Topical mitomycin C chemotherapy for conjunctival melanoma and PAM with atypia

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Abstract

***Aim*—To evaluate topical mitomycin C (MMC) chemotherapy in the treatment of conjunctival melanoma and primary acquired melanosis with atypia.**

***Methods*—In a phase I clinical trial, 10 patients with conjunctival melanoma and/or primary acquired melanosis with atypia were treated with topical MMC 0.04% four times daily. Four patients were given MMC for 28 days as a primary treatment. Six patients were treated with MMC for 7 days after excision and cryotherapy in an effort to improve local control. In this series, 10 patients have been followed for an average of 29 months.**

***Results*—All patients were noted to develop transient keratoconjunctivitis during treatment. One patient also developed a transient corneal epithelial defect. Decreased conjunctival pigmentation was noted in the four patients where topical chemotherapy was used as a primary treatment. Nodular tumours were resistant to topical MMC chemotherapy. