ORIGINAL RESEARCH PAPER

Ophthalmology

RECURRENCE OF NON-INVASIVE PRIMARY OCULAR SURFACE SQUAMOUS NEOPLASIA (OSSN) FOLLOWING TREATMENT WITH TOPICAL MITOMYCIN C (MMC).

KEY WORDS: mitomycin C (MMC), non-invasive primary ocular surface squamous neoplasia(OSSN), recurrence

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ABSTRACT

Aim: To determine the rate of recurrence following the use of mitomycin C (MMC) for management of non-invasive primary ocular surface squamous neoplasia(OSSN).

Design: Retrospective non-comparative case series.

Methods: Clinical practice setting of 15 patients treated consecutively with topical MMC (0.4 mg/mL) for OSSN observed for clinical recurrence.

Results: Clinical recurrences were diagnosed in 2 of 15 (13%) eyes following topical treatment. The mean time to recurrence was 35.5 months. There was no greater risk of recurrence identified for variables including lesion size, lesion location, gender, age, treatment type or duration.

Conclusions: Topical MMC are an effective treatment modality for a wide range of non-invasive OSSN. Topical therapy avoids the morbidity of excisional surgery with equivalent or reduced recurrence rates and should be considered as primary therapy.

INTRODUCTION

Ocular surface squamous neoplasia (OSSN) encompasses a spectrum of lesions arising from the squamous cells of the conjunctiva and/or cornea.[1] Excessive exposure to ultraviolet B radiation is the major etiologic factor, however other causes, such as human papillomavirus type 16 and 18 and HIV seropositivity, have also been implicated.[1,2] OSSN is described as a relatively low-grade malignancy, as invasive disease is uncommon and tends to be preceded by dysplasia and carcinoma in situ.[1] However, a lack of appropriate and effective treatment for OSSN can result in malignant change followed by local invasion and rarely metastasis. Surgical excision with adequate margins and adjunctive cryotherapy is a well-established treatment for OSSN, although this is an invasive option with numerous disadvantages.

Tabinet al[3] described high recurrence rates following surgical excision (33% at 10 years despite histologically clear surgical margins). Evidence suggests that the microscopic changes associated with OSSN extend beyond the macroscopic margin, thereby surgical excision to achieve clear margins is difficult.[4]

Due to the multifocal nature of OSSN, surgical excision results in wide collateral damage to adjacent areas of normal epithelium including the potential for limbal stem cell deficiency and visually disturbing corneal scarring.[4]

A recent study by Galor et al examined the rates of recurrence following surgical excision using various techniques was 10% at 1 year, and 21% at 5 years.[5] The authors identified tarsal involvement and positive pathologic margins as the strongest predictors of clinical recurrence following surgical excision of OSSN lesions. High grade lesions, large lesions and a previous patient history of OSSN were associated with an increased risk of tumor recurrence. The mean time to clinical recurrence following surgical excision was 2.5 years.

The aim of this study was to identify OSSN recurrence following topical treatment of non-invasive primary OSSN, using a retrospective case series. The study examined the rates of recurrence of OSSN after the use of topical treatment of mitomycin C (MMC).

Identification of risks for recurrence would potentially allow for better management plans, with the aim of improving treatment success.

Methods

In this retrospective non-comparative case series study, clinical data of 15 eyes diagnosed with primary OSSN were reviewed.

OSSN was diagnosed principally by clinical examination.

Treatment with MMC continued until either clinical resolution was achieved, or the treatment was deemed to have failed. Treatment failure was defined as lack of response after 4 cycles of treatment with MMC .

The diagnosis of OSSN was made by corneal consultant experienced in examining ocular tumors.

In the primary cases, this was performed clinically, relying on the characteristic features of OSSN – gelatinous, papilliform or leukoplakic lesion with characteristic tufted superficial "corkscrew" vessels.

Patients were commenced on a regimen of MMC 0.04% qid for one week, followed by three weeks off treatment.
At each follow-up visit, ophthalmic examination and data recording occurred as per the initial consultation.

Inclusion Criteria

All cases of primary non invasive ocular surface squamous neoplasia (OSSN).

Exclusion Criteria

Recurrent or invasive ocular surface squamous neoplasia (OSSN).

RESULTS

A total of 15 patients who had received treatment with MMC for OSSN Of these, 2 eyes had recurrence (13%) with mean treatment of 3.2 cycles. 3 cycles were given to 12 patients, 4 cycles to 3 patients.

Table 1.Average number of cycles/ months of topical mitomycin C to achieve clinical resolution of ocular surface squamous neoplasia.

Cycle of MMC	Patient
3	12
4	3
Total patient	15
Mean cycle	3.2

Adverse effects occurred in 8(53%) patients using MMC .The most common side effects reported were conjunctival hyperemia or irritation (MMC 2 (13%), followed by localised allergic/toxic reactions (defined as papillary conjunctivitis and/or lid swelling) (MMC 12 (9.3%))

Table 2. Analysis For Primary Noninvasive Ocular Surface Squamous Neoplasia Recurrence.

Factor	Descriptive - n	Percentage (%)
Age(year)	20-60	
Gender	Male - 11 Female - 4	73% 27%
Previous treatment	None	
Lesion size	< 2 mm – 9 2 – 6 mm – 4 >6 mm – 2	60% 27% 13%
Lesion location	Conjunctiva - 1 Limbal - 12 Cornea - 2	7% 80% 13%
Treatmen	MMC 3 CYCLE - 12 4 CYCLE - 3	 80% 20%
Treatment duration (AVERAGE)	3.2 CYCLE	

Images :

Slit lamp photography from the right eye of an 58 year old male.

