Mitomycin C as an adjunct in the treatment of localised ocular surface squamous neoplasia

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SCIENTIFIC REPORT

Mitomycin C as an adjunct in the treatment of localised ocular surface squamous neoplasia

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Aim: To report the outcome of topical mitomycin C (MMC) used as adjunctive treatment following primary excision of ocular surface squamous neoplasia (OSSN).

Method: Prospective, non-comparative interventional case series of 27 primary OSSN lesions from 26 patients treated in a single ocular oncology centre over a 4 year period.

Result: 27 cases of OSSN received a treatment regimen of surgical excision, followed by topical MMC. Mean follow up of 27 (SD 12) months (range 12–50, median 25 months) revealed zero recurrences.

Conclusion: MMC treatment following surgical excision decreases the recurrence rate of primary ocular surface neoplasia and should be considered as adjunctive therapy in primary treatment.

Ocular surface squamous neoplasia (OSSN) consists of a spectrum of dysplasia which is relatively common in clinical ophthalmology practice.[1] Primary surgical excision remains the mainstay of treatment but the recurrence rate is high and various adjunctive therapies have been described.[2] Mitomycin C (MMC) has been used in the treatment of OSSN since 1994.[3] MMC has been recommended for treatment of recurrent OSSN.[4 5] We present a series of 27 eyes with localised primary OSSN treated with surgical excision and adjunctive MMC. The aim of this study is to report the recurrence rate following treatment of primary OSSN using adjunctive MMC in a single ocular oncology centre over a 4 year period.

METHODS

A single centre, prospective, non-comparative, interventional case series of 27 eyes in 26 patients with primary OSSN was carried out between November 1998 and February 2003.

Inclusion criteria included histologically confirmed non-invasive limbal OSSN (with associated corneal involvement) of less than 4 clock hours in extent. All treatment was carried out by a single ocular oncologist (JM). All of the lesions were completely excised superficially from the cornea and limbus with a 2 mm margin on the conjunctival aspect. Lamellar dissection was not performed as this increases the risk of intraocular spread if invasive disease. Double freeze-thaw cryotherapy with a nitrous oxide cryoprobe was applied to the superificial limbal base and to the full thickness of the elevated conjunctival edge. Cryotherapy was not available in all centres where the treatment was undertaken and therefore not used in all cases. Patients were treated with chloramphenicol and Prednefrine Forte eye drops four times daily until wound healing.

All cases were treated with at least two 1 week courses of topical MMC 0.04% four times a day, after complete epithelial healing.[6] Each course was followed by 1 week free of MMC. The patients were examined at 6 monthly intervals. The primary outcome measure was clinical recurrence of OSSN.

RESULTS

There were 26 patients, seven females and 19 males, with 27 primary OSSN (table 1). The mean age was 64 (SD 13) (range 47–87) years.

Five patients developed granuloma following excision of OSSN, all of which resolved rapidly with continued topical steroid treatment. Nineteen patients received three courses of MMC. Eight patients received two courses because of allergy to MMC with redness, swelling, and significant itching, which developed late in the second course. All MMC allergy symptoms resolved rapidly following discontinuation of treatment.

All patients have been followed up. The mean follow up period for the 26 patients was 27 (SD 12) months (range 12–50 months, median 25 months). There was no evidence of clinical recurrence in any of these cases.

DISCUSSION

Ocular squamous surface neoplasia (OSSN) is characterised by a localised, slow growing lesion with low metastatic potential. Histopathologically, there is a spectrum of intraepithelial change before the basement membrane is breached and invasive squamous cell carcinoma results.[1 2]

Our study represents the largest series to date of primary OSSN treated with adjunctive topical MMC. The authors believe MMC treatment following surgical excision is effective for local control as attested by the zero recurrence rate at a mean of 27 months.

Primary excision has been the mainstay of treatment for OSSN.[5] The authors feel that superficial excision remains the important initial step in management 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.[7] The disadvantage of primary excision alone is the high recurrence rate which ranges from 15% to 52%.[8] Therefore, numerous adjunctive treatments have been described in an attempt to decrease the rate of recurrence and the efficacy of various adjunctive therapy have been debated.

Intraoperative cryotherapy is commonly used as adjunctive therapy as it is known to decrease the recurrence rate by destruction of any residual tumour tissue beyond the horizontal or deep surgical margin of the wound.[8] In this study, there is no difference in the overall recurrence rate in those who received cryotherapy compared with those who did not. Further randomised controlled trials comparing excision with MMC versus excision, MMC, and cryotherapy will help determine the efficacy of cryotherapy in conjunction with MMC.

