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Comparison of topical 5-fluorouracil and interferon alfa-2b as primary treatment modalities for ocular surface squamous neoplasia

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Abstract

Purpose: To compare the efficacy of topical 5-fluorouracil 1% (5FU) and interferon alfa-2b 1 MIU/mL (IFN) eye drops as primary treatment modalities for ocular surface squamous neoplasia (OSSN).

Design: Retrospective, comparative, interventional case series.

Methods: Fifty-four patients who received 5FU and 48 patients who received IFN as primary therapy for OSSN were included. Primary outcome measures were the frequency of clinical resolution and time to OSSN recurrence by treatment modality. Secondary outcome was the frequency of side effects with each therapy.

Results: The mean age of patients was 68 years. More Hispanics were treated with 5FU. In a univariable analysis, frequency of OSSN resolution was higher with 5FU (96.3%, n = 52) than with IFN (81.3%, n = 39), p=0.01. In a multivariable analysis, treatment modality did not remain a significant predictor of resolution. In patients whose OSSN resolved, time to resolution was similar with both agents, (5FU - mean 6.6 months, standard deviation (SD) 4.5 versus IFN - mean 5.5 months, SD 2.9, p = 0.17). Of the 52 eyes whose OSSN resolved with 5FU, 11.5 % of lesions (n=6) recurred while of the 39 eyes whose OSSN resolved with IFN, 5.1% of lesions (n = 2) recurred, p=0.46. Kaplan Meier survival curves of OSSN recurrence were similar between groups (log rank=0.16). One-year recurrence rates were 11.4% with 5FU and 4.5% with IFN. Eyelid edema (p=0.04) and tearing (p=0.02) were more significant with 5FU.

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Conclusions: This is the first direct comparison study between 5FU and IFN eye drops as primary treatment modalities for OSSN. Both modalities resulted in a high frequency of tumor resolution and low recurrence rates and are effective treatment options for OSSN.

Introduction

Ocular surface squamous neoplasia (OSSN) is the most common malignancy of the ocular surface.¹ It comprises a spectrum of epithelial squamous conditions ranging from dysplasia to invasive carcinoma.² The strongest risk factors for OSSN include prior history of OSSN, ultraviolet light exposure, prior skin cancer, older age and male gender.^{3,4} Less strongly associated factors include human immunodeficiency virus (HIV), human papilloma virus (HPV), and smoking.^{4,5}

Historically, surgical excision using a no-touch technique with adjuvant alcohol and cryotherapy has been the gold standard of treatment for OSSN.⁶ Surgical excision is often both diagnostic and therapeutic and allows for rapid resolution of lesions.^{3,7,8} However, there is often subclinical microscopic disease beyond the excised lesion that is not completely addressed, and this can lead to recurrence frequencies as high as 56%.^{9,10} Surgery can also lead to sequelae such as conjunctival hyperemia, conjunctival scarring and limbal stem cell deficiency.¹¹

Medical management of OSSN has been gaining increasing momentum as the primary therapy for OSSN.^{12,13} Topical chemotherapeutic agents have the ability to treat the entire ocular surface, which is beneficial in addressing microscopic subclinical disease as well as recurrent and multifocal lesions.¹⁴ These agents can be employed as primary treatment or as adjuvant therapy to surgical excision. However, with topical agents there are often longer resolution times and increased out of pocket costs for patients. Associated adverse effects and patient compliance can also limit use.¹¹

The chemotherapeutic agents employed for treatment include interferon alfa-2b (IFN), 5-fluorouracil (5FU), and mitomycin C (MMC). IFN is an endogenous glycoprotein released by various immune cells with antiviral, antimicrobial and antineoplastic activities that is used in recombinant form.¹⁵ 5-FU is an antimetabolite that inhibits the action of thymidylate synthase, therefore interrupting the synthesis of nucleosides used for DNA formation.¹⁶ MMC is an alkylating agent that acts in all phases of the cell cycle and inhibits RNA and protein synthesis.¹⁷ All of these agents, despite their differing mechanisms of action, have been shown to be effective in the treatment of OSSN, with varying resolution rates.^{11,18-20}

