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Immunosuppression as a possible risk factor for interferon non-response in ocular surface squamous neoplasia

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Abstract

Purpose—The mechanism by which ocular surface squamous neoplasia (OSSN) responds to topical interferon-alpha-2b (IFNα2b) is not known. We herein report on 3 cases of immunosuppressed patients whose tumors did not respond to topical IFNα2b therapy. The purpose of this series is to shed light on potential mechanisms of IFNα2b in OSSN.

Methods—Retrospective case series of 3 immunosuppressed patients whose biopsy proven OSSN did not respond to topical IFNα2b treatment.

Results—Three white, immunosuppressed males (mean age 70 years, range 66-76) were diagnosed with OSSN. Topical IFNα2b 1 million units/ml was started four times a day and utilized for a mean of 5 months (range 2-7 months) without adequate response. All patients were then switched to 5-fluorouracil (5-FU). Successful eradication of OSSN was achieved in two cases, and improvement of OSSN in another. The latter patient was switched to mitomycin C (MMC) with subsequent resolution of OSSN.

Conclusion—These cases suggest that an intact immune system may be an important link between IFNα2b therapy and tumor resolution. As such, topical IFNα2b may not be an optimal choice in patients with underlying immunosuppression. It may be more effective in this patient population to switch to a non-immune modulating therapy such as 5-FU or MMC.

Introduction

Ocular surface squamous neoplasia (OSSN) includes a spectrum of epithelial squamous malignancies, ranging from dysplasia to invasive carcinoma, and is more commonly found in the older, white males. Treatment options for OSSN include surgical excision with a no-touch technique and cryotherapy and medical therapy with mitomycin-C (MMC), 5-fluorouracil (5-FU), and interferon-alpha-2b (IFNα2b). Topical IFNα2b is favored given its high success rate (~80% of tumors completely respond to therapy) and minimal toxicity.

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Conversely, up to 20% of tumors do not respond to IFN α 2b and it is currently not possible to predict which patients will fail treatment.¹⁻³

Interferon signaling exerts multiple activities including anti-viral, cytotoxic, anti-angiogenic, anti-proliferative, immune-modulatory, and enhanced host antitumor surveillance.⁴⁻⁵ The exact mechanism by which interferon acts on OSSN, however, is largely unknown. This leaves opportunity for continued investigation of interferon's actions on OSSN in an effort to better guide therapeutic decisions, such as pursuing a surgical approach directly, or using a different agent in patients in whom interferon is less likely to be effective. We herein present 3 patients with various causes for immunosuppression in whom topical IFN α 2b was not effective in treating OSSN. The purpose of this case series is to propose the idea that perhaps an intact immune system is a key player in interferon's therapeutic effects on OSSN.

Methods

This retrospective study was approved by the institutional review boards of the Miami Veterans Affairs Hospital and the University of Miami. The methods adhered to the tenets of the Declaration of Helsinki and were compliant with the Health Insurance Portability and Accountability Act. The medical records of 10 patients with biopsy proven OSSN who presented to Bascom Palmer Eye Institute and the Miami Veterans Affairs Hospital between September 2010 and July 2016 and who received topical IFN α 2b with incomplete resolution of the tumor were reviewed. Of these patients, 3 were found to have various causes for immunosuppression, including lymphoma on rituximab therapy, leukemia, and multiple myeloma.

Patient records were reviewed for demographic information (age, race, and ethnicity), co-morbidities, and OSSN characteristics (eye, location, size, involved ocular structures, appearance, pathologic grading of tumor). Documented treatment information included dose, frequency, length of IFN α 2b treatment, and subsequent therapy after IFN α 2b failure.

Results

Three cases were identified of immunosuppressed patients whose OSSN did not respond to initial treatment with topical IFN α 2b therapy.

Case 1

A 66 year old male had a past medical history of anemia, diabetes, and history of low grade non-Hodgkin's follicular low-grade B cell lymphoma diagnosed in 1988, status post allogeneic bone marrow transplantation. Recurrent lymphoma was noted on surveillance 14 years later in the lacrimal gland with involvement of mediastinal and abdominal lymph nodes, prompting treatment with rituximab. While receiving treatment, the patient presented to Miami Veterans Affairs (VA) eye clinic for evaluation of conjunctival lesions in both eyes. Best corrected visual acuity (BCVA) was 20/30-2 in the right eye and 20/25 in the left eye. Slit lamp examination revealed a gelatinous limbal lesion in the right eye extending from 7:30 to 10 o'clock with 1 mm extension into cornea (Figure 1a). In the left eye, an opacity involving the limbus and cornea was noted at approximately 4 o'clock (Figure 1b). Anterior

