Original Article

# Mitomycin C: An effective adjuvant in the management of ocular surface squamous neoplasia

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## ABSTRACT

**Background:** Ocular surface squamous neoplasia (OSSN) forms a spectrum of dysplasia from conjunctival-corneal intraepithelial neoplasia to an invasive squamous cell carcinoma (SCC). Management of OSSN is surgical excision; however, with a high reported recurrence rates (33 to 56%). Hence, Mitomycin C, a tumor-targeted deoxyribonucleic acid (DNA) synthesis inhibitor is considered as an adjuvant following excision of primary OSSN. **Aim:** To report the cure and recurrence rate with excision of primary OSSN with Mitomycin C as an adjunctive ina single ocular center over 1 year period. **Materials and Methods:** Twelve eyes of 12 patients with histologically proven primary were included in the study between 1st Jan 2009 and 31st Dec. 2009. Protocol for the management comprised of surgical excision of the lesion with a 3 mm of healthy rim with cryotherapy followed by topical Mitomycin C 0.04% four times a day to all postoperative patients in 3-4 cycles of alternate on and off weekly courses. At each visit, looked for recurrence of tumor and corneal alterations like keratitis or erosions. Efficacy of Mitomycin C as an adjuvant therapy was measured in terms of clinical cure and recurrence of the tumor. **Results:** Average age 45.25 years with 42% below 40 years with 83% male preponderance. With a follow up period of 44.5 months, 91.7% success rate found despite late stage presentation in our study. **Conclusion:** Hence, we conclude that, Mitomycin C treatment following surgical excision decreases the recurrencerate of primary ocular surface neoplasia and should be considered as adjunctive therapy in primary treatment.

**Key words:** Mitomycin C, ocular surface squamous neoplasia, recurrence of ocular surface squamous neoplasia

## INTRODUCTION

Ocular surface squamous neoplasia (OSSN) forms a spectrum of dysplasia from conjunctival-corneal intraepithelial neoplasia to an invasive squamous cell carcinoma (SCC). Management of OSSN is surgical excision;[1] however, reported recurrence rates after surgical excision alone are as high as 33% in patients with tumor-cleared margins and 56% with positive margins with the longest follow-up.[2] Hence, the adjuvants like cryo-therapy, Mitomycin C, 5-fluorouracil, interferons, immune modulators have been tried.[3] Mitomycin C, a tumor-targeted deoxyribonucleic acid (DNA) synthesis inhibitor is hence, considered as an adjuvant following excision of primary OSSN in various studies.[4,5] The study is done to report the cure and recurrence rate with following treatment of primary OSSN using adjunctive Mitomycin C in a single ocular center over 1 year period.

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| Quick Response Code: | Website: www.ccij-online.org |
| | DOI: 10.4103/2278-0513.121518 |

## MATERIALS AND METHODS

Twelve eyes of 12 patients with primary OSSN who presented between 1st Jan 2009 and 31st Dec. 2009 were included in this study. A detailed history on demographic details, symptoms and its durations, exposure to risk factors were taken. The institutional ethical committee approval was obtained and written consent taken from all patients.

Clinical examination included visual acuity, refraction, anterior segment, evaluation for shape, size, extent,

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mobility of the lesion, anterior chamber reaction, involvement of cornea, sclera, fluorescein, and 1% rose bengal staining under slit-lamp biomicroscopy, lymphadenopathy to make a clinical diagnosis. Routine laboratory work up including human immunodeficiency virus (HIV) serology tests was done. Fitness for surgery local anesthesia was obtained in all patients. Inclusion criteria were clinically diagnosed cases of OSSN by slit-lamp bio microscope and OSSN with < 5 clock hour involvement/15 mm in diameter. While exclusion criteria were those which would interfere with the outcome like HIV/acquired immune deficiency syndrome diseases, immune compromised status, xeroderma pigmentosa, and ocular conditions like severe dry eye, limbal stem cell deficiency.

Protocol for the management comprised of surgical excision of the lesion with a 3 mm of healthy rim, using no irrigation and single touch technique, instruments were changed once the tumor was removed, followed by cryotherapy to the cut end of conjunctival under surface for 20 seconds and the cornea and limbus for 10 seconds using double freeze thaw technique. The ocular surface was left to heal or amniotic membrane grafting was done if the ocular surface defect was bigger than 25 × 25 mm. Specimen sent for histopathological examination. On confirming epithelial healing, topical Mitomycin C 0.04% four times a day to all postoperative patients in 3-4 cycles of alternate on and off weekly courses was advised. Preoperative topical Mitomycin C was instilled in cases of large mass or when surgery had to be postponed on nonmedical grounds. Patients were followed up weekly after the start of treatment protocol and monthly after treatment ended. At each visit, slit-lamp examination with rose bengal 1% and sodium fluorescein 1% drops was performed along with routine examination for recurrence of tumor and corneal alterations like keratitis or erosions. Efficacy of Mitomycin C as an adjuvant therapy was measured in terms of clinical cure and recurrence of the tumor.

