Original Research Article

Topical 0.02% Mitomycin C for management of primary corneal-conjunctival intraepithelial neoplasia as primary therapy: A long term follow up

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Abstract

Background: The corneal-conjunctival intraepithelial neoplasia (CCIN) is an ocular surface neoplasia commonly found among populations exposed to strong UV light. Although surgical excision is mainstay treatment, topical Mitomycin-C (MMC) 0.02% has been tried as a sole therapeutic treatment of non- invasive Ocular Surface Squamous Neoplasia (OSSN).

Aim: The aim of this study was to report the long term outcome of treatment of non invasive ocular surface squamous neoplasia with topical Mitomycin C (0.02%) as primary therapy.

Materials and methods: Total six eyes of six patients with CCIN were treated with topical mitomycin C (0.02%) alone as a sole therapy. All patients received topical MMC (0.02%) four times daily as a cycle therapy of two week ON and two week OFF for 12 weeks. The patients were followed up to two years.

Results: All patients showed total cure with no recurrence during 2 years follow up period. Ocular irritation and mild conjunctival hyperemia were observed in 4 eyes during treatment with MMC. There were no serious complications noted at the end of the follow-up period.

Conclusion: We concluded that Topical Mitomycin C (0.02%) may be used as a sole therapeutic treatment of non invasive Ocular surface squamous neoplasia with close on going follow-up.

Key words

Ocular Surface Squamous Neoplasia (OSSN), Mitomycin C (MMC), Corneal-Conjunctival Intraepithelial Neoplasia (CCIN).

Introduction

Ocular surface squamous neoplasia (OSSN) describes a spectrum of benign, pre-malignant and malignant unilateral slowly-progressive epithelial lesions of the conjunctiva and cornea. Ocular surface squamous neoplasia term was given by Lee and Hirst.

Risk factors include ultraviolet light exposure, human papilloma virus (type 16) infection, AIDS, xeroderma pigmentosum, stem cell therapy, genetic predisposition, smoking and immunosuppression. According to limbal transition theory of Lee and Hirst, any alteration in the limbal stem cells may lead to abnormal epithelial maturation and metaplasia.

It generally occurs in the inter palpebral fissure, usually at the limbus, although it may be found elsewhere. Presentation is usually in late adulthood life with ocular irritation or a mass. Although occurring most commonly in the elderly, these lesions are also seen in young adults, especially in association with xeroderma pigmentosa and HIV infection [1-3]. The lesions appear macroscopically as gelatinous, leukoplakic, papilliform, nodular or diffuse, and may be flat or elevated. A feeder vessel is sometimes present.

Diagnosis is most often made clinically. Although definitive diagnosis is provided histopathologically with either incisional or excisional biopsy, other less invasive modalities, such as impression cytology [4, 5], exfoliative cytology [6, 7] and fine-needle aspiration biopsy, have been utilized. Confocal microscopy has shown promising results in the evaluation of ocular surface lesions [8-10], however, it requires contact with the eye, examines a small area and does not provide a cross-sectional assessment of the lesion. Ultra-high-resolution optical coherence tomography (UHROCT), although still in its nascent stages, holds promise in providing a cross-sectional evaluation of the lesion and thus, in a way, an 'optical biopsy' with a resolution between 2 and 5 µm [11], without the need for direct contact with the eye. UHROCT has been a valuable addition to the diagnosis of OSSN, especially in equivocal cases, and has helped to monitor the resolution of disease in medically treated lesions [11].

The conventional therapy for CCIN is wide surgical excision and cryotherapy. However, high recurrent rates of up to 50% [12,13], have been noted with multiple consequences such as destruction of normal limbal stem cells and conjunctiva causing corneal neovascularization and symblepharon formation. Adjunctive therapies such as beta radiation [14], immunotherapy [15, 16] and topical chemotherapy [17, 18] have been used in an attempt to decrease the recurrences and to prevent or minimize scarring from repeated surgeries.

Topical MMC has been used for the treatment of CCIN since 1994 by several investigators [18-24]. They reported favourable results from using various concentrations and durations of MMC for the treatment of primary and recurrent CCIN. However, corneal complications from MMC treatment are main concerns leading to dose and duration adjustment in later studies [19-21].

It would be interesting to know whether topical MMC 0.02% concentration would be effective in the treatment of primary CCIN as a primary therapy.

Materials and methods

After permission from institutional ethical committee, the study was conducted as hospital based prospective non-comparative interventional case series carried out in the

Department of Ophthalmology, S.P. Medical College and associated group of hospital.

The study included six eyes of six patients of localized non invasive ocular surface squamous neoplasia. All patients were male. The patients were in age group of 40 to 80 years. A detailed slit lamp examination of all eyes was done. Patients' demographic, pathologic and clinical data before treatment were recorded, these data included age, sex, history, tumour location, extent and size and visual acuity (**Table - 1**).

Incision biopsy of the lesion was done and tissue was subjected to histopathological study. Test for HIV infection was also done which was negative in all the patients. After clinical examination and histopathological examination, diagnosis of Ocular Surface Squamous Neoplasia was made.

MMC 0.02% solution was prepared by adding 10 ml of sterile distilled water to 2 mg MMC. The solution was refrigerated and protected from light. All patients received freshly prepared topical MMC (0.02%) 4 times a day in form of eye drop and continued for three cycles with 2 weeks ON and 2 weeks OFF (period free from drug instillation) for 12 weeks.

The main outcomes measured were tumour response and medication related complications.

The patients were followed up using slit lamp biomicroscopy for recurrences or any other ocular manifestation at 1 week, 2 weeks, and every month for 6 months then every 3 months for another 18 months.

Results

A total of six patients completed the study. Demographic data of the patients and clinical features were listed in **Table - 1**. All patients were male. CCIN was on nasal side in 4 patients and on temporal side in 2 patients. Histopathological study of all incised neoplasia showed positivity for CCIN. Ocular irritation and mild conjunctival hyperemia was observed in 5 eyes during treatment period. These symptoms were relieved by topical preservative free artificial tears. There were no serious complications that necessitated stopping the treatment. No recurrence was seen in any of the patient during follow up of 2 years. Total cure was achieved in all eyes after MMC (0.02%) therapy (**Table - 1**). Successful treatment was defined as the patient being clinically free from the tumor as observed using slit-lamp biomicroscopy at last follow up. There were no long term complications detected at the end of the follow up period.

Table – 1: Demographic data, clinical features and results of treatment.

Age/ Sex	Location	Size of lesion in clock hours	Symptoms	Results
40/ M	Temporal limbus	7	FB sensation	S
50/ M	Nasal limbus	6	FB sensation	S
60/ M	Nasal limbus	7	FB sensation	S
65/ M	Nasal limbus	7	FB sensation +DOV	S
70/ M	Nasal limbus	8	FB sensation	S
72/ M	Temporal limbus	6	FB sensation + DOV	S

(FB – Foreign body sensations, DOV – Diminution of vision, S – Successful)

Discussion

The CCIN is an ocular surface neoplasia commonly found among populations exposed to strong UV light. The tumor is usually found at the limbus, where the highest proliferative activity of the cells occurs.

Excision remains an important step in management of localised CCIN. Excision allows an immediate histopathological diagnosis and excludes life-threatening invasive malignancies such as SCC or amelanotic malignant melanoma [25]. It also helps to exclude masquerading lesions such as viral papilloma, where MMC is not effective, and keratoacanthoma and solar keratosis, where MMC is not necessary. Surgical debulking of the lesion makes adjuvant treatment more effective, as MMC is being utilised against a lower tumour load.