Several studies have retrospectively reviewed the efficacy of these agents in the primary treatment of OSSN.¹¹ One study compared topical IFN and MMC and found similar response frequencies between both agents (89% IFN and 92% MMC, $p=0.67$) with shorter resolution times with MMC (1.5 months MMC versus 3.5 months IFN, $p < 0.005$).²¹ Another study compared IFN therapy to surgical excision and found comparable recurrence rates (3% at 1 year with IFN vs 5% at 1 year with surgery, $p = 0.80$) with the most common complication being mild discomfort in both groups.³ A gap in the literature, however, is a head-to-head comparison between 5FU and IFN as primary treatment modalities for OSSN.

As such, the primary purpose of this research study was to compare the efficacy and safety of topical 5FU and IFN as primary treatment modalities for OSSN.

Methods

Study population:

The institutional review board of the University of Miami approved this retrospective study, and the methods adhered to the tenets of the Declaration of Helsinki and were compliant with the Health Insurance Portability and Accountability Act. A pharmacy database was used to identify all patients with OSSN that were treated with either topical 5FU or IFN as primary treatment modalities for OSSN at the Bascom Palmer Eye Institute between January 2013 and July 2016 (n=346). Retrospective chart reviews were conducted. Patients were excluded if either agent was used as adjuvant surgical therapy, if IFN was administered as a peri-lesional injection, if treatment was not completed, if patients were lost to follow-up, if patients were still in active treatment, or if patients were not primarily managed at our institution. This left 54 patients who received 5-FU as the primary treatment modality and 48 patients who received IFN topically as the primary treatment modality for OSSN for final analysis.

Topical 5 FU:

All patients were treated with topical 5FU at a concentration of 1%. The drops were administered four times daily for one week, followed by a drug holiday for three weeks. This monthly cycle was continued until clinical resolution, after which the drops were discontinued. Patients were initially seen on a two-month basis to assess treatment response.

Topical IFN:

All patients were treated with topical IFN at a concentration of 1 MIU/mL. The drops were administered four times daily continuously without any cessation of therapy. Patients were initially seen on a two-month basis to assess treatment response.

Data extracted:

Patient records were reviewed for demographic information (age, gender, race, ethnicity) and OSSN risk factors (history of skin cancer, HPV, HIV, smoking, sun exposure - defined as patient subjectively noting to spend a large quantity of time outdoors, presence of pterygium or prior pterygium surgery, and prior history of OSSN). Characteristics of the current lesion were also documented including the involved eye, tumor location, tumor size and involved ocular structures (conjunctiva, cornea, limbus, orbit), uni- vs. multi-focality, and appearance (leukoplakic, gelatinous, papillomatous, flat/opalescent) based on descriptions and photographs. The tumor size and location provided the basis for American Joint Committee on Cancer (AJCC) clinical stage of the tumor.²² Of the 24 patients that underwent biopsy, pathologic grading of the tumor (mild, moderate, or severe carcinoma in situ or invasive squamous cell carcinoma) and margin positivity were also recorded. Treatment information documented included the primary modality of treatment, and for medical therapy included the dose, frequency, and length of treatment.

Main outcome measures:

The main outcome measures were the frequency of clinical resolution and time to OSSN recurrence with each treatment modality. A secondary outcome was the frequency of side effects.

Response information was recorded in terms of time to complete resolution of the lesion (defined as disappearance of the lesion clinically and/or by anterior segment optical coherence tomography (AS-OCT)). Not all patients had AS-OCT imaging in both groups. Recurrence was defined as a reappearance of a lesion, either in the same or similar location as the original tumor or on any part of the ocular surface, after complete resolution of the original tumor. Follow up was carried out from the time of clinical resolution of the lesion until the last visit. Documented complications included those volunteered by the patient as well as those elicited by the examiner during the clinic visit; no formal survey was used. The presence of side effects was assessed at each visit and recorded by one author (CLK). Specifically, patients were asked about pain, redness, lid swelling, light sensitivity, tearing, itching, and blurred vision. Side effects evaluated for on examination included hyperemia, keratopathy and limbal stem cell deficiency.

