Topical Interferon Alfa-2b for Management of Ocular Surface Squamous Neoplasia in 23 Cases

Outcomes Based on American Joint Committee on Cancer Classification

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Objective: To evaluate the efficacy of topical interferon alfa-2b in the management of ocular surface squamous neoplasia (OSSN).

Methods: Clinically visible OSSN in 20 patients (23 tumors) was managed with topical interferon alfa-2b, 1 million IU/mL, 4 times daily. Tumor control and complications were evaluated according to American Joint Committee on Cancer classification.

Results: Complete tumor resolution was achieved in 19 tumors (83%) following topical interferon alfa-2b treatment for a median period of 6 months (mean, 7 months; range, 1-12 months) and maintained for up to 24 months of follow-up. Of the 4 tumors with partial resolution (17%), tumor surface area was reduced 44% (median) during 4 months (median) without further response and alternative therapy was used. Based on American Joint Committee on Cancer classification, complete control was achieved in 2 of 3 Tis (67%), 17 of 20 T3 (85%), 19 of 23 N0 (83%), and 19 of 23 M0 (83%) category tumors. Tumors involving the cornea responded earlier compared with those without corneal involvement ($P = .01$). Initial tumor size did not correlate with time to response ($P = .27$). Recurrence was noted in 1 case (Tis, 4%) at 3 months. Adverse effects included conjunctival hyperemia (2 [10%]), follicular hypertrophy (2 [10%]), giant papillary conjunctivitis (1 [5%]), irritation (1 [5%]), corneal epithelial defect (1 [5%]), and flu-like symptoms (1 [5%]); all resolved within 1 month of medication discontinuation.

Conclusion: According to American Joint Committee on Cancer classification, complete control with topical interferon alfa-2b can be achieved in 67% of Tis, 85% of T3, and 83% of all OSSN.

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Ocular surface squamous neoplasia (OSSN) encompasses a broad spectrum of neoplastic squamous epithelial abnormalities, including squamous dysplasia, squamous cell carcinoma in situ (also known as conjunctival intraepithelial neoplasia [CIN]), and invasive squamous cell carcinoma. These neoplastic conditions can affect the conjunctiva as well as the corneal surface and occasionally invade into the globe, orbit, and nasolacrimal system. In a survey on 1643 conjunctival tumors from an ocular oncology tertiary care center, 179 tumors (11%) were classified under the category of OSSN. The proposed etiologic risk factors for OSSN include environmental exposure to UV-B solar radiation, cigarette smoke, human papilloma virus, human immunodeficiency virus, petroleum products, medical immunosuppressive agents for organ transplant, and corneal graft.

In more recent years, the management of OSSN has involved the use of topical chemotherapeutic agents, such as mitomycin C, fluorouracil, and interferon alfa-2b. These medications have a distinct advantage over surgical resection in that they have the ability to coat the entire surface of the eye and deliver treatment not only to the affected site but also to remote preclinical sites, potentially eliminating subclinical OSSN. Topical interferon alfa-2b is an ideal medication for treatment of OSSN because it is relatively nontoxic. Most previous studies have focused on its efficacy and safety for noninvasive CIN. Comparison of the results from different studies becomes challenging when the definitions of tumor diagnosis (clinical vs histopathologic), vertical tumor extent (eg, dysplasia, intraepithelial neoplasm, and invasive neoplasm), horizontal tumor extent (eg, bulbar conjunctiva, cornea, and tarsal conjunctiva), and tumor response (ie, cure, failure, and recurrence) are not uniform. The American Joint Committee on Cancer (AJCC) classification has established criteria for defining and staging...
METHODS

This study was approved by the institutional review board of Wills Eye Institute, Philadelphia, Pennsylvania. The medical records of 80 patients who received interferon alfa-2b (either topical application or subconjunctival injection) for the clinical diagnosis of OSSN at the Oncology Service at Wills Eye Institute were reviewed. Only patients receiving topical interferon alfa-2b as primary treatment for a clinically visible tumor were included in this study. Patients who received subconjunctival interferon alfa-2b injection preceding topical interferon alfa-2b and those whose condition was managed with interferon alfa-2b for histopathologic positive margins were excluded. The treatment protocol included use of interferon alfa-2b (Intron-A, Schering-Plough) in a topical formulation of 1 million IU/mL compounded by the Jefferson Pharmacy, Philadelphia, by reconstitution of 1 mL of interferon alfa-2b, 10 million IU/mL, with 9 mL of distilled sterile water and stored in refrigeration. The cost of this therapy was $179 per month. The eyedrops were administered 4 times daily until at least 1 month beyond complete clinical resolution of the tumor. The response to treatment was monitored on follow-up visits every 3 to 6 months, and the duration of the treatment was modified on the basis of tumor response.

