination therapy, 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.[36]

Results

Advantages of medical therapy for the treatment of OSSN include its ability to treat the entire ocular surface, theoretically thus also treating any microscopic or subclinical disease. Extensive surgical excisions and their complications (e.g. limbal stem cell deficiency) are avoided and inexcisable, diffuse or recurrent lesions can be controlled successfully. One of the criticisms for the use of topical chemotherapy as monotherapy for clinically diagnosed OSSN lesions has been the lack of tissue diagnosis. Biopsy of any suspicious lesion that lacks the typical features of OSSN should be undertaken prior to initiation of topical chemotherapy; this can easily be done at the slit lamp with topical anesthesia.

Alternatively, an "optical" biopsy can be done using ultra high-resolution optical coherence tomography (UHR-OCT).[58,59] Studies using a custom built UHR-OCT providing up to 2 μm resolution have been useful in the diagnosis and treatment of OSSN.[58-60] Distinctive features for the diagnosis of OSSN and its differentiation from other ocular surface pathologies include the presence of a thickened hyper-reflective epithelial layer, an abrupt transition from normal to diseased epithelium, and a distinct plane between the lesion and underlying tissue (if the lesion is adequately thin) (Figure 3).[60] UHR-OCT can detect subclinical disease and define the "margins" of the lesions, which are commonly different than what is apparent on clinical examination. Thus, management can be tailored accordingly to ensure that the neoplasia has been treated completely before topical chemotherapy is stopped.[58-60]

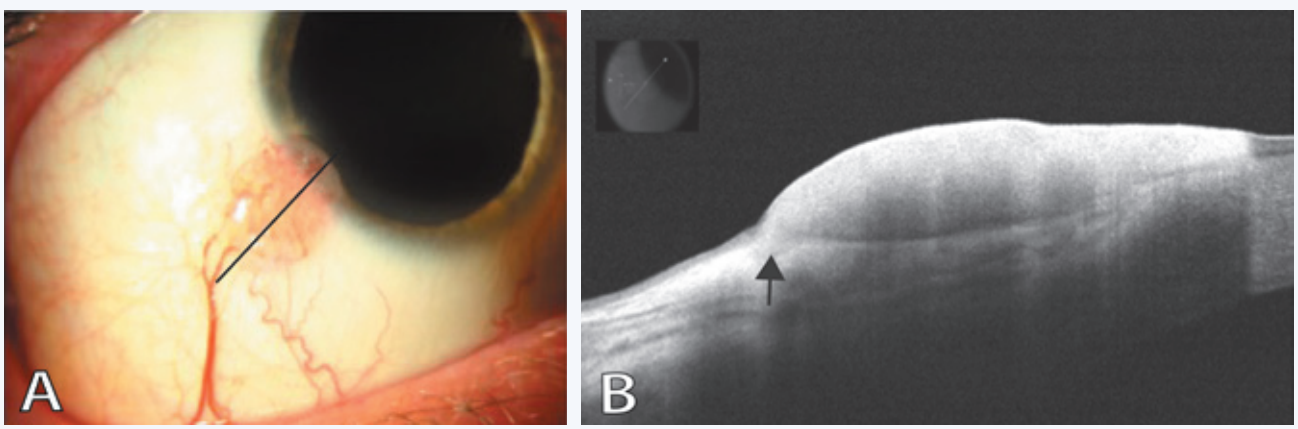

Figure 3. Slit lamp photograph (A) and ultra high-resolution optical coherence tomography (UHR-OCT) image of an ocular surface squamous neoplasia at the corneoscleral limbus. The UHR-OCT section shown is indicated with a black line in (A) and in the inset in (B). A thickened hyper-reflective epithelium and an abrupt transition zone from normal to abnormal epithelium (arrow) are characteristic features of ocular surface squamous neoplasia lesions on UHR-OCT.

The standard of care for the treatment of OSSN appears to have undergone a noticeable shift over the last decade. The use of topical agents as monotherapy or in conjunction with surgery has become increasingly popular among corneal specialists according to the results of a 2003 and a 2012 web-based survey and the rate of surgical excision alone has been declining.[61,62] This paradigm shift from surgery to topical therapy can be attributed to the increasing evidence that topical chemotherapy, and in particular, interferon, provides comparable tumor control to surgical excision.[53,63] In the only studies that compared the use of medical therapy (topical or subconjunctival interferon) to surgical excision for the treatment of primary OSSN, there was no statistically significant difference in the rate of tumor recurrence between the two groups.[53,63]

Regarding the agent of choice for topical therapy, MMC was the preferred one in 2003, while interferon became the most popular one in the 2012 survey. This is not surprising given the increasing evidence over the last decade on the adverse effects of MMC and 5-FU and the favorable safety profile of interferon.[61,62]

Conclusion and Recommendation

Surgical excision with wide margins, a "no-touch" technique, and cryotherapy has been the traditional gold standard for the treatment of OSSN lesions. It is, however, associated with high recurrence rates and extensive excisions can potentially lead to limbal stem cell deficiency. Topical chemotherapeutic agents have the theoretical advantage of treating the entire ocular surface including subclinical and microscopic disease. They are thus useful alternatives or adjuncts in recurrent, corneal, or diffuse disease. The main options include MMC, 5-FU, and IFN-α2b drops or subconjunctival injections. Topical interferon can be successfully used as an adjunct in patients with positive margins after surgical excision. The use of topical chemotherapy as monotherapy has become increasingly popular among corneal specialists over the last decade. We predict that with the advent of new imaging techniques such as UHR-OCT that allow for early diagnosis and management of subtle or recurrent lesions, the pendulum will continue to swing away from surgical excision and towards medical therapy.

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