



REVIEW ARTICLE

Effectiveness of Topical Chemotherapy in Pigmented and Squamous Lesions of the Ocular Surface: Literature Review

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Abstract

Introduction: The standard of care for the treatment of ocular surface lesions seems to have changed from surgery to topical chemotherapeutic agents as supplements to it or even as sole therapy, despite the scarcity of long-term studies in the published literature.

Methods: A search in the academic search engines of PubMed, Google academic and Cochrane, of articles published in English language from the years 1997 to 2020 on chemotherapeutic management of ocular surface diseases.

Conclusion: Topical or perilesional chemotherapy as a single therapeutic agent has proven to be an effective treatment avoiding the risks of repeated surgical interventions. Larger controlled studies with longer follow-up periods are recommended to confirm the long-term efficacy and safety of these treatments.

Keywords

Chemotherapy, Topical, Mitomycin C, 5-fluorouracil, Interferon, Squamous neoplasia, Melanocytic lesions, Ocular surface

Introduction

Topical chemotherapy is becoming the preferred approach in treating ocular surface lesions, especially for diffuse, annular, or multifocal lesions which are difficult to manage surgically. Ocular surface neoplasms can present as a pigmented or non-pigmented lesion of the conjunctiva or cornea, usually near the limbus. Ocular surface squamous neoplasms (OSSN) can be

diagnosed clinically by their gelatinous, papillary, or leukoplakic appearance. They often spread as a cell growth on the cornea. Pigmented or melanocytic lesions of the conjunctiva and cornea include nevi, primary acquired melanosis (PAM) with or without atypia and conjunctival melanoma.

Inadequate initial therapy is a major risk factor for recurrence. Treatment strategies are affected by tumor staging according to the American Joint Cancer Committee (AJCC) T-stage at presentation [1,2], so any suspicious lesion requires a histopathological diagnosis currently assisted by imaging studies such as anterior segment optical coherence tomography (AS-OCT) [3-5].

Current chemotherapeutic treatments in ophthalmology include Interferon alfa 2b (IFNa2b), 5-fluorouracil (5FU) and Mitomycin C (MMC) mainly. Many studies in other entities that have taken interest in recent years, such as the use of nucleases in dry eye or previous uveitic diseases, have been very popular with good and bad results [6-11]. The purpose of this review is to familiarize general ophthalmologists with ocular surface chemotherapy treatments, as well as to summarize the essential published literature on the use of agents for corneal and conjunctival neoplasms.

Methods

We review different articles in the relevant medical literature that describe the use of topical chemotherapy agents as a treatment for neoplastic melanocytic and



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non-melanocytic entities and OSSN.

A search was carried out in the academic search engines of PubMed, Academic Google and Cochrane, for articles published in English language from the years 1997 to 2020 on the diagnosis and management of ocular surface diseases. Only original articles, case reports, case series and scientific comments were included. Review articles, letters to the editor, and articles in a language other than English were excluded.

Search included the following keywords individually and in combination: chemotherapy, topical, mitomycin C, 5-fluorouracil, interferon, conjunctival neoplasia, conjunctival tumor, conjunctival nevi, primary acquired melanosis, conjunctival melanoma, squamous cell carcinoma, squamous surface ocular neoplasm and conjunctival papilloma.

Interferon in ocular surface lesions

Interferons (IFNs) are a group of glycoproteins that form a network of complex interactions with other cytokines and connect innate and adaptive immunity. They exhibit a variety of biological functions, including antiviral, anti-proliferative, immunomodulatory, and cytotoxic activities. It is currently the most studied molecule since it has been shown to be effective and safe as a treatment for primary or recurrent ocular surface lesions with minimal adverse effects, providing a less invasive approach [12,13].

Currently, it is Interferon alpha 2b (IFNa2b) that is frequently used in ophthalmology, and it appears to be as successful as cryotherapy and surgical excision, which are the traditional forms of treatment for suspicious ocular surface lesions [14,15]. It is used topically, subconjunctival and/or perilesional injection or in conjunction with surgery.

Topical IFNa2b avoids the risks of further destruction of limbal stem cells and damage from surgical excision and could even be cost-effective for patients [16]. If invasive disease is diagnosed at any stage, topical therapy is contraindicated and surgical excision is required [18,19]. An important mechanism of action of IFNa2b is the reduction of the viral load of human papillomavirus (HPV) in infected cells of the conjunctiva in the squamous epithelium (Kostkowski and Herman 2004). Patients with primary or recurrent OSSN or large papillomas treated topically or with subconjunctival injections of IFNa2b until tumor resolution have had excellent results with low recurrence rates and a median resolution of up to 1.4 months [20,21]. IFNa2b, when properly combined with surgical excision in OSSN, provides proliferative control of up to 95% of cases, reaching rates of 90% in tumors *in situ*, in 100% of T1, 100% of T2, 94% of T3 and in 100% of T4 tumors according to the AJCC classification [22].

