# Treatment of ocular surface squamous neoplasia with Mitomycin C

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## ABSTRACT

**Aim** To report the outcome of treatment of non-invasive ocular surface squamous neoplasia (or conjunctival-corneal intra-epithelial neoplasia (CCIN)) where topical mitomycin C (MMC) has been used in the treatment regimen.

**Design** Prospective, non-comparative interventional case series.

**Participants** 91 primary or recurrent CCIN lesions from 90 patients treated in a single ocular oncology centre over a 10.5-year period.

**Intervention** 73 cases of localised, non-invasive CCIN and eight cases of recurrent CCIN received a treatment regimen of surgical excision±cryotherapy, followed by two to three 1-week cycles of adjuvant topical MMC (0.04% four times a day). 10 cases of diffuse CCIN received two to three 1-week cycles of topical MMC (0.04% four times a day) as sole primary treatment.

**Main outcome measure** Successful treatment was defined as no clinical recurrence of CCIN.

**Results** Mean follow-up of 56.8 months (range 5.8 to 119.8) and median 57.3 months, revealed no recurrences (0%) in the localised primary group, and one persistent case and two recurrences (30%) in the diffuse primary group. There was one recurrence (12.5%) in the recurrent group, but this was in the only eye with a diffuse type of recurrence.

**Conclusions** MMC treatment following surgical excision appears to decrease the recurrence rate of localised CCIN and should be considered as adjuvant therapy in primary treatment. MMC should also be considered as adjuvant therapy in the treatment of localised recurrent disease. MMC may be used as sole therapy in more diffuse disease, but close ongoing follow-up is recommended in view of the significant risk of persistent or recurrent disease.

Ocular surface squamous neoplasia (OSSN) is a spectrum of dysplastic disease of the cornea and conjunctiva ranging from carcinoma-in situ (conjunctival-corneal intra-epithelial neoplasia (CCIN)) to invasive squamous cell carcinoma (SCC). It is reported to be a common malignancy of the ocular surface, particularly in areas with high ultraviolet light exposure.[1] Currently, there are many suggested treatment options including surgical excision with or without cryotherapy,[1–3] radiotherapy,[4–6] excimer laser,[7] topical mitomycin C (MMC),[3 8–15] topical 5-fluorouracil (5-FU),[16 17] and perilesional and topical interferon α 2b (IFA 2B).[18–20]

MMC is a well-established treatment modality for CCIN. It has been reported to be efficacious as primary and adjuvant therapy.[3 8–15] The authors present a large series of 91 eyes aiming to report the outcome of the treatment of CCIN where MMC has been used in the treatment regimen.

## METHODS

### Statistics

A prospective, non-comparative interventional case series of 91 eyes with primary or recurrent CCIN lesions in 90 patients was undertaken. All cases were treated in a single ocular oncology centre over a 10.5-year period between November 1998 and April 2009. The patients with recurrent lesions had all received primary treatment elsewhere.

### Definitions

CCIN lesions were classified into three main categories: localised primary, diffuse primary and recurrent (table 1). The arbitrary cut-off level of less than or equal to 5 clock hours as a definition for localised disease was made by the authors due to their concern of the increased risk of limbal stem cell failure if 180° or more of limbus was damaged (based on personal experience and presented at International Congress of Ocular Oncology, Philadelphia, May 1999). Diffuse disease of over 5 clock hours of limbal involvement was therefore considered too hazardous to excise.

### Method of diagnosis

The method of diagnosis varied depending on the lesion type. Localised and recurrent lesions were diagnosed primarily by excision biopsy and diffuse lesions by multiple incision biopsies or impression cytology.

### Treatment

Treatment of all cases was carried out by a single ocular oncologist (JM). The treatment regimens for localised, diffuse and recurrent CCIN are summarised in table 1. Excision involved complete superficial dissection (not lamellar) from the cornea and limbus with a 2 mm margin on the conjunctival aspect. Double freeze–thaw cryotherapy with a nitrous oxide cryoprobe was applied to the limbal base and to the full thickness of the elevated conjunctival edge in the majority of patients. All patients were treated with chloramphenicol and prednisolone acetate 1% eye-drops four times daily until wound healing was complete.

MMC 0.04% (0.4 mg/ml) four times a day was used on a week-on week-off basis for two to three cycles (one cycle of treatment=1 week on+one week off). Table 2 shows the number of cycles of treatment received by patients. Three patients with difficult access to the treatment centre were treated with a continuous 2-week course of MMC.

**Table 1** Lesion types

| Lesion type | Definition | Treatment regimen |
|---|---|---|
| Localised primary conjunctival-corneal intra-epithelial neoplasia | Excisable limbal lesions (with associated conjunctival and corneal involvement) 5 clock hours or less | Excision+cryotherapy+MMC 0.04% four times daily 7 days×2–3 cycles |
| Diffuse primary conjunctival-corneal intra-epithelial neoplasia | Limbal lesions (with associated conjunctival and corneal involvement) greater than 5 clock hours | MMC 0.04% four times daily 7 days×3 cycles |
| Recurrent conjunctival-corneal intra-epithelial neoplasia | Recurrent limbal lesions (with associated conjunctival and corneal involvement); all but one were localised and excisable in this series | Excision+cryotherapy+MMC 0.04% four times daily 7 days×3 cycles (the diffuse recurrence was treated with MMC 0.04% four times daily 7 days×3 cycles) |

One cycle of mitomycin C (MMC) treatment=1 week on+1 week off.

Treatment was only commenced after complete epithelial healing in cases with prior excision. Punctal plugs were not used in any of the cases.

### Follow-up

Patients were examined at 1 month and 3 months following completion of MMC treatment, then at 6-monthly intervals for 2 years, then yearly for a total of 5 years (indefinitely if diffuse disease). The primary outcome measure was no clinical recurrence of CCIN.

## RESULTS

Ninety-one eyes from 90 patients were enrolled in the study. The age of patients ranged from 41 to 87 years (median 66 years). There were 70 males and 20 females in the study, and 51 right and 40 left eyes were treated. The minimum follow-up interval was 5.8 months. All but one patient had a minimum follow-up of 12 months. The one patient with 5.8 months' follow-up was included, as there was evidence of recurrent disease at this time. The mean follow-up was 56.8 months (median 57.3 months, range 5.8 to 119.8). All lesions involved the limbus, and there were no patients in this series with involvement of the non-bulbar conjunctiva. Table 2 presents the number and percentage recurrence rates of CCIN.

No recurrences were noted in the localised group (73 eyes in total). There was one eye in the localised group where a new separate focus of disease was noted. This responded to 5-FU 1% four times daily for 2 weeks. In the diffuse group (10 eyes in total), there was one case with persistent disease (partial regression) and two with recurrence. The diffuse persistent lesion was subsequently successfully treated with topical 5-FU 1% four times a day for 2 weeks. Of the two diffuse lesions that showed recurrence, the one with diffuse recurrence responded to 5-FU, and the one with a more localised recurrence responded to local excision. There have been no further recurrences in these patients to date. In the recurrent group, there was one recurrence in the only patient with a diffuse type of recurrence of a diffuse lesion previously treated with 5FU. This patient is currently awaiting treatment with topical IFA 2B. All patients with localised recurrent lesions responded to excision, cryotherapy and MMC.

There were no serious complications noted in this study. A localised allergic reaction was seen in 23% of patients during the second or third cycle of treatment but settled rapidly on cessation of treatment in all. Of these patients, one developed a secondary levator disinsertion ptosis requiring surgical correction. Fifteen per cent of patients developed epiphora, most of which settled following simple syringing of the involved nasolacrimal system. Of these patients, one developed the epiphora only 3 years after treatment with MMC and therefore may be unrelated. Another patient subsequently required a dacryocystorhinostomy (DCR) but also required a DCR in the contralateral eye that did not receive treatment. Finally, two patients with diffuse disease developed a corneal epithelial defect but no stromal melt. There were no incidences of severe complications such as hypotony, corneo-scleral melt or limbal stem cell failure.

## DISCUSSION

To our knowledge, this is the largest series of primary and recurrent CCIN lesions treated with MMC as adjuvant or sole therapy. The authors note that better control is achieved for localised compared with diffuse disease (recurrence rate 0% vs 30%). For localised disease, the best control is achieved with excision and cryotherapy followed by topical MMC (no recurrences in 73 eyes).

Excision remains an important step in management of localised CCIN. The authors prefer primary excision where possible,

**Table 2** Recurrence rates

| Conjunctival-corneal intra-epithelial neoplasia type | No of patients | No of eyes | No of eyes receiving two treatment cycles | No of eyes receiving three treatment cycles | Recurrence or persistence (no) | Recurrence or persistence (%) |
|---|---|---|---|---|---|---|
| Localised primary (≤5 clock hours) | 72 | 73 | 47* | 25* | 0 | 0% |
| Diffuse primary (>5 clock hours) | 10 | 10 | 2 | 8 | Two recurrent<br>One persistent | 30% |
| Recurrent | 8 | 8 | 4 | 4 | 1 | 12.5% |

One patient was included in both localised and recurrent group, since the two eyes had different conjunctival-corneal intra-epithelial neoplasia types.
*One eye in this group received only one treatment cycle.

as it allows an immediate histopathological diagnosis and excludes life-threatening invasive malignancies such as SCC or amelanotic malignant melanoma.[3] 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.