Statistical analyses:

Statistical analyses were performed using the SPSS 22.0 (SPSS Inc, Chicago, IL) statistical package. Frequencies of demographic and clinical variables were calculated for each group. Categorical variables were compared using a Chi square analysis or Fisher exact test as appropriate; continuous variables were compared using the student t-test. Time-to-event curves were generated using the Kaplan-Meier method. Logistic regression analysis was employed to evaluate factors associated with disease resolution. Cox proportional hazards analysis was employed to evaluate factors associated with disease recurrence. Forward stepwise multivariable analyses were conducted to adjust for potential confounders for primary outcome measures.

Results:**Demographics:**

Demographics of the study population are presented in Table 1. The majority of patients affected with OSSN were white males in their late 60s. There was a higher number of patients of Hispanic ethnicity in the 5FU compared to the INF group, $p = 0.04$. More tumors were located in the inferior bulbar conjunctiva in the 5FU compared to the IFN group (38.9% vs 18.8%, $p=0.03$). Mean follow-up was 15.8 months, standard deviation (SD) 9.7 in the 5FU group and 20.9 months, SD 13.3 in the IFN group ($p=0.03$).

Frequency of resolution of OSSN between 5FU therapy and IFN therapy:

Of the 54 eyes treated with 5FU, 96.3% of lesions ($n=52$) completely resolved (median number of cycles was 4, range 2 to 12, mean 4.2, SD 1.9). Of the 48 eyes treated with IFN therapy, 81.3% of lesions ($n = 39$) completely resolved (median number of months treated 4, range 2 to 8, mean 4.2, SD 1.5). The difference in frequency of response to each treatment was statistically significant ($p=0.01$) by univariable analysis.

To evaluate and adjust for potential confounders between the two treatment groups, a multivariable analysis was performed that considered the effects of demographics and tumor characteristics on clinical resolution. While the univariable analysis showed significant superiority of 5FU in clinical resolution (96.3% vs 81.3% $p=0.01$), the multivariable analysis did not show a significant difference in resolution rates between the two treatments. The only factor found to predict clinical resolution was ethnicity. Patients of Hispanic ethnicity were 7.7 times more likely to respond to medical therapy (95% confidence interval 1.5 to 38.8, $p = 0.01$) compared to non-Hispanics.

Time to resolution of OSSN between 5FU therapy and IFN therapy:

Of the lesions that resolved completely with 5FU and IFN therapy, there was no statistically significant difference in the time to resolution between the two agents (5FU – mean 6.6 months, SD 4.5; IFN – mean 5.5 months, SD 2.9; log rank = 0.62). (Figure 1).

Treatment failures:

Two of 54 patients failed treatment with 5FU of which both were treated for two cycles. One was switched to IFN for three additional cycles and the other to MMC for two cycles. Both patients had resolution of their tumor after the switch of therapy.

Nine of 48 patients failed treatment with IFN after being treated between two to seven months. All nine were subsequently switched to 5FU. Six patients responded to the 5FU while three needed additional therapy. Of these, two patients were then switched to MMC and one underwent surgical excision. All patients had complete resolution of their lesions with these alternative therapies.

Recurrences after treatment:

Of the 52 eyes whose OSSN resolved with 5FU therapy, 11.5 % of lesions ($n=6$) recurred after a mean of 7.7 months, SD 9.1. Of the 39 eyes whose OSSN resolved with IFN therapy, 5.1% of lesions ($n = 2$) recurred after a mean of 9.9 months, SD 11.4, $p=0.46$ for frequency of recurrence. With Kaplan Meier survival analysis, at 1 year, recurrence was 11.4% in the 5FU group and 4.5% in the IFN group (log rank = 0.16). (Figure 2). There was no significant difference in frequency of recurrence or time to recurrence by multivariable analysis of demographic factors, tumor characteristics or treatment method.

