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Originally published by BMJ –
http://bjo.bmj.com/content/94/5/555

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10th January 2013

http://hdl.handle.net/2440/61467
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. Currently, there are many suggested treatment options including surgical excision with or without cryotherapy, radiotherapy, excimer laser, topical mitomycin C (MMC), topical 5-fluorouracil (5-FU) and perilesional and topical interferon α 2b (IFN 2b). MMC is a well-established treatment modality for CCIN. It has been reported to be efficacious as primary and adjuvant therapy. 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.
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 (indeed 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 57.3 months, range 5.8 to 119.8). All lesions involved the limbus, and there were no patients in this series with localised recurrent lesions responded to excision, cryotherapy and MMC.

No recurrences were noted in the localised group (73 eyes in total). There was one eye in the localised group where a new focus of disease was noted. This responded to 5-FU 1% four times daily. One recurrent 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,
as it allows an immediate histopathological diagnosis and excludes life-threatening invasive malignancies such as SCC or amelanotic malignant melanoma. It also helps to exclude masquerading lesions such as viral papilloma, where MMC is not effective, and keratoacanthoma and solar keratoses, 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%. 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 reveal 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, 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, 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. Chen and Muecke, 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, 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, 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 and IFA 2B. Yeatts et al 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. Some studies have shown success with 5-FU in cases refractory to MMC. 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.

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) 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

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

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

**Provenance and peer review** Not commissioned; externally peer reviewed.

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Treatment of ocular surface squamous neoplasia with Mitomycin C

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Br J Ophthalmol 2010 94: 555-558
doi: 10.1136/bjo.2009.168294

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