Whether via subconjunctival/perilesional or topical,

IFNa2b in giant OSSN above 20 mm treated with subconjunctival injection achieved almost complete tumor control (immunotherapy) in most of the patients reported in Kim, et al. study and a partial tumor control with reduction in size (immunoreduction) which allows subsequent surgical excision. A combination of topical and injectable IFN 2b completely resolved tumors larger than 30 mm during a period of up to 6 months in follow-up [23,24].

Many forms of synergistic treatment combinations to enhance the effectiveness of IFNa2b in those patients with associated systemic conditions have been made [25,26]. An example in ocular surface is the use of topical interferon alpha 1 million IU/ml drops 4 times a day in combination with retinoic acid 0.01% once every two days, which seems to be effective in the treatment of CIN lesions with minimal side effects, with faster resolution and longer tumor-free period compared to other studies using interferon alfa-2b alone [27].

In a large study conducted at the Bascon Palmer Eye Institute from 2001 to 2010, the recurrence rate in patients treated with IFNa2b at 1 year was 10% and 21% at 5 years. In those patients with positive margins of lesions, the use of postoperative topical therapy reduced the recurrence rate to a level similar to patients with negative margins [28]. Other comparative studies report recurrence rates between surgery and topical therapy at 1 year of 5% in surgery groups versus 3% in the IFNa2b groups. This leads us to conclude that both topical IFNa2b and surgical excision appear to be effective for the primary OSSN [29,30].

The efficiency of interferon in pigmented lesions has been documented in some studies, but its use has not been as well studied as with MMC, but even in some patients with recurrences to other treatments it has shown to be effective [31]. In both precursor lesions as PAM with atypia or conjunctival melanoma, Garip, et al. demonstrated a mean decrease in tumor size of 66% after a first treatment cycle, 55% after a second and up to 74% after a third cycle showing promising results with minimal side effects [32].

Use of interferon in other disease

IFN-a, IFN-b and IFN-g type interferons exist in recombinant form and are used in a clinical setting for the treatment of various immunosuppressive diseases such as Kaposi's sarcoma in HIV / AIDS, hepatitis type B and C, condylomata acuminata, multiple sclerosis, gliomas and herpes virus or HPV infections (IFN-b) [33-35]. In addition, IFN-a2b has been tested in patients with Behcet uveitis relapsed to corticosterides and patients with multiple sclerosis (MS), as well as systemically recombinant human interferon alfa-2a (rhIFNa-2a) at doses of 6 million units subcutaneously per day has had positive results, improving vision and in some cases a complete remission of ocular vasculitis

in ocular Behcet and multiple sclerosis [36-39]. Some findings suggest that IFN plays a key role in promoting conjunctival squamous metaplasia and apoptosis in dry eye and provide information on the immune response of keratoconjunctivitis sicca [40,41].

Mitomycin C

The uses of MMC on ocular surface have been widely studied. Topical MMC application is an effective treatment for squamous intraepithelial lesions and even conjunctival squamous cell carcinoma with excellent long-term results [42-45]. MMC is an antineoplastic antibiotic (alkylating agent) isolated from *Streptomyces caespitosus* that acts inhibiting DNA synthesis [46].

Combination therapies with mitomycin seem promising. Its use with topical cyclosporin A (0.05%) combined with mitomycin C (0.01%) as adjunctive treatment after surgical excision in cornea and conjunctival intraepithelial neoplasia and squamous cell carcinoma prevents tumor recurrence especially in extensive lesions, when surgical excision cannot guarantee a tumor-free margin or even in failed IFNa2b treatment [47-49].

In pigmented lesions, variable responses have been reported. Side effects of local chemotherapy generally resolve after treatment interruption, being a good alternative to surgical excision and cryotherapy in treatment of nevi with atypia, PAM with atypia and even melanoma [50-52]. Treatment with topical MMC not only reduces the size and degree of clinical pigmentation lesions, in conjunctiva and lesions involving corneal epithelium, but also eradicates residual atypical conjunctival melanocytes [53,54].