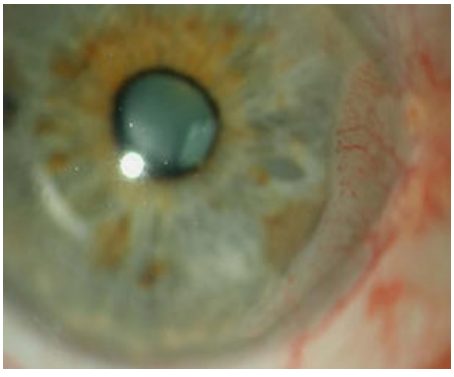

Figure 1 Primary nasal limbal ocular surface squamous neoplasia (leukoplakic with corkscrew vessels) extending from 2.30 to 5.30 onto the peripheral cornea.

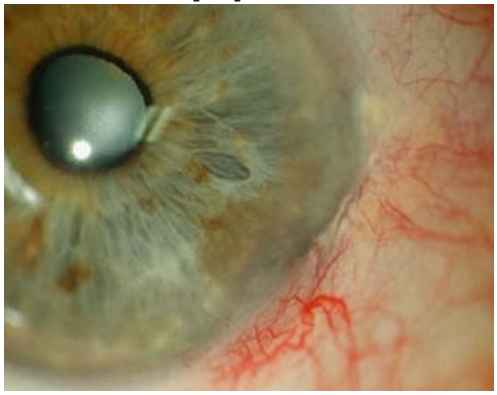

Figure 2 Appearance of nasal limbal ocular surface squamous neoplasia after 2 cycles of topical mitomycin-C over 2 months showing regression.

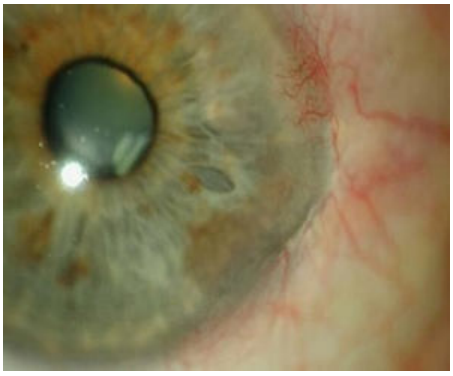

Figure 3 - Recurrence of nasal limbal ocular surface squamous neoplasia from 2.00 to 3.00 at 32 months following regression of the initial lesion.

DISCUSSION

The use of topical treatment of MMC for OSSN has been well-documented and give a number of advantages when compared to surgical excision, including delivery of treatment to the entire ocular surface, thereby treating microscopic disease and subclinical dysplasia, reduced risk of stem cell deficiency from wide surgical excision, reduced patient morbidity, ease of application and cost-efficacy.[4,6,7] The traditional surgical approach has limitations with microscopic evidence of the tumor often extending far beyond the macroscopic edges, and the risk of compromising the ocular surface and limbal stem cells, especially with large tumors and those involving the limbus.[2] Surgical excision of OSSN was generally regarded as the "gold standard" management in the past, as the tumor is confirmed by histopathology.

There are limitations to the use of topical management. Clinically, the experienced ophthalmologist needs to perform a slit-lamp assessment to diagnose OSSN and newer diagnostic techniques including toludine blue and ultra- high resolution OCT have been reported to aid in the diagnosis.[8,9] If there is any uncertainty, impression cytology or incisional biopsy can improve diagnostic accuracy, however both are limited to the tissue sampled and may not necessarily be representative of the whole lesion. There is also the potential risk of seeding neoplastic cells into deeper tissue layers with incisional biopsy. It is also difficult to be certain on clinical examination alone regarding the depth of the lesion, however invasive disease more characteristically is less mobile due to involvement of the underlying sclera. It may be possible early malignant lesions in this series have been topically treated with success and no recurrence, but this is not a recommended practice. It is likely malignant lesions, would fail topical treatment, resulting in excision and subsequent histological confirmation.

In the current study, for primary OSSN lesions, topical MMC was utilized as first-line therapy . The cost-benefit ratio favours this topical approach compared to surgical intervention that involves doctors' fees, operating theatre fees and consumables, and the cost of loss of income for the patient during post-operative recovery.

The findings from the present study suggests topical treatment is effective for primary OSSN. Lesion size and location, gender, age and/or treatment duration were not identified as predictive factors for recurrence of OSSN following topical therapy with MMC in the present study. This suggests that topical treatment can be utilized for presumed non-invasive primary OSSN lesions over a range of patient presentations. True recurrence of a lesion is difficult to determine with certainty as opposed to inadequate treatment with regrowth of residual tumor cells. The lesions in this study were clinically examined to have resolved, however

histological confirmation would be more ideal. In practice, biopsy of a resolved region is not generally performed unless there is clinical evidence of recurrence. The observation of a recurrence also depends on duration of follow- up and it is possible more lesions would eventually recur if followed for a longer period. In our study recurrences occurred in 1 patient after 32 month and 2nd patient on 39 month of follow-up, indicating follow-up should be more frequent in early period following cessation of treatment.

CONCLUSION

The findings of this study show topical therapy can be utilized as first-line therapy for both primary and recurrent clinically diagnosed non-invasive OSSN.

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