Treatment side effects:

There were no long-term complications associated with the use of 5FU or IFN. With 5FU, the common side effects were pain ($n=12$, 22.2%), tearing ($n=12$, 22.2%), redness ($n=11$, 20.4%), eyelid edema ($n=5$, 9.3%) and keratopathy ($n=4$, 7.4%). Common side effects with IFN also included pain ($n=9$, 19.6%), redness ($n=6$, 13.0%) and blurred vision ($n=6$, 13.0%). Tearing (5FU 22.2% vs IFN 4.3%, $p=0.02$) and eyelid edema (5FU 9.3% vs IFN 0%, $p=0.04$) were notably more common in the 5FU group than the IFN group. One patient stopped 5FU therapy due to eyelid pain. There were no cases of eyelid edema or keratopathy in the IFN group. Limbal stem cell deficiency was not seen in either the 5FU or IFN treatment groups.

Discussion

To conclude, our study showed that both 5FU and IFN were viable and effective treatment modalities for OSSN, with a high frequency of clinical resolution and low recurrence rate in both groups. Topical 5FU was first reported for the treatment of premalignant lesions of the cornea, conjunctiva and eyelid in 1986.²³ Since then, several studies encompassing 129 individuals evaluated 5FU for as a primary agent for OSSN, with a high frequency of resolution (average 91%, range 82–100%).^{18,24–27} Our 96% frequency of resolution fits well within this range. Our cycle parameters (mean of 4 cycles, 7 days on, 21 days off) are also within the reported range of 5FU being used for 2 to 7 days followed by a 30 to 45 day holiday (range of 1 to 6.5 cycles). Our study represents the largest cohort of patients treated with 5FU (n=54) in the literature with a cycled protocol. Recurrences in our and other studies were low, with a range of 0 to 28%, all of which occurred in the first year.^{24,25,27} Benefits of 5FU are its low cost (approximately \$37 per cycle. Downsides include its side effects, most commonly ocular pain, and lid inflammation, but these are generally manageable, and only 1 individual in our cohort stopped therapy due to ocular pain.

Topical IFN is another commonly used therapy for OSSN, first described in the late 1990s.^{28–30} Since then, several studies encompassing 332 individuals have evaluated its use as a primary agent in OSSN, again with a high frequency of resolution (average 95%, range 75 to 100%). Similar to 5FU, recurrences were uncommon (range 4–20%) and most occurred in the first year.^{3,20,28,29,31–37} Our 81% frequency of resolution fits well within this range. Most studies, including ours, used a concentration of 1 million IU/mL administered 4 times daily for a time period of a few months (range 2 to 6 months). Others have used a higher concentration (3 million IU/ml) with one study reporting a 100% resolution frequency after 2 months with no recurrences during a mean 10.2 month follow-up using this higher concentration.³¹ Other studies, however, found no significant differences in efficacy by IFN concentrations.^{38,33} An advantage of IFN is its gentleness. A downside of treatment is its cost (approximately \$500 dollars per month in the US), need for continuous treatment, and requirement for refrigeration. In addition, some patients, such as those with immunosuppression in the setting of a hematologic malignancy, may do better with 5FU than IFN.³⁹ Perilesional injections of IFN (not included in this study) have been associated with a flu-like syndrome.⁴⁰

Another treatment modality for OSSN is MMC, first reported in 1994.⁴¹ Ten studies, encompassing 212 patients, found an average 90% resolution frequency with MMC.^{19,35,42–49} In our cohort, MMC was used in 3 patients as a salvage therapy after failure of OSSN to respond to either 5FU or IFN. All 3 patients had clinical resolution after an average of 2 cycles of MMC administered in a cyclical fashion (7 days on, 14 days off). MMC costs approximately \$300 dollars per bottle in the US and has a higher frequency of side effects (pain, punctal stenosis and limbal stem cell deficiency) compared to 5FU and IFN.⁵⁰

In our study, the diagnosis of OSSN was made primarily by clinical examination with AS-OCT imaging used as an adjuvant modality given the distinctive and reproducible features that identify this condition.⁵¹ We have previously found that AS-OCT has a high sensitivity

(range 94–100%) and specificity (100%) for the diagnosis of OSSN as compared histopathologic diagnosis.^{52,53}

The largest limitation of our study is its retrospective nature. Our two treatment groups were not identical but were sufficiently similar to allow comparisons of efficacy and recurrence rates. It is interesting to note that Hispanics responded more favorably to treatment than non-Hispanics in our cohort. The reasons for this are unclear. As with all studies, unmeasured confounders could have affected our data such as tumor genetics and host immune response. Furthermore, we did not have pathologic grading in all patients, but in the ones available, there were no differences between the groups.

Other limitations included a non-standardized method for evaluating side effects and treatment compliance and a lack of information on out of pocket patient costs. A strength of our study is that there were no systemic biases in choosing treatment modality by demographic or tumor characteristics. We offer all patients both treatments and a final decision is based on other factors (cost, frequency of administration), allowing us to study efficacy in this paper. Ultimately, a prospective study comparing 5FU and IFN will be needed to further validate our retrospective results.

Despite these limitations, our study, with a large cohort of over 100 patients, showed that topical 5FU 1% eye drop is comparable in efficacy to IFN in the treatment of OSSN. Both modalities resulted in a high frequency of tumor resolution and low recurrence rates. The final message from this study is that 5FU, like IFN, is a viable option in the treatment of OSSN.

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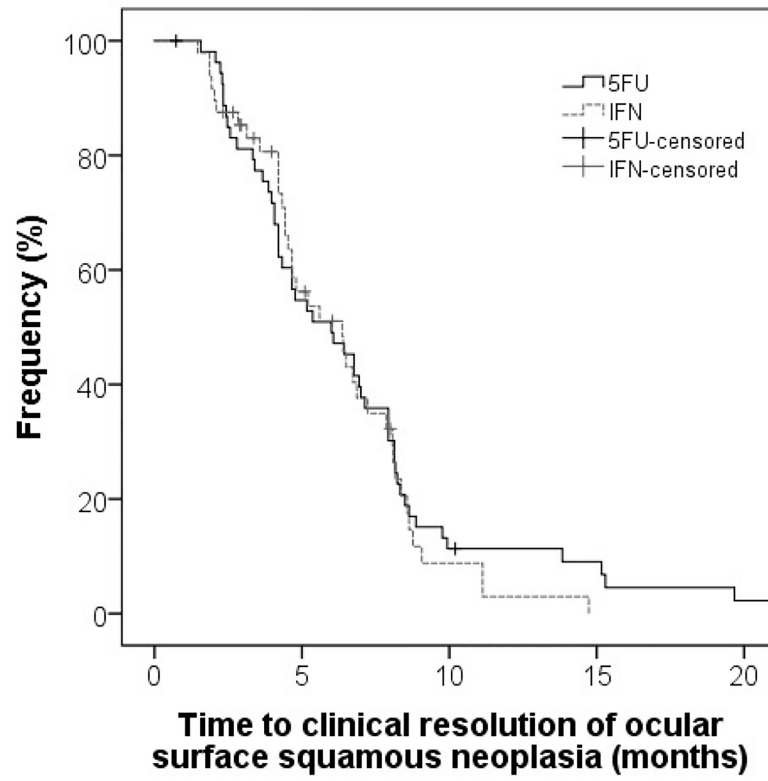


Figure 1 – Kaplan-Meier survival curve: time to clinical resolution

Kaplan-Meier survival curve showing differences in time to clinical resolution of OSSN after treatment with 5FU and IFN.

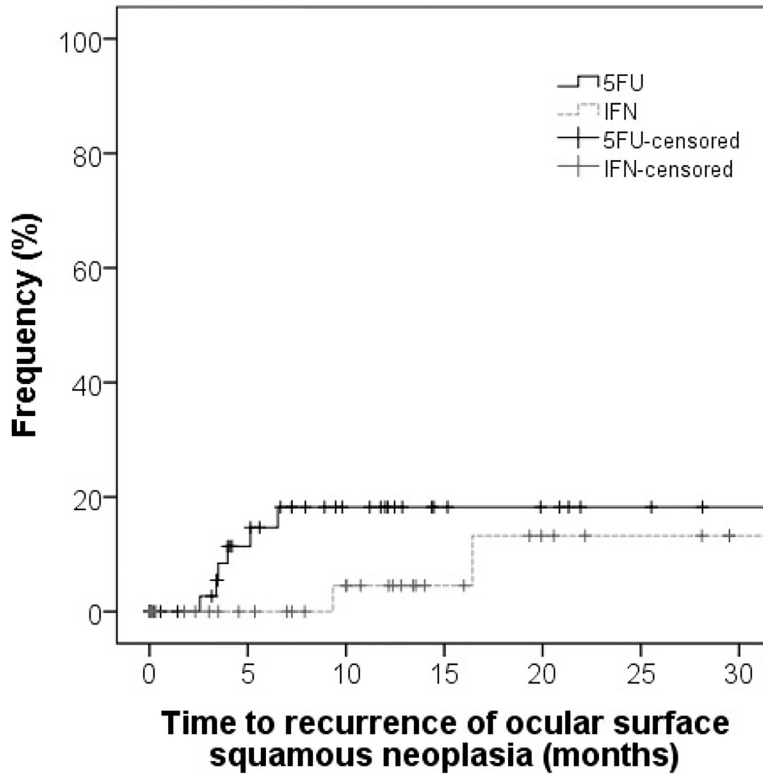


Figure 2 –. Kaplan-Meier survival curve: time to recurrence
Kaplan-Meier survival curve showing differences in time to recurrence of OSSN after treatment with 5FU and IFN.

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Table 1

Demographic and clinical information of patients with ocular surface squamous neoplasia treated with 5-fluorouracil or Interferon alfa 2b eye drops

Demographic and clinical factors	5-fluorouracil (n=54) mean (SD)	Interferon alfa-2b (n=48) mean (SD)	p value
Age	70.0 (12)	65.0 (14)	0.09
Gender			
Male gender	74.1 (40)	60.4 (29)	0.20
Race			0.26
White	70.0 (35)	70.5 (31)	
Black	10.0 (5)	2.3 (1)	
Other	20 (10)	27.3 (12)	
Hispanic ethnicity	70.6 (36)	48.9 (22)	0.04
Current smoker	9.6 (5)	11.4 (5)	0.56
Sun exposure	87.5 (21)	75.0 (21)	0.31
History of pterygium	22.4 (11)	21.3 (10)	0.82
History of OSSN	20.4 (11)	12.5 (6)	0.41
History of skin cancer	25.0 (10)	37.8 (14)	0.33
History of HIV	2.0 (1)	0.0 (0)	0.34
History of HPV	10.8 (4)	9.7 (3)	1.00
Area (mm²)			
	47.9 (62.1)	44.5 (38.1)	0.74
Location^a			
Nasal	51.9 (28)	54.2 (26)	0.85
Temporal	42.6 (23)	60.4 (29)	0.08
Superior	16.7 (9)	16.7 (8)	1.00
Inferior	38.9 (21)	18.8 (9)	0.03
Corneal involvement	79.6 (43)	75.0 (36)	0.64
Corneal and conjunctival involvement	48.1 (26)	66.7 (32)	0.08
AJCC clinical stage^b			0.14
T1a	20.8 (11)	12.8 (6)	
T2a	18.9 (10)	17.0 (8)	
T2b	11.3 (6)	2.1 (1)	
T3a	49.1 (26)	68.1 (12)	
Appearance^c			
Leukoplakia	25.9 (14)	27.7 (13)	1.00
Papillomatous	22.2 (12)	21.3 (10)	1.00
Gelatinous	38.9 (21)	42.6 (20)	0.84
Flat/Opalescent	50.0 (27)	31.9 (15)	0.07

Demographic and clinical factors	5-fluorouracil (n=54) mean (SD)	Interferon alfa-2b (n=48) mean (SD)	p value
Pathologic grade ^d	n=13	n=11	1.00
CIS (mild-severe dysplasia)	24.1	22.9	
SCC	0.0 (0)	0.0 (0)	

Data are no. (%) unless otherwise indicated

^a Tumors could involve more than 1 quadrant; for example, a tumor involving the superior and temporal bulbar conjunctiva would appear in both the superior and temporal location categories.

- Sun exposure was defined as patient noting to spend a large quantity of time outdoors

^b AJCC = American Joint Committee on Cancer clinical stage

^c Tumors could have more than 1 descriptor for appearance

^d CIS = Carcinoma in situ; SCC = Squamous Cell Carcinoma. Pathologic grade was determined only for biopsied specimens, n =24