Its use as an adjuvant agent after completed surgical resection [55,56] has been corroborated in many studies. Birkholz, et al. complementary used of MMC with a significantly reduced prevalence of recurrence of 5.9% vs. 66.7% when it was not used. In invasive melanomas and adjuvant brachytherapy achieves high rates of local tumor control with little ocular morbidity, except in nodular tumors where they appear to be resistant to topical chemotherapy with MMC. Without caruncular involvement, disease-specific mortality is rare [57,58] and when surgical margins are positive in extensive lesions, the use of MMC is associated with a lower prevalence of tumor recurrence [59,60]. Long-term studies have evaluated the recurrence and effectiveness of MMC in neoplastic pigmented lesions, such as the study by Kurlly and Finger, which followed a 12-year follow-up in patients with PAM with atypia and conjunctival melanoma. Both entities responded to topical chemotherapy with 0.04% MMC; Subepithelial nests were resistant to treatment, and they concluded that as primary or adjunctive therapy, topical MMC produced an overall recurrence rate of 50% [61].

5-Fluorouracilo

5-Fluorouracil (5-FU) is an effective and well tolerated agent as primary treatment for OSSN, with up to an 82% favorable response rate [62]. Despite being a treatment sparsely used nowadays due to the rise of new therapies such as IFNa2b [67], topical 5-FU, as single or combined therapy, can be considered a safe and effective long-term treatment for OSSN as corneal toxicity is minimal [63].

Several comparative studies have been conducted of measure the efficacy of topical treatment with 5-FU and IFNa2b (1 MIU/ml) as primary treatment modalities for OSSN. Both modalities have yielded similar results with a high rate of lesion resolution and low recurrence. Usually, doses used topically are 4 times a day for 1 week followed by a 3-week drug break [64,65].

Subconjunctival/perilesional 5-FU injections are also an effective and safe treatment for OSSN. In a study carried out by Sun & Hua in China they used 10 to 25 injection doses, with an average duration of treatment between 6 to 20 weeks, resulting in the disappearance of both intratumoral and conjunctival feeding vessels in OSSN demonstrated by OCT-AS [66].

Side Effects of Topical Therapies

Interferon

The adverse effects of topical use of interferon have been widely studied and described. Even the systemic use has repercussion in different presentations, from effects at the anterior segment to secondary retinopathies including retinal ischemia, choroidal neovascularization and ischemic optic neuropathy [68-72]. Retinal changes are usually reversible with discontinuation of therapy. Local adverse effects include conjunctival hyperemia, follicular hypertrophy, giant papillary conjunctivitis, irritation, epithelial corneal defects, and flu-like symptoms. All these effects usually resolve on average one month after discontinuation the medication [73].

Galor, et al, concluded that there were no significant differences between patients who used doses of 1 million IU/ml versus 3 million IU/ml for the treatment of conjunctival intraepithelial neoplasms (CIN) topically with results and similar side effects. The average duration of treatment is variable and in most of the studies it has been used until lesions are resolved, all side effects generally disappear when the treatment is suspended. For melanocytic lesions, topical doses of 1 drop 5 times a day for 6 weeks are suggested with few or no side effects [75,16].

Mitomycin C

In the largest study of topical MMC complications in ocular surface neoplasia by Khong & Muecke (2006), allergic reaction and point stenosis were the

most common complications with no medium-term complications [76].

Histologically, nuclear enlargement, cellular hyperchromasia in the superficial layers of the epithelium were the main secondary effects observed. Cytoplasmic eosinophilia, unicellular necrosis, and occasionally chronic subepithelial inflammation were also observed [77,78]. Ditta, et al. evaluated the long-term complications (6 months) of MMC therapy in patients with conjunctival melanoma. The most common complications included injection, tearing, irritation, pain, and limbal stem cell deficiency [46]. Other complications reported have been keratopathy, cataract [79] or even metastasis [80], according to the same authors could be associated with treatment delay.

5-Fluorouracilo

Some of the adverse effects reported are conjunctival inflammation, epithelial defects, skin and epiphora erythema. The use of subconjunctival injections of

5-FU after glaucoma surgery can lead to squamous metaplastic changes and nuclear atypia and apoptotic cell death in the conjunctival epithelium in a short period. Adverse effects are generally transient and mild [62,81].