Mitomycin C is an alkylating agent which acts by inhibiting DNA synthesis and produces cell death by apoptosis and necrosis.[9] The drug has a preferential action

Table 1 Details of treatment and follow up for the 27 primary OSSN cases

Patient	Age of Dx	R/L eye	Location	Histopathology	Complications	Treatment	No of course	(MMC S/e)	Follow up (months)	Recurrence
1	56	R	Temporal limbal	CIN I	Granuloma	E, MMC	3	Nil	20	No
2	75	L	Temporal limbal	CIN I		E, C, MMC	3	nil	33	No
3	86	R	Limbal	CIN III		E, C, MMC	3	Nil	12	No
4	57	R	Nasal limbal	CIN I		E, MMC	2	Allergy	38	No
5	52	L	Nasal limbal	CIN II		E, C, MMC	3	Nil	40	No
6	57	R	Nasal limbal	CIN I		E, MMC	2	Allergy	36	No
7	57	R	Inferonasal limbal	CIN I		E, C, MMC	2	Allergy	41	No
8	61	R	Nasal limbal	CIN II		E, MMC	2	Allergy	20	No
9	53	R	Nasal limbal	CIN III	Granuloma	E, C, MMC	3	Nil	20	No
10	62	R	Nasal limbal	CIN I	Nil	E, C, MMC	3	Nil	29	No
11	50	L	Nasal limbal	CIN III		E, C, MMC	3	Itch	7	No
12	53	R	Nasal limbal	CIN II		E, C, MMC	3	Nil	14	No
13	69	R	Limbal	CIN I		E, C, MMC	3	Nil	50	No
14	70	R	Nsal	CIN II		E, MMC	2	Allergy	42	No
15	41	R	Temporal limbal	CIN I	Granuloma	E, C, MMC	3	Nil	26	No
16	63	L	Temporal	CIN III		E, C, MMC	2	Allergy	17	No
17	61	R	Nasal limbal	CIN I		E, MMC	2	Allergy	40	No
18	75	L	Temporal limbal	CIN I	Granuloma	E, MMC	3	Nil	37	No
19	76	R	Limbal	CIN I		E, MMC	3	Nil	25	No
20	57	L	Temporal limbal	CIN III		E, C, MMC	3	Nil	25	No
21	82	L	Temporal limbal	CIN III		E, C, MMC	3	Nil	20	No
22	49	L	Nasal limbal	CIN III		E, MMC	3	Nil	40	No
23	47	R	Nasal	CIN II	Granuloma	E, C, MMC	2	Allergy	23	No
24	73	R	Nasal limbal	CIN III		E, MMC	3	Nil	22	No
25	67	L	Temporal	CIN I	Nil	E, C, MMC	3	Nil	24	No
26	87	L	Limbal base	CIN III		E, C, MMC	3	Nil	10	No
27	82	R	Limbal	CIN I		E, C, MMC	3	Nil	13	No

E = excision, C = cryotherapy, MMC = mitomycin C, CIN = conjunctival intra-epithelial neoplasia.

for rapidly dividing cells and has significant anti-tumour activity. Since 1994 several groups have reported the use of MMC in the treatment of both primary and recurrent OSSN.[10–16] We think that it is unwise to use MMC without excision biopsy for localised OSSN, as invasive disease may be undiagnosed and MMC is unlikely to penetrate to the required level to reach the invasive cells.

MMC allows treatment of the entire ocular surface, including the conjunctival fornices, and may reach and destroy subclinical disease and prevent new tumours arising elsewhere on the ocular surface. Complications of MMC are common but are largely confined to ocular surface toxicity. The largest problem with MMC in our series was local allergy necessitating termination of treatment, as seen in eight cases (30%). None of our patients experienced significant corneal epitheliopathy and this may be attributed to the week on, week off regimen which prevents damage to more slowly dividing epithelial cells and limbal stem cells, allowing them to repair their DNA. We believe that allowing time for complete epithelial healing before application of MMC is important in avoiding the more serious complications such as scleral ulceration, uveitis, cataract, and glaucoma.[4 10 14] We noted no systemic side effects as a result of topical MMC treatment.

In conclusion, our study demonstrates that MMC treatment following surgical excision decreases recurrence rate of primary ocular surface neoplasia and should be considered as an adjunctive therapy in primary excision. As there was no difference in recurrence rate with two courses of MMC, the authors intend to use only two courses in the future.

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