## RESULTS

Mean age of patients was 45.25 years (range: 23-73 years). A total of 5 of 12 (42%) patients were below 40 years and with male preponderance (83%) [Table 1]. A total of 10 of 12 (83%) patients had temporal limbal lesions.

Symptoms at presentation mainly were foreign body sensation followed by mass per eye, redness, injury, burning sensation, and so on, as shown in Table 2.

Duration of symptoms showed 58% presented beyond 6 months [Table 3].

Sunlight exposure was present in eight (67%) patients and four (33%) were smokers [Table 4].

Smallest mass measured 2 × 3 mm, while the largest was 15 × 14 mm. Size of the mass was more than 8 mm in diameter or more than 3 clock hours in nine patients (75%). Corneal infiltration was evident in six (50%) cases. Visual acuity remained stationary/improved in cases where lesion covered the visual axis postsurgery; clinically, OSSN may be leukoplakic lesion [Figure 1] to large cauliflower-surfaced gelatinous lesion. Histopathologically, nine (75%) cases had SCC either with well or moderate differentiation as shown in Figure 2, with three (25%) having carcinoma *in situ* [Figure 3] as shown in Table 5. Only three (25%) cases showed marginal clearance, while five (42%) had at least one margin showing dysplasia and four (33%) cases had at least two margins showing dysplasia [Table 6].

Mean follow-up of 44.5 months (range: 40-49 months) revealed recurrence in one eye with success rate being 91.7%. A repeat protocol for the recurrent lesion resulted in 100% success.

**Table 1: Demographic details**

| | No. of patients (%) |
|---|---|
| Age range in years | |
| 20-40 | 5 (42) |
| 41-60 | 4 (33) |
| 61-80 | 3 (25) |
| Gender | |
| Male | 10 (83) |
| Female | 2 (17) |

**Table 2: Symptoms of OSSN**

| Symptoms | No. of patients (%) |
|---|---|
| Foreign body sensation | 2 (17) |
| Foreign body sensation+mass per eye | 4 (33) |
| Mass per eye | 4 (33) |
| Injury+redness | 1 (8) |
| Redness | 1 (8) |

OSSN: Ocular surface squamous neoplasia

**Table 3: Duration of presentation of OSSN**

| Duration of symptoms | No. of patients (%) |
|---|---|
| <2 weeks | 2 (17) |
| 2 weeks-<2 months | 1 (8.3) |
| 2 months-<4 months | 1 (8.3) |
| 4 months-<6 months | 1 (8.3) |
| >6 months | 7 (58) |

OSSN: Ocular surface squamous neoplasia

**Table 4: Risk factors in OSSN**

| Risk factors | No. of patients (%) |
|---|---|
| Sunlight | 6 (50) |
| Sunlight+smoking | 2 (17) |
| Smoking | 2 (17) |
| Petroleum products | 2 (17) |