Conclusion

Topical or perilesional chemotherapy on the ocular surface as a single therapeutic agent has proven to be an effective treatment avoiding the risks of repeated surgical interventions and their effects such as scar conjunctival changes. The three drugs revised in this study seems to be effective and safe, but larger controlled studies with longer follow-up periods are recommended to confirm long-term efficacy and safety of these treatments. Its use for residual or recurrent lesions should be carefully considered and closely monitored to avoid metastasis, especially in melanocytic lesions. The main results and recommended doses of the larger studies included in this review are summarize in [Table 1](#).

Table 1: Summary of effectiveness of the different topical therapies per study.

Study (year of publication and number of patients in each study)	Main Results			Used Doses
	IFNa2b	MMC	5-FU	
Venkateswaran, et al. [64]	81.3% resolution (n: 48) (OSSN)		96.3% effectiveness (n: 54) (OSSN)	5FU 1%, 4x/day for one week/monthly) until resolution. IFN 1 MIU/mL. 4x/day continuously.
Pe'er, et al. [50]		> 80% (n: 12) (PAM)		Two to five courses of 0.04% (0.4 mg/ml) MMC
Galor, et al. [28]	81% of eyes in the 1 million IU/ml group vs. 92% in the 3 million IU/ml group. (CIN)			10 patients were treated with 1 million IU/ ml of topical IFN-a2b; 9 patients were treated with 3 million IU/ml of topical IFN-a2b. Both groups used 4x/daily
Birkholz, et al. [59]		Significantly reduced prevalence of recurrence (5.9% vs. 66.7%). In positive surgical margins, MMC reduced the tumor recurrence (12.5% vs. 55.6%). With negative margins, MMC reduced recurrence (0% vs. 83.3%) (OSSN)		Weck cel sponge soaked 0.02% or 0.04% of MMC to the subconjunctival surface at the edge of the surgical excision for 1-3 min. Postop, 1 drop of topical MMC 0.02% 3 times daily for 2 weeks. In most cases, 3 cycles of 2 weeks on and 2 weeks off were used.
Boehm [74]	85% successful rate. (OSSN)			1 million IU/ml 4 times daily until lesion resolution

Zaki, et al. [47]		All eyes showed total cure with no recurrence during the 2-year follow-up period.		Topical cyclosporine A (0.05%) and topical mitomycin C (0.01%) 4 times daily for 12 weeks after surgery.
Shah, et al. [73]	Complete resolution in 19 tumors (83%). Partial resolution (17%), tumor surface area was reduced 44% (median). (OSSN)			Topical interferon alfa-2b, 1 million IU/mL, 4 times daily
B. Damato and SE Couplan [57]		Excision of invasive melanoma with adjunctive brachytherapy and topical chemotherapy, recurrence occurred in six patients. (if treatment did not include radiotherapy) (Conjunctival melanoma)		Topical MMC 0.02%, four times daily for a total of 4 weeks, initially in two 14-day cycles, separated by a 2-week interval, and latterly in four 7-day cycles over 8 weeks.
T Finger, et al. (1997) n: 10		Decreased conjunctival pigmentation in the four patients where topical chemotherapy was used as a primary. treatment. Nodular tumors were resistant to topical MMC chemotherapy. (PAM with atypia)		0.04% MMC ophthalmic solution each week for 28 days. When was used as an adjuvant, drops were given for 7 days starting within 2 weeks of primary excision and cryotherapy
T. Finger, et al. [31]	Patients with T2 and T3 of AJCC. 2 patients had regression of recurrent disease. (Conjunctival melanoma)			One drop of interferon alfa-2b (1 million units/ml) was placed into the superior fornix four times daily for three months.
Frucht-Pery, et al. [78]		10 patients had disease-free after one course of treatment. 1 case, residual CCIN remained very small without regrowth. In the one patient with invasive SCC and in 5 patients with CCIN, regrowth occurred after 6 months.		MMC 0.02% to 0.04% four times daily from 7 to 28 days.
Garip, et al. [32]	Decrease in tumor size after the first cycle 66%, after the second cycle 55%, and after the third cycle 74%. (Melanoma and PAM with atypia)			IFN α -2b, 1 million units/ml, 5 times daily (range 1-6 cycle).
Halas, et al. [52]		Topical therapy after primary excision. No presence of relapse of pigmentation in excision area with or without using MMC during the surgery in patients with PAM.		MMC (0.04% = 0.4 mg/l) as a topic treatment after excision two times for 5 min in the operating room. The patients did not receive MMC fluid for use at home.