The demographic data recorded included age, sex, race, and skin color. History of risk factors, including smoking status, human papilloma virus infection, human immunodeficiency virus infection, chronic use of corticosteroids or other immunosuppressive medications, organ transplant, and corneal graft, was recorded. Any treatment modalities used before referral (excisional biopsy, cryotherapy, and topical chemotherapy) were documented. Recorded clinical findings included best-corrected visual acuity, diagnosis (squamous cell carcinoma or CIN), tissues involved (bulbar conjunctiva, cornea, tarsal conjunctiva, limbal conjunctiva, caruncle, and semilunar fold), number of tumors, maximal tumor basal diameter (in millimeters), tumor surface area (in millimeters squared), quadrant or location involved (superior, nasal, inferior, and temporal quadrants; upper tarsus; and lower tarsus), number of clock hours of limbal involvement, distance from the limbus, growth type (flat sessile, dome, and pedunculated), presence of leukoplakia, presence of feeder and intrinsic vessels, presence of internal cysts, and color of the lesion. Based on clinical findings, the AJCC clinical stage of the tumor was determined (Table 1).

The number of months of topical interferon alfa-2b treatment and the reason for interruption or termination of treatment were recorded. The best-corrected visual acuity, maximal tumor basal diameter, tumor surface area, percentage of tumor remaining, and interferon alfa-2b–related toxicity were recorded at each of the follow-up visits (0 to <3, ≥3 to 6, ≥6 to 12, >12 to 24, and >24 months). The tumor surface area was calculated using a geometric formula for area depending on the shape of the lesion. Irregular lesions were divided into smaller regular (rectangular, triangular, or circular) areas, and the tumor surface area was calculated by adding the surface area of these smaller components of the lesion.

Slitlamp biomicroscopy was performed with documentation on large conjunctival drawings and clinical photographs at each visit. Complete response was defined as 100% reduction of tumor surface area with topical interferon alfa-2b treatment alone, and partial response was defined as tumor regression of less than 100%. Recurrence was defined as the reappearance of a tumor at the same location after complete resolution following treatment. New tumor was defined as appearance of a tumor at a location distant from the original lesion. Any other treatment administered after topical interferon alfa-2b for further tumor control was noted. Recorded treatment outcomes included recurrence of a tumor, appearance of a new tumor, characteristics of a recurrent or new tumor, treatment of a recurrent or new tumor, posttreatment visual acuity, reason for any visual loss, metastasis, site of metastasis, death, cause of death, and the date of each of these outcomes. Metastasis to regional lymph nodes was assessed by history and palpation of preauricular, submental, submandibular, and cervical lymph nodes at each visit. Distinct metastasis was assessed by history at each visit, physical examination once a year, and additional imaging, if needed.

Statistical analysis (unpaired t test and Pearson correlation test) was performed using commercial software (SPSS, version 16.0; SPSS Inc) to test the association of time to response with factors such as corneal involvement and initial tumor size.

RESULTS

Of 80 patients with OSSN managed with interferon alfa-2b at the Ocular Oncology Service at Wills Eye Institute, 20 patients met inclusion criteria for this study. The median patient age was 63 years (mean, 63 years; range,
22-89 years); 14 were male (70%) and 6 were female (30%); 18 were white (90%) and 2 were African American (10%). A history of risk factors for OSSN included smoking (6 [30%]), human papilloma virus infection (2 [10%]), use of a corticosteroid or other immunosuppressive drug (2 [10%]), and corneal graft (1 [5%]). None of the patients in this series had human immunodeficiency virus infection or organ transplant. The median visual acuity at presentation was 20/30 in the affected eye.