Although surgical excision is the mainstay treatment, one third of the patients require more than one surgical excision due to incomplete excision or recurrences high recurrence rate, which ranges from 15% to 52% [26]. CCIN may also be a multifocal disease. Impression cytology studies have revealed that areas of clinically normal limbus remote from the tumour may be positive for dysplasia. Localised surgery does not address these areas of possible preclinical dysplasia [27], therefore, numerous topical adjuvant treatments have been described in an attempt to decrease the rate of recurrence.
When treating disease involving more than five clock hours of limbus, excision is potentially hazardous due to the risk of limbal stem cell failure [28] and so is avoided by the authors. MMC is used as sole therapy for cases with diffuse limbal involvement. Several chemotherapeutic agents such as topical MMC, 5 –Fluorouracil and interferon have been tried in an attempt to minimize the tumor recurrence and the complications of extensive surgery.

MMC is a potent cytotoxic agent isolated from Streptomyces caespitosus. It undergoes metabolic activation to become an alkylating agent that is cytotoxic to both proliferating and non-proliferating cells. It functions in all phases of cell cycle, especially in rapidly dividing cells. It acts by inhibiting DNA synthesis preferably in G1 and S phase. The drug is available in a vial of (2 mg/ml).

Various concentrations and duration of treatment of MMC have been tried. Frucht-Pery et al [18-21] reported the efficacy of 0.02% and 0.04% MMC 4 times daily for 4 consecutive weeks in the treatment of CCIN. Many investigators recommended prescribing topical MMC as a cycle therapy to avoid the side effects of the medication, such as 1 or 2 weeks of treatment followed by a few weeks of quiescence [17, 18, 21].

This study demonstrates that topical MMC 0.02% alone is effective for treating the primary CCIN. All patients received topical MMC 0.02% 4 times daily as two week on two week off cycle therapy for 12 weeks. None of the patients showed recurrence up to two years of follow up. Complications of topical MMC as noted in our study were irritation, mild tearing and conjunctival hyperemia. All signs and symptoms were relieved by topical preservative free artificial tears and topical NSAID flurbiprofen four times a day. No serious or long -term complications were noted up to two years follow up. There have been no cases of complicating limbal stem cell failure in this series.

Topical MMC provides an alternative to extensive and repeated surgery for CCIN, and its use has also been reported in a number of studies. The results have been summarised in table 2 and compared with the current study. These studies all support a role for utilising MMC in the treatment of CCIN.

One of the major limitations of topical MMC therapy is the lack of a recommended optimal dose and duration of treatment. Previous studies have used 0.02 or 0.04% concentrations for durations of 1–5 weeks (results outlined in **Table - 2**) [18, 21, 23, 27, 30-32]. The lack of major complications is supportive of this treatment regime. Limbal toxicity from MMC has been reported [29], hence, a two week-on two week-off regime is used to minimise toxicity to normal healthy ocular surface and periocular tissues, especially limbal stem cells.

Table – 2: Summary of results of studies utilising Mitomycin C for treating Ocular Surface Squamous Neoplasia.

Study	No of patients	Mitomycin C dose and drop regime	Control/recurrence rates
Frucht-Perry, et al. [21]	3	0.02% four times daily for 10–22 days	0% recurrence
Wilson, et al. [32]	7	0.04% four times daily for 7 days in alternate weeks	~86% resolution 14% partial regression
Frucht-Perry, et al. [18]	17	0.02–0.04% four times daily for 7–28 days	35% recurrence
Daniell, et al. [23]	20	0.02–0.04% four times daily for 1–5 weeks in alternate weeks	20% recurrence
Shields, et al. [31]	10	0.04% four times daily for 1–4 weeks in alternate weeks	0% recurrence
Hirst, et al. [27]	26	0.04% four times daily for 3 weeks	0.8% recurrence
Current study	6	0.02% four times daily cycle therapy 2 weeks on 2 weeks off for 12 weeks	0% recurrence

Conclusion

We concluded that Mitomycin C (0.02%) with 2 weeks on and 2 weeks off cycle therapy for 12 weeks is a well tolerable dose with no serious side effects for treatment of non invasive Ocular Surface Squamous Neoplasia. However, to avoid potential damage to limbal stem cells from extensive excision, MMC may be used as sole therapy but close ongoing follow-up is recommended in view of the risk of recurrence and complications of MMC.

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