The disadvantage of primary excision alone is the high recurrence rate, which ranges from 15% to 52%.[1] 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;[15] therefore, numerous topical adjuvant treatments have been described in an attempt to decrease the rate of recurrence. The authors believe that the combination of excision (with or without adjuvant cryotherapy) followed by MMC has resulted in the absence of recurrences seen in their series of cases with localised excisable disease.

When treating disease involving more than five clock hours of limbus, excision is potentially hazardous due to the risk of limbal stem cell failure,[21] and so is avoided by the authors. MMC is used as sole therapy for cases with diffuse limbal involvement. There have been no cases of complicating limbal stem cell failure in this series. However, the lack of prior surgical debulking resulted in the higher persistence and recurrence rates noted in cases with diffuse disease. Fortunately, all but one of these cases responded to subsequent treatment with topical 5FU or excision and have remained free of further recurrences.

Intraoperative cryotherapy is commonly used as adjuvant therapy,[1–3] as it is known to decrease the recurrence rate by destruction of any residual tumour tissue beyond the horizontal or deep surgical margins of the wound.[22] Chen and Muecke,[3] however, found no difference in the recurrence rate of localised CCIN in patients who received cryotherapy compared with those who did not, when MMC was also used as adjuvant treatment. The authors continue to use cryotherapy to the limbal base because of the possibility of invasive disease deep to the excision margin.

Topical MMC provides an alternative to extensive and repeated surgery for CCIN, and its use has also been reported in a number of smaller studies. The results have been summarised in table 3 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 3). The strength of this study lies in the fact that it is largest reported cohort of patients all treated with a standard dose of MMC of 0.04%. The lack of major complications is supportive of this treatment regime.

The rationale for the authors' regimen of adjuvant MMC is to use the highest tolerable concentration of chemotherapy (0.04%) against the lowest possible residual tumour load. Limbal toxicity from MMC has been reported;[23] hence, a week-on week-off regime is used to minimise toxicity to normal healthy ocular surface and periocular tissues, especially limbal stem cells. In a previously published study by Khong and Muecke,[24] there were no serious complications noted in a similar number and spectrum of patients.

Other topical chemotherapy agents have been used such as 5-FU[16 17] and IFA 2B.[18–20] Yeatts *et al*[17] evaluated the efficacy of pulse dosing of 5-FU in the treatment of CCIN in a prospective, non-comparative case series. Seven patients were treated with 5-FU 1% for an average of 3.75 cycles (range 2 to 5 cycles). Three patients had disease recurrence with a mean follow-up period of 18.5 months.[17] Some studies have shown success with 5-FU in cases refractory to MMC.[16] The success of 5-FU in these studies and in ours (when treating persistent or recurrent disease) suggests effectiveness of 5-FU due to a difference in the mechanism of cytotoxicity of the two agents.[16]

IFA 2B has been used with favourable outcomes in primary and recurrent cases of CCIN. The above studies, however, indicate that IFA 2B requires a longer duration of treatment (1–10 months)[18–20] than is required with MMC, which may be a disadvantage. However, IFA 2B may be useful in cases resistant to MMC or 5FU.

In conclusion, this is the largest study evaluating the treatment of CCIN where MMC has been used in the regimen. There were few recurrences and no serious complications. MMC treatment following surgical excision of primary or recurrent localised CCIN appears to decrease the recurrence rate. A higher incidence of persistent or recurrent disease is noted when MMC

**Table 3** Summary of results of studies utilising mitomycin C for treating conjunctival-corneal intra-epithelial neoplasia

| Study | No of patients | Mitomycin C dose and drop regime | Control/recurrence rates | Follow-up period (months) |
|---|---|---|---|---|
| Frucht-Perry *et al*[9] | 3 | 0.02% four times daily for 10–22 days | 0% recurrence | 4–12 |
| Wilson *et al*[13] | 7 | 0.04% four times daily for 7 days in alternate weeks | ~86% resolution<br>14% partial regression | 2–16 |
| Frucht-Perry *et al*[8] | 17 | 0.02–0.04% four times daily for 7–28 days | 35% recurrence | NA |
| Daniell *et al*[11] | 20 | 0.02–0.04% four times daily for 1–5 weeks in alternate weeks | 20% recurrence | 3–26 |
| Shields *et al*[10] | 10 | 0.04% four times daily for 1–4 weeks in alternate weeks | 0% recurrence | 6–50 |
| Hirst *et al*[15] | 26 | 0.04% four times daily for 3 weeks | 0.8% recurrence | 6–12 |
| Current study | 91 | 0.04% four times daily for 2–3 weeks in alternate weeks | 0% recurrence in localised, 12.5% in recurrent group; 30% recurrence/persistence in diffuse group | 5.8–119.8 |

is used as sole therapy for diffuse disease. 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 significant risk of recurrence.