There were 23 distinct tumors identified in 21 eyes of 20 patients. The AJCC clinical categories included Tis (3 [13%]), T3 (20, [87%]), N0 (23 [100%]), and M0 (23 [100%]). There were no cases of T1, T2, or T4 category tumors (Table 1). The tumor quadrant was temporal (5 [22%]), nasal (4 [17%]), inferior (2 [9%]), and multiple (12 [52%]). The median tumor involvement was 4 clock hours (mean, 7 months; range, 1-10 clock hours). The median distance of the tumor from the limbus was 0 mm (mean, 0.1 mm; range, 0-1 mm). Only 3 tumors (13%) had leukoplakia involving 25%, 50%, and 100% of the tumor surface (1 tumor each). None of the tumors showed internal cysts.

The tumor characteristics are described in Table 2.

Treatments before referral included excisional biopsy (9 [39%]), cryotherapy (2 [9%]), topical mitomycin C (1 [4%]), and topical interferon alfa-2b (3 [13%]). Despite prior treatments in these cases, all displayed a clinically visible tumor. Histopathologic diagnosis before referral was available in 8 of 9 cases that had excisional biopsy. This included invasive squamous cell carcinoma (n=4), conjunctival intraepithelial neoplasia (n=3), and large-cell acanthoma (n=1), with tumor extending to the surgical margin in 6 cases. The primary reason for use of topical interferon alfa-2b was extensive, unresectable OSSN in 15 tumors (65%), poor surgical candidate in 6 tumors (26%), and poor visual acuity of the contralateral eye in 2 tumors (9%). All patients received a 1 million–IU/mL formulation of topical interferon alfa-2b 4 times daily for a median treatment duration of 11 months (mean, 10 months; range, 3-24 months).

Complete tumor resolution was achieved in 19 tumors (83%) following topical interferon alfa-2b treatment during a median period of 6 months (mean, 7 months; range, 1-12 months). The tumor control based on AJCC classification is summarized in Table 3 and shown in Figure 1. The rate of tumor surface area reduction is summarized in Table 4 and shown in Figure 2. The mean tumor surface area reduction was 58% before 3 months, 79% by 3 months to 6 months, 98% by later than 6 months to 12 months, and 100% by later than 12 months to 24 months. In the 4 tumors (17%) with partial response to topical interferon alfa-2b, the median percentage of tumor surface area remaining was 56% (mean, 60%; range, 46%-84%) after interferon alfa-2b therapy for a median period of 4 months (mean, 4 months; range, 3-6 months). In these cases, further complete control was achieved with excisional biopsy (n=2) and photodynamic therapy combined with single subconjunctival injection of interferon alfa-2b, 5 million IU/mL (n=1). One patient with xeroderma pigmentosum and numerous previous OSSN achieved tumor regression with topical interferon alfa-2b therapy to 49% of the original tumor surface area within 4 months and then maintained stability for 8 months; therefore, long-term topical interferon alfa-2b therapy was advised for this patient.

Tumors involving the cornea (n=19) responded within a mean of 6 months, and those sparing the cornea (n=4)
responded within a mean of 12 months. The difference in the time to response between these 2 groups was statistically significant ($P = .01$, $t$ test). When time to response was evaluated according to the initial tumor surface area, no statistically significant correlation was noted ($P = .27$, Pearson correlation test).

Overall, recurrence was noted in 1 case (4%) (Tis) at 3 months. New tumor development at a different site was found in 2 cases (9%) (both T3) during a median of 8 months. Recurrent and new tumors were managed with cryotherapy, topical interferon alfa-2b, and/or surgical excision. For all cases, the median duration of follow-up after the initiation of topical therapy was 12 months (mean, 17 months; range, 3-53 months). Posttreatment visual acuity improved by 3 or more lines in 3 of 21 eyes (14%), remained stable with fewer than 3 lines difference in 17 of 21 eyes (81%), and worsened by 3 or more lines in 1 of 21 eyes (5%). The reduction of visual acuity was due to cataract progression. There was no systemic metastasis or death.

Adverse effects of topical interferon alfa-2b included conjunctival hyperemia (2 [10%]), follicular hypertrophy (2 [10%]), giant papillary conjunctivitis (1 [5%]), irritation (1 [5%]), corneal epithelial defect (1 [5%]), and flulike symptoms (1 [5%]). These adverse effects resolved within 1 month of discontinuation of topical therapy.

**COMMENT**

Interferons are protein molecules that bind to cell receptors and trigger synthesis of effector proteins that can inhibit viruses, activate immunocompetent cells, and regulate oncogenes. They are a natural defense mechanism. Interferon alfa-2b is a recombinant form of interferon alfa that is approved by the US Food and Drug Administration for treatment of chronic hepatitis B and C, malignant melanoma, hairy cell leukemia, multiple myeloma, follicular lymphoma, condyloma acuminata, and AIDS-related Kaposi

**Table 4. Reduction of Tumor Surface Area During Time Interval in 19 Cases With Complete Response**

<table>
<thead>
<tr>
<th>Tumor Reduction</th>
<th>&lt;3 mo (n = 19)</th>
<th>3-6 mo (n = 19)</th>
<th>&gt;6-12 mo (n = 15)</th>
<th>&gt;12-24 mo (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>58</td>
<td>79</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>Median (range)</td>
<td>50 (10-100)</td>
<td>100 (0-100)</td>
<td>100 (80-100)</td>
<td>100</td>
</tr>
</tbody>
</table>

* Some patients did not complete a follow-up for as long as 24 months.
The use of interferon alfa-2b for OSSN is off-label but supported by scientific evidence.31,32 Topical application of chemotherapeutic agents, such as mitomycin C, fluorouracil, or interferon alfa-2b has been used for control of OSSN.14-27 According to a review by Poothullil and Colby,16 the rates of CIN regression with these 3 agents are comparable (80%-88%). Esquenazi and associates33 found that interferon alfa-2b is more expensive ($300 per treatment) than mitomycin C ($150 per treatment) and fluorouracil ($100 per treatment) in the treatment of CIN, but its superior safety profile makes it preferable.

The standard dose of topical interferon alfa-2b is 1 million IU/mL. Galor and associates20 compared this dose with a 3 million IU/mL dose and found no comparative difference in tumor response, time to resolution, recurrence rate, and adverse effects. Topical therapy with interferon alfa-2b, 1 million IU/mL, has been reported in several publications20-27 to be successful in achieving tumor control in 80% to 100% of OSSN classified as CIN. In our study, all 23 tumors (100%) showed a response and 19 tumors (83%) displayed complete response with topical interferon alfa-2b alone. Based on AJCC classification, 2 TisN0M0 category tumors (67%) and 17 T3N0M0 category tumors (85%) showed complete response. Therefore, topical interferon alfa-2b demonstrates efficacy in controlling both Tis- and T3-category tumors. These findings are important, since most previous studies have focused on topical interferon alfa-2b for Tis (CIN) category tumors, whereas our study further explored the role of topical interferon alfa-2b for more advanced tumors, such as T3. We found that T3 tumors, with local invasion into the cornea, fornix, and palpebral conjunctiva, show complete response to treatment with topical interferon alfa-2b in most (85%) cases.

In our analysis, the median time to complete tumor resolution was 6 months (mean, 7 months; range, 1-12 months). Other studies have found time to resolution of CIN with interferon alfa-2b ranging from 2 to 3 months20,21 and with a mean treatment duration ranging from 3 to 5 months.22-27 The longer duration to cure in our study could be the result of our treatment of more advanced tumors. Previous reports20-27 evaluated early OSSN (Tis), whereas we largely evaluated advanced OSSN, most classified as T3. Therefore, we suspect that treatment of T3 lesions, possibly a more deeply penetrating malignant neoplasm, could require longer duration of topical interferon alfa-2b therapy compared with Tis category lesions, a more superficial premalignant condition.

Recurrence after interferon alfa-2b use has been recognized in none to 29% of patients at intervals ranging from 2 to 28 months following treatment.20-27 In previous studies, recurrent tumors have been managed by retreatment with topical interferon alfa-2b21,27 or topical interferon alfa-2b combined with mitomycin C.21,23 In our series, recurrence was noted in 1 case (4%) at 3 months after complete initial resolution and was managed with cryotherapy and long-term topical interferon alfa-2b therapy.

In our series, one patient developed a new tumor in each eye 8 months after discontinuing topical interferon alfa-2b following complete initial tumor control with 12 months of treatment. The new tumors responded to resumption of topical interferon alfa-2b therapy for an additional 12 months and required resection and cryotherapy for complete control. We speculate that these new tumors would not have developed if interferon alfa-2b therapy was continued for a longer duration to allow complete control of a subclinical tumor. Overall, we concur that OSSN, especially squamous cell carcinoma, may require long-term follow-up for detection of recurrent or new tumors. Reducing the frequency of topical interferon alfa-2b use from 4 to 2 times a day after complete tumor control is achieved for an additional 6 to 12 months might be a reasonable approach to prevent new or recurrent tumors.

Karp and associates27 suggested the possibility that larger lesions may require a longer time to resolve and that corneal lesions may respond more rapidly than conjunctival lesions, based on their series of 5 patients. In our study, no significant difference was noted in the time to response based on initial tumor size (P = .27). However, we found that lesions (n = 19) with corneal involvement responded within a shorter duration (mean, 6 months) than did those (n = 4) sparing the cornea (mean, 12 months) and that this difference was statistically significant (P = .01). Of the 4 lesions sparing the cornea, 3 involved the tarsal conjunctiva in addition to the bulbar conjunctiva. Although formal thickness measurements were unavailable, we suspect that these 4 lesions were thicker than the remaining 19 lesions, and the hindrance to penetration of topical interferon alfa-2b may account for different response rates. It may be that the biological behavior and immunoregulation of these 2 subsets of OSSNs may differ and contribute to different response rates.

The duration for which topical interferon therapy should be continued beyond tumor resolution is not well known. It has been continued up to tumor resolution,24-26 up to 1 month beyond tumor resolution,20,21,26,27 and up to 4 months beyond tumor resolution27 in various studies. In our study, the treatment was recommended to be continued for at least 1 month after achieving tumor resolution.

Lack of toxicity of topical recombinant interferon on rabbit eyes has been documented.34 Studies investigating use of topical interferon alfa-2b, 1 million IU/mL, for OSSN in human eyes have reported low rates of reversion.

Figure 2. Topical interferon alfa-2b for management of ocular surface squamous neoplasia in 23 cases. Graphical representation of the residual tumor surface area after initiation of interferon alfa-2b therapy (date of first treatment [DFT]) to the last follow-up examination in 19 cases with complete response.
ible complications, such as ocular discomfort and photophobia in 10%,
20 conjunctival hyperemia in 12%,
21 follicular conjunctivitis in 7% to 20%,
22,23 irritation in 10%,
24 and superficial keratitis in 1 reported case.35 Our study showed similar rates of self-resolving complications. In one study, 24 57% of treated patients developed conjunctival hyperemia and follicular conjunctivitis, most likely attributed to the vehicle (benzyl alcohol, glycyne, and human albumin) used to deliver interferon alfa-2b. The vehicle in our preparation was sterile distilled water, and our rate of conjunctival hyperemia was 10% (2 patients), with no cases of follicular conjunctivitis and 10% (2 patients) with follicular hypertrophy.

A physician survey in 2005 conducted to assess the standard of care in the treatment of OSSN showed that less than 5% of the physicians reported interferon alfa-2b36 as their primary choice of therapy and, among those who routinely used adjunctive topical therapy after surgical excision, only 18% preferred interferon alfa-2b. Our primary strategy for management of OSSN is surgical excision, surrounding cryotherapy, and alcohol keratectomy, with histopathologic confirmation of the tumor. However, there are circumstances in which surgical excision is not feasible, especially with extensive disease or elderly patients ineligible for surgical intervention, as occurred with several cases in this study. In this study, we found reliable efficacy of topical interferon alfa-2b as primary treatment of advanced OSSN. Nevertheless, when topical interferon alfa-2b is used for clinically diagnosed OSSN (without histopathologic confirmation), as with many of the cases in our series, we recommend exercising caution and considering surgical excision whenever feasible, especially in atypical lesions, for diagnostic and therapeutic purposes.

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