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Short Communication

# Immunotherapy in the Treatment of Ocular Surface Squamous Neoplasia

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**Received:** April 23, 2018; **Published:** June 20, 2018

***Keywords:*** *Conjunctiva; Cornea; Dysplasia; Fluorouracil; Intraepithelial Neoplasia; Interferon; Mitomycin C; Ocular Surface; Squamous Cell Carcinoma*

## Abbreviations

AJCC-TNM: American Joint Committee on Cancer-Tumor Node Metastasis; CIN: Conjunctival Intraepithelial Neoplasia; US-FDA: United States Food and Drug Administration; FU: Fluorouracil; IFNa2b: Interferon Alpha-2b; ml: Milliliters; mm: Millimeters; MMC: Mitomycin C; HIV: Human Immunodeficiency Virus; HPV: Human Papilloma Virus; IU: International Units; OSSN: Ocular Surface Squamous Neoplasia; SCC: Squamous Cell Carcinoma

Ocular surface squamous neoplasia (OSSN) is a slowly progressive tumor of the conjunctiva with a disease ranging from dysplasia to conjunctival intraepithelial neoplasia (CIN) to invasive squamous cell carcinoma (SCC) [1]. It can spread from conjunctiva to the limbus, cornea, nasolacrimal system, orbit, and globe. It occurs most commonly in the elderly males. Common risk factors associated with it are exposure to ultraviolet B sunrays, human papilloma virus (HPV 16 and 18), human immunodeficiency virus (HIV), cigarette smoking, petroleum products, xeroderma pigmentosa, genetic inheritance and/or immunocompromised status (post organ transplantation). Clinically, it appears as a gelatinous, leukoplakic or papillomatous, flat or elevated, dense or nodular lesion with prominent feeder blood vessels. It is located most commonly in the interpalpebral region of the bulbar conjunctiva with or without extension towards the limbus into the cornea. OSSN is considered as giant if the lesion is ≥ 15 mm in basal dimension involving more than 6 clock hours at the limbus [2,3]. Despite of treatment, it may recur and can metastasize to the regional lymph nodes or distantly metastasize leading to poor local ocular (blindness) and systemic outcomes [4]. American joint committee on cancer-TNM (AJCC-TNM) has classified the OSSN into various stages (Table 1) depending on the extent of primary disease, regional lymph nodal and metastasis status [5]. Diagnosis is mostly by clinical ophthalmic examination, but incisional or excisional biopsy provides the definitive diagnosis. New optical coherence tomography techniques with ultra high resolution are helpful both in diagnosis and in follow-up after treatment.

| Clinical stage | Definition |
|---|---|
| **Primary tumor (T)** | |
| Tx | Primary tumor cannot be assessed |
| T0 | Tumor absent |
| Tis | Tumor present as carcinoma insitu (CIN) |
| T1 | Tumor present with largest basal diameter < 5 mm |
| T2 | Tumor present with largest basal diameter > 5 mm, without invasion of adjacent structures |
| T3 | Tumor invades adjacent structures excluding orbit |
| T4 | Tumor invades orbit with or without further extension |
| T4a | Tumor invades orbital soft tissues without bone invasion |
| T4b | Tumor invades bone |
| T4c | Tumor invades adjacent paranasal sinuses |
| T4d | Tumor invades brain |
| **Regional lymph node (N)** | |
| Nx | Regional lymph node cannot be assessed |
| N0a | No regional lymph node metastasis, biopsy done |
| N0b | No regional lymph node metastasis, no biopsy done |
| N1 | Regional lymph node metastasis |
| **Distant metastasis (M)** | |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

***Table 1****: AJCC-TNM classification of the conjunctival SCC.*

*Source: Edge SE, Byrd DR, Carducci MA, Compton CA, eds. Carcinoma of the conjunctiva. In AJCC Cancer Staging Manual. 7th edition. New York, NY: Springer; 2010.*

*AJCC: American Joint Committee on Cancer; TNM: Tumor, Node and Metastasis; CIN: Carcinoma In Situ; SCC= Squamous Cell Carcinoma.*

Treatment options for OSSN are surgical excision ± topical chemotherapy and non-surgical methods such as topical chemotherapy and immunotherapy with interferon alpha-2b (IFNα2b). Surgical excision (no touch technique) with 3 - 4 mm margins, alcohol keratectomy and cryotherapy is the primary treatment option for OSSN [6,7]. Wide excision of OSSN can lead to limbal stem cell deficiencies, ocular surface irregularities and scarring. Also post excision, positive tumor margins cause higher rates of tumor recurrence than negative tumor margins. Topical chemotherapy agents (mitomycin C (MMC) or 5-fluorouracil (5-FU)) have emerged as alternative treatment methods for OSSN especially for the larger, recalcitrant or recurrent annular lesions [8-12]. These chemotherapeutic agents can be used either preoperatively to decrease the tumor size (chemoreduction) or post-operatively to treat the positive margins or recurrent tumors. The advantage of the topical chemotherapy medications is the ability to treat the entire ocular surface including the fornices and prevention of the surgical complications. Mitomycin C (0.02-0.04%) is a cytotoxic alkylating agent with antiproliferative properties that targets the proliferating neoplastic cells. Apart from being used as adjuvant therapy (0.02%) along with surgical excision, when MMC was used as a solo therapy (0.04% 4 times a day for 1 week with 1 week break cycle till complete response) for diffuse disease, there were higher chances of persistence or recurrence of OSSN [8,9]. Ocular toxicities such as local allergy, corneal epitheliopathy, limbal stem cell deficiency, scleral ulceration, punctal stenosis, uveitis, cataract and glaucoma has limited its utility and made it less favorable [6,9,10]. 5-fluorouracil (1% 4 times a day for 1 week, followed by drug holiday for 3 weeks, up to 4 cycles or till complete tumor elimination) is considered to be an effective option for preinvasive OSSN to completely eradicate it (82% of cases) [11,12]. It was well tolerated and has minimal side effects (such as pain, photophobia, tearing, itching, swelling, conjunctiva injection, corneal epitheliopathy, and intolerance) and no long-term toxicities. OSSN recurrences (15% at 2 year follow-up) were also noted following 5-FU topical chemotherapy [11,12]. The ocular toxicity and the recurrence pattern SCC following topical chemotherapy medication has limited their utility over years.

Advances in medicine have lead to the evolution of interferon alpha-2b for the treatment of various malignancies. IFNα2b, a recombinant interferon has been approved by the US Food and Drug Administration (FDA) to treat various malignancies such as hairy cell leukemia, chronic myelogenous leukemia, malignant melanoma, multiple myeloma, follicular lymphoma, carcinoid tumors and chronic hepatitis B and C [2,7,13-15]. It has antiviral, immunomodulating and antineoplastic activities. IFNα2b alone or combined with surgical excision has brought a remarkable change in the treatment response of SCC of conjunctiva and cornea by causing complete tumor eradication and prevention of recurrence [3,7,13-15]. Interferon's are the natural glycoprotein's secreted by the peripheral blood leukocytes. They induce a cytotoxic effect by binding to the target cell membrane receptors, activate the target protein cells and suppress cellular proliferation. This cytokine contains163 amino acids and has a molecular weight of 19, 000 Daltons. Based on the available scientific data; it is being used as an off-label product and is available as a compounding agent from selective pharmacies. It is a non-toxic topical medication that covers the entire ocular surface and treats not only clinical disease but also preclinical OSSN. It can be applied either topically as immunotherapy (1 - 3 million IU/ml 4 times a day for 1-3 months or till complete response) or as periocular injections (1 - 3 million IU/1ml every week for 1 month) for immunoreduction. In the pharmacy, 1 million IFNα2b i.e. 10 million IU/ml is mixed with 9 ml of sterile distilled water that can make the formulation of 1 million IU/ml and stored in a refrigerator. Subconjuctival injections are combined with topical IFNα2b to treat OSSN in order to prevent persistence and tumor recurrences [7,15]. CIN was completely eliminated at a median duration of 3 months in 81% of cases with a dose of 1 million IU/ml and in 92% of cases with a dose of 3 million IU/ml of topical IFNα2b at median duration of 2 months. Over a period of 2 years, few cases of CIN had recurrences with topical IFNα2b [13]. In another study at a median duration of 6 months, compete tumor resolution was seen in 83% of cases and recurrence only in 4% of cases following topical application of IFNα2b [14]. As per the AJCC classification of OSSN, 67% of Tis, 85% of T3, and 83% of N0 and M0 showed complete response following immunotherapy with topical IFNα2b over median treatment duration of 11 months [14]. When interferon immunotherapy was combined with surgical excision, there was complete resolution of OSSN in 95% of overall cases, 90% of Tis lesions, 100% of T1, T2, and T4 lesions, and 94% of T3 lesions. Recurrence was seen in 5% of cases at a median follow-up of 1 year [7]. When recombinant IFNα2b perilesional or subconjunctival injections at a dose of 3 million IU/0.5 ml were given for the OSSN, 87% of cases had complete tumor resolution at median duration of 1.4 months and ≈7% had recurrence after 4 months of treatment [15]. With the combination of weekly subconjunctival

injections and topical IFNα2b medication, OSSN resolved faster with less recurrence rate [7]. IFNα2b controlled not only small tumors but also giant OSSN with complete resolution in 72% of cases (immunotherapy) and decrease in the size in 28% of cases (immunoreduction) [3]. Studies have reported minimal ocular and systemic toxic effects with immunotherapy (IFNα2b) for OSSN [7,13-15]. Ophthalmic side effects of IFNα2b include irritation, photophobia, conjunctival hyperemia, follicular hypertrophy, giant papillary conjunctivitis, corneal epithelial defects and superficial keratitis. Systemic side effects include transient flu-like symptoms, malaise and fever. Patients tolerated this medication well. There was no loss or injury to the limbal stem cells with this immunotherapy unlike surgery or with use of other topical chemotherapeutic agents [7,13-15].

Immunotherapy with IFNα2b is considered to be very effective method for the treatment of ocular surface squamous neoplasia. It can be also be used as a sole primary treatment modality without surgical intervention especially in elderly patients who are not eligible for surgery, or an extensive OSSN that cannot be excised surgically. It decreases the burden of surgery to the patients with pre-invasive disease and in CIN cases. It is a well-tolerated medicine and causes minimal ocular or systemic side-effects compared with other topical chemotherapeutic agents. It is not covered by some insurance companies, so may be costly to some patients and due to compounding pharmacy issues, there is limited availability of this medication. In conclusion, IFNα2b a cost effective, non-invasive therapeutic method/agent has been successful in completely resolving the OSSN, preserving the visual function and avoiding the surgical burden.

## Conflict of Interest

None of the authors have any conflicts of interest in the medication or device used in this paper.

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**Volume 9 Issue 7 July 2018**