Herold & Hintschich [75]		9 patients showed regression and lost pigmentation. 3 patients required a second cycle (PAM with atypia and/or conjunctival melanoma)		5 × 1 drop/day topically for 6 weeks.
Holcombe, et al. [18]	8 of 10 patients achieved clinical resolution from topical IFN- ₂ b treatment. 1 patient developed invasive SCC			Topical IFNa2b (1 million IU/ml) four times a day until clinical resolution or until the lesion appeared nonresponsive.
Joag, et al. [62]			Complete resolution of OSSN in 82% of patients; 18% were considered treatment nonresponders.	5-FU 1% topically 4 times daily for 1 week followed by a drug holiday of 3 weeks. (Mean: 4 cycles)
Karp, et al. [19]	All patients had complete resolution of the CIN lesion. Mean time to clinical resolution was 11.6 weeks.			Topical IFNa2b million IU/ml four times a day, until clinical resolution.
Kim, et al. [24]	In 72% of giant OSSNs IFNa2b achieved complete control (immunotherapy); there was a reduction in size (immunoreduction) in 28% of giant OSSNs.			Patients with giant OSSN was managed with topical IFNa2b (1 million IU/ml) 4 times daily or with injection IFN- ₂ b (a portion of 10 million IU/ml vial)
Krilis, et al (2012) n: 89	Complete resolution of the CIN lesions was in 87 of the 89 eyes treated. (97.75%).			1 million IU/ml drops 4 times daily and retinoic acid 0.01% once every second day.
Kusumesh, et al. [12]	Complete remission of the tumor was observed in 22 patients (91.6%). 8.3% did not respond to the treatment.			Topical IFNa2b (1 million IU/mL) 4 times daily until resolution.
Parrozzani, et al. [63]			Complete regression was achieved in all patients. Only 3 patients (7.3%) treated with 5-FU alone recurred. Recurrences were successfully treated with additional 5-FU courses.	Topical 5-FU four times/day for 4 weeks (one course until clinical and cytological tumour regression.).
Shields, et al. [24]		Complete tumor regression in 100% of the cases was achieved in conjunctival or corneal SCC, even in extensive recurrent tumor		Topical MMC 0.04% one drop four times daily/1 week followed by 1 week without medication.

Shields, et al. [22]	IFNa2b immunotherapy complete response in 75% Tis, in 100% of T1, and in 70% T3. In combination with surgical excision achieved tumor control in 100% Tis, in 100% T1, in 100% T2, in 100% T3, and in 100%. Topical and/or injection) was used as alone or combined with additional surgery, complete tumor control was achieved 95%.			The topical IFNa2b eye drops were prepared at a dose of 1 MIU/m. The IFNa2b injection was 1-mL syringe with undiluted Intron-A (10 MIU/mL).
Sturges, et al. [29]	Comparative study: 15 patients elected topical IFNa2b and 14 chose surgical excision. No patient in either group developed a recurrence during the study period (primary OSSN)			Topical INFa2b (1 million U/ml) 4 time per day until clinical resolution.
Vann, et al. [23]	All six patients had complete clinical resolution of the CIN lesion within 6 weeks of initiation of treatment.			Single subconjunctival/perilesional injection of recombinant INFa2b 3 million (IU) in 0.5 ml and then started topical INFa2b drops (1 million U/ml) four times a day
Prabhasawat, et al.		Before MMC treatment, 6 eyes (85.7%) had recurrences after surgical excision. The tumor-free period ranged from 2 to 19 months. Two patients had multiple recurrences.		Topical 0.002% MMC 4 times daily. (2-14 cycles)
Ballalai, et al. [45]		Complete resolution of the lesion was achieved in all patients after 1 month of treatment. Recurrence occurred in 1 patient (4.3%) after 24 months of treatment		Topical MMC 0.02%, four times per day, for 28 consecutive days.
Chen, Louis, Dodd, et al. [60]		All the lesions were completely excised superficially from the cornea and limbus with a 2 mm margin on the conjunctival aspect. There was no evidence of clinical recurrence in any cases		Topical MMC 0.04% four times a day per 1-week, at least two courses or after completing epithelial healing.
Sun and Hua [66]			3 years after initiation of treatment complete tumor regression to final visit according to AS-OCT was 32.5 ± 4.2 months (OSSN)	Subconjunctival/perilesional 5 FU injections (mean number of doses 17.0 ± 8.6)
Gichuhi, et al. [67]			Comparative study: Aftersurgical excision of OSSN, recurrences occurred in 11% of 5FU group, and 36% of 47 in the placebo group.	Topical 5FU 1% or placebo four times a day for 4 weeks.

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