**Competing interests** None.

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## REFERENCES

1. **Lee GA,** Hirst LW. Ocular surface squamous neoplasia. *Surv Ophthalmol* 1995;**39**:429—50.
2. **Khokhar S,** Soni A, SinghSethi H, *et al*. Combined surgery, cryotherapy, and mitomycin-C for recurrent ocular surface squamous neoplasia. *Cornea* 2002;**21**:189—91.
3. **Chen C,** Louis D, Dodd T, *et al*. Mitomycin C as an adjunct in the treatment of localised ocular surface squamous neoplasia. *Br J Ophthalmol* 2004;**88**:17—18.
4. **Cerezo L,** Otero J, Aragon G, *et al*. Conjunctival intraepithelial and invasive squamous cell carcinomas treated with strontium-90. *Radiother Oncol* 1990;**17**:191—7.
5. **Elkon D,** Constable WC. The use of strontium-90 in the treatment of carcinoma in situ of the conjunctiva. *Am J Ophthalmol* 1979;**87**:84—6.
6. **Lommatzsch P.** Beta-ray treatment of malignant epithelial tumors of the conjunctiva. *Am J Ophthalmol* 1976;**81**:198—206.
7. **Spadea L,** Petrucci R, Balestrazzi E. Excimer laser phototherapeutic keratectomy for recurrent intraepithelial corneoconjunctival carcinoma. *J Cataract Refract Surg* 2002;**28**:2062—4.
8. **Frucht-Pery J,** Sugar J, Baum J, *et al*. Mitomycin C treatment for conjunctival-corneal intraepithelial neoplasia A multicenter experience. *Ophthalmology* 1997;**104**:2085—93.
9. **Frucht-Pery J,** Rozenman Y. Mitomycin C therapy for corneal intraepithelial neoplasia. *Am J Ophthalmol* 1994;**117**:164—8.
10. **Shields CL,** Naseripour M, Shields JA. Topical mitomycin C for extensive, recurrent conjunctival-corneal squamous cell carcinoma. *Am J Ophthalmol* 2002;**133**:601—6.
11. **Daniell M,** Maini R, Tole D. Use of mitomycin C in the treatment of corneal conjunctival intraepithelial neoplaisa. *Clin Experiment Ophthalmol* 2002;**30**:94—8.
12. **Heigle TJ,** Stulting RD, Palay DA. Treatment of recurrent conjunctival epithelial neoplasia with topical mitomycin C. *Am J Ophthalmol* 1997;**124**:397—9.
13. **Wilson MW,** Hungerford JL, George SM, *et al*. Topical mitomycin C for the treatment of conjunctival and corneal epithelial dysplasia and neoplasia. *Am J Ophthalmol* 1997;**124**:303—11.
14. **Tseng SH,** Tsai YY, Chen FK. Successful treatment of recurrent corneal intraepithelial neoplasia with topical mitomycin C. *Cornea* 1997;**16**:595—7.
15. **Hirst LW.** Randomized controlled trial of topical mitomycin C for ocular surface squamous neoplasia: early resolution. *Ophthalmology* 2007;**114**:976—82.
16. **Yamamoto N,** Ohmura T, Suzuki H, *et al*. Successful treatment with 5-fluorouracil of conjunctival intraepithelial neoplasia refractive to mitomycin-C. *Ophthalmology* 2002;**109**:249—52.
17. **Yeatts RP,** Engelbrecht NE, Curry CD, *et al*. 5-Fluorouracil for the treatment of intraepithelial neoplasia of the conjunctiva and cornea. *Ophthalmology* 2000;**107**:2190—5.
18. **Schechter BA,** Schrier A, Nagler RS, *et al*. Regression of presumed primary conjunctival and corneal intraepithelial neoplasia with topical interferon alpha-2b. *Cornea* 2002;**21**:6—11.
19. **Boehm MD,** Huang AJ. Treatment of recurrent corneal and conjunctival intraepithelial neoplasia with topical interferon alfa 2b. *Ophthalmology* 2004;**111**:1755—61.
20. **Karp CL,** Moore JK, Rosa RH Jr. Treatment of conjunctival and corneal intraepithelial neoplasia with topical interferon alpha-2b. *Ophthalmology* 2001;**108**:1093—8.
21. **Basti S,** Macsai MS. Ocular surface squamous neoplasia: a review. *Cornea* 2003;**22**:687—704.
22. **Kaines A,** Davis G, Selva D, *et al*. Conjunctival squamous cell carcinoma with perineural invasion resulting in death. *Ophthalmic Surg Lasers Imaging* 2005;**36**:249—51.
23. **Dudney BW,** Malecha MA. Limbal stem cell deficiency following topical mitomycin C treatment of conjunctival-corneal intraepithelial neoplasia. *Am J Ophthalmol* 2004;**137**:950—1.
24. **Khong J,** Muecke J. Complications of mitomycin C therapy in 100 eyes with ocular surface neoplasia. *Br J Ophthalmol* 2006;**90**:819—22.

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