OSSN: Ocular surface squamous neoplasia

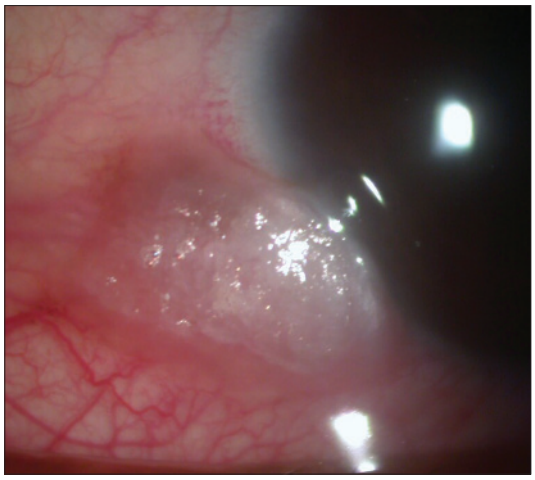

**Figure 1:** Leukoplakia at limbus

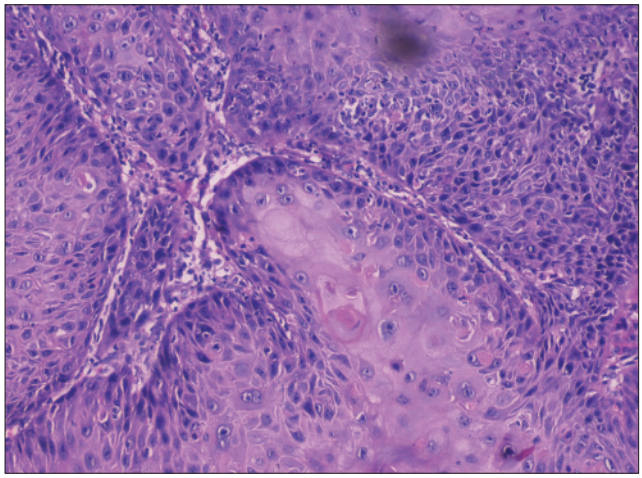

**Figure 2:** Histopatholgy slide of well-differentiated squamous cell carcinoma

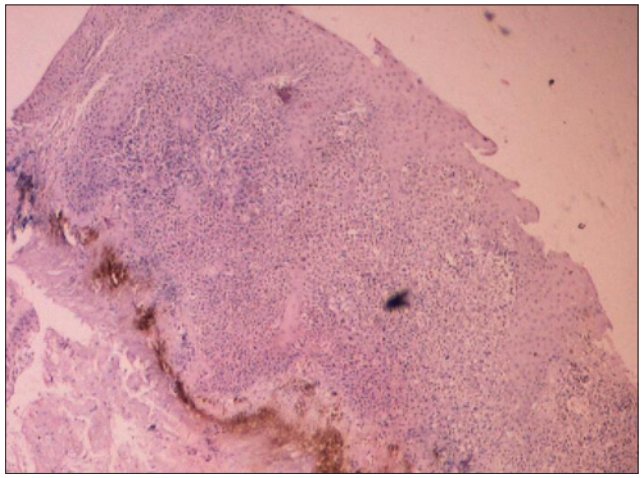

**Figure 3:** Histopatholgy slide of carcinoma *in situ*

## DISCUSSION

OSSN though previously considered being an uncommon entity, a number of reports have been appeared in world literature in recent years;[6,7] however, another study had 26 cases over 7 years period. OSSN is no more a rare entity;[8] we had 12 patients with primary OSSN between 1st Jan and 31st December 2009. Mean age at presentation was 45.25 years (range: 23-73 which is much lesser than that observed in other studies; 64 years (range: 47-87),[9] 69 years (range: 32-94).[10]

**Table 5. Histological findings in OSSN**

| Type | No. of patients (%) |
|---|---|
| Carcinoma in situ | 3 (25) |
| Well differentiated SCC | 1 (8) |
| Moderately differentiated SCC | 8 (67) |

SCC: Squamous cell carcinoma; OSSN: Ocular surface squamous neoplasia

**Table 6. Marginal clearance post-surgery**

| Margin showing dysplasia | No. of patients (%) |
|---|---|
| Free margin | 3 (25) |
| At least one margin | 5 (42) |
| With two margin | 4 (33) |

Most common risk factors were exposure to sunlight and smoking similar to other studies.[3,11] A total of 83% of eyes had FB sensation as the presenting symptom and 58% presented beyond 6 months, similar to that reported by Prabhasawat *et al*.[12] A total of 75% of patients had larger than 8 mm sized tumors and 50% of them had corneal infiltration (6 of 12 eyes) at presentation. A total of 75% had SCC similar to Babar *et al*'s study;[13] these presentations in our study suggested that our patients presented at an advanced stage.

Primary excision has been the mainstay of treatment for OSSN, as it is impossible to exclude invasive disease on clinical grounds or with impression cytology. Excision allows an immediate histopathological diagnosis, surgical debulking, and excludes life-threatening invasive carcinoma.[14] As per Kaines *et al*'s study (Kaines A, Malhotra R, Selva D, *et al*. Conjunctival squamous cell carcinoma with perineural invasion. Arch Ophthalmol, [in press]), the disadvantage of primary excision alone is the high recurrence rate which ranges from 15% to 52%.Therefore, numerous adjunctive treatments have been described in an attempt to decrease the rate of recurrence and the efficacy of various adjunctive therapies has been debated.

Despite the effort to excise the tumor with a wide healthy rim, only three cases (25%) had marginal clearance and the rest had residual dysplastic edges, suggestive of multifocal origin of OSSN or macroscopically invisible tumor edges. In such a situation, a repeat surgery to clear residual edges with safety margins would leave not only a large defect in ocular surface but also would lead to limbal stem cell deficiency.[14] Hence, Mitomycin C, an alkylating agent

which acts by inhibiting DNA synthesis and produces cell death by apoptosis and necrosis was used.[15] As the drug has a preferential action for rapidly dividing cells, acts as a significant antitumor agent and since 1994, several groups have reported the use of MMC in the treatment of both primary and recurrent OSSN.[16-22]

Post operative MMC in such cases not only avoids repeat surgery but also can treat the entire ocular surface, destroy subclinical disease, and prevent new tumors arising elsewhere on the ocular surface and, thereby would contribute for a better outcome.

## CONCLUSION

As surgical excision alone does not suffice in the management of OSSN, combined therapy with post operative topical Mitomycin C has synergistic effect and certainly prevent recurrence; more so, when patients presents late and less likely to come for follow-up. Hence, we conclude that Mitomycin C is an effective adjuvant in the management of OSSN.

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**Cite this article as:** Puttaswamy S, Mala B, Nagaraju G, Raviprakash D, Prakash KH. Mitomycin C: An effective adjuvant in the management of ocular surface squamous neoplasia. Clin Cancer Investig J 2013;2:298-301.

**Source of Support:** Nil, **Conflict of Interest:** No.