segment high-resolution ocular coherence tomography (HR-OCT) demonstrated a thick hyper-reflective epithelium with a sharp border between normal and abnormal epithelium, consistent with OSSN in both eyes (Figure 1c). The patient elected for empiric therapy with IFN α 2b (1 million units/mL), 1 drop four times daily in both eyes. Despite 6 months of therapy, persistent OSSN was noted in both eyes (Figures 1d,e). An incisional conjunctival biopsy was performed in the left eye, which confirmed the diagnosis of OSSN with severe dysplasia. The patient was started on 5-fluorouracil (5-FU) 1% four times daily. After two cycles (1 week on, 3 weeks off), clinical and OCT evaluation were consistent with resolved OSSN in both eyes.

Case 2

A 69 year old male with newly diagnosed leukemia (not yet treated), diabetes mellitus (hemoglobin A1c 8.8), atrial fibrillation, and hypertension presented to the eye clinic with a right temporal conjunctival lesion. BCVA was 20/25 in the right eye and 20/30 in the left eye. Slit lamp examination revealed a gelatinous lesion with foci of leukoplakia in the temporal conjunctiva of the right eye (Figure 2a). HR-OCT demonstrated typical features of OSSN (Figure 2b). An incisional biopsy confirmed the diagnosis of OSSN with severe dysplasia. The patient elected for therapy with IFN α 2b (1 million units/mL), 1 drop four times daily. After 2 months of therapy, the lesion was noted to have grown slightly (Figure 2c). As such, the patient was switched to 5-FU 1% four times daily (1 week on, 3 weeks off). After 4 cycles, complete resolution of the OSSN was noted.

Case 3

A 76 year old white male had a past medical history of multiple myeloma treated with lenalidomide 25mg for the last 6 years. He presented to the eye clinic for evaluation of conjunctival lesion in right eye. BCVA was 20/30 in the right eye and 20/100 in the left eye. Ocular tensions were normal. Slit lamp examination revealed a gelatinous limbal lesion in the right eye extending from 3 to 5 o'clock with 3 mm extension into cornea (Figure 3a). Anterior segment HR-OCT demonstrated thick hyper-reflective epithelium extending throughout the cornea and conjunctiva, consistent with OSSN (Figure 3b). The patient elected for empiric therapy with IFN α 2b (1 million units/mL), 1 drop four times daily. Despite 7 months of therapy, persistent OSSN was noted (Figure 3c). As such, an incisional conjunctival biopsy was performed which confirmed OSSN with severe dysplasia. The patient was started on 5-FU 1% four times daily. After 2 cycles (1 week on, 3 weeks off), he demonstrated very slow response. He was therefore started on MMC 0.04% four times daily. After 4 cycles of this therapy (1 week on, 3 weeks off), clinical and OCT evaluation (Figure 3d) were consistent with resolved OSSN.

Discussion

Hereby, we report on three patients with immunosuppression of various causes whose OSSN did not resolve with initial treatment with topical interferon therapy. This suggests that perhaps an intact immune response is necessary in order for interferon to act therapeutically on OSSN. While the detailed mechanism by which interferon acts on OSSN is not known, it is likely that interferon can cause T-cell and macrophage induced apoptosis in OSSN.

Furthermore, knowledge on its mechanism of action also can be gleaned from its biomolecular roles, as well as other models in which interferon is used therapeutically, namely in hepatitis C and cervical intraepithelial neoplasia.

Clinical immunosuppression has been found to be a limitation in achieving therapeutic efficacy of interferon in hepatitis C treatment. One study found that in patients co-infected with hepatitis C and HIV, a lower CD4+ cell count was associated with poorer response to therapy.⁶ Other immunological factors implicated in an inadequate hepatitis C response to interferon include alcohol intake, drug use, low weight, advanced age, and diabetes. Interestingly, elevated levels of IL-6, IL-8, IL-10, IL-1beta, and TNF- α , among other immunological disturbances, have been associated with poor response to IFN- α therapy.⁷ Together, this points to a complex interface between interferon and the rest of the immune system.

In cervical intraepithelial neoplasia, immune factors such as current smoking, lower Th1 cell derived interleukins, and decreased NK cell activity have been associated with poorer tumor resolution with IFN- α treatment.⁸⁻⁹ Similarly to hepatitis C, higher levels of inflammatory modulators such as IL-4, IL-10, and TGF-beta, as well as an increase in lymphocytes expressing T regulatory cell marker FOXP3, were all associated with poorer treatment outcomes.^{4,5,9} As such, it may be true that tumor regression in OSSN depends on a certain immunity profile.

Interferon acts as an immunomodulatory agent that is involved in intrinsic crosstalk between almost all other players in the immune system.⁵ Various ligands activate a set of pattern recognition receptors, including toll-like receptors (TLRs), which generate type I interferons and various cytokines such as IL-12 and IL-15.¹ This initiates apoptotic pathways through caspase-8, as well as NK cell activation, which produce type II interferons.¹⁰⁻¹¹ IFN- α/β also modulate the activation of CD8+ T lymphocytes and produce additional INF- γ , as well as engage distant antiviral responses to signal Jak1 and Tyk2 phosphorylation to initiate various STAT pathways.^{4,5,7,10} The importance of interferons in building immune integrity is highlighted by their overlap with humoral immunity, as well as their need in promoting cytotoxic T-cell response, as demonstrated in the aforementioned hepatitis and cervical cancer treatment models.¹²⁻¹³ With respect to its antitumor effects, IFN- α affects intrinsic differentiation, apoptosis, growth inhibition, cell migration, and production of secondary mediators. Additionally, it stimulates immune regulation by means of increased antigenic expression, antigen presenting cell activation, myeloid-derived suppressor cell inhibition, and up-regulation of stress ligands.⁵ Nonetheless, literature is lacking regarding the integrity of interferon's immune-modulating actions in a compromised immune system.

Of all patients in our study, OSSN partially or completely responded to 5-FU following insufficient response to IFN- α 2b, and one responded to MMC. This may be explained by different mechanisms of action for 5-FU and MMC when compared to interferon. Whereas IFN- α works on immunological factors, MMC and 5-FU inhibit nucleic acid synthesis.¹⁴⁻¹⁵

In conclusion, our case series highlights that immunosuppression may be a risk factor for treatment failure of IFN α 2b in OSSN. Our findings are supported by risk factors for

treatment failure in hepatitis C and cervical intraepithelial neoplasia and by the known interface of type I interferon within a complex immune system. However, our study's conclusions must be evaluated within its limitations, which include a retrospective design with a limited number of patients. Based on this study, we are unable to comment on whether there is a differential treatment response by HIV status, as none of our treatment failures were HIV positive. Additionally, it is important to consider other possible factors affecting treatment response, including age, medication compliance, and genetic/cytogenetic contributions. Despite these limitations, our study suggests that topical IFN α 2b may not be the optimal choice in patients with OSSN and immunosuppression due to a hematologic malignancy. In these patients, surgical excision or another medical therapy (e.g. 5-FU or MMC) may be a better first line therapeutic option. Further large-scale studies are necessary to confirm our findings.

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Figure 1.

Photographs of case 1 illustrating (a) a gelatinous limbal lesion with leukoplakia in the right eye extending from 7:30 to 10 o'clock with 1 mm extension into the cornea, and (b) an opacity involving the limbus and cornea at approximately 4 o'clock in the left eye (black arrows). (c) Anterior segment high resolution ocular coherence tomography (HR-OCT) with thick hyper-reflective epithelium (black asterisk) and a sharp border between normal and abnormal epithelium (white arrow); (d, e) Following 6 months of IFN α 2b, persistent OSSN was noted in both eyes (black arrows).

Figure 2.

Photographs of case 2 illustrating (a) gelatinous lesion with foci of leukoplakia in the temporal conjunctiva of the right eye (black arrow); (b) HR-OCT with typical features of OSSN of thickened hyper-reflective epithelium (black asterisk), and an abrupt transition from normal to abnormal epithelium (white arrow); (c) Following 2 months of IFNα2b (1 million units/mL), the tumor showed no response and slightly increased in size (black arrow).

Figure 3.

Photographs of case 3 illustrating (a) corneal and limbal gelatinous lesion in the right eye, extending from 3 to 5 o'clock (black arrow); (b) HR-OCT demonstrating thick hyper-reflective epithelium consistent with OSSN; (c) persistent OSSN staining with Rose Bengal after 7 months of IFN α 2b, extending 3 mm into the cornea from 4 to 5 o'clock OD (black arrow); (d) HR-OCT demonstrating thin, normalized, hypo-reflective corneal and conjunctival epithelium, consistent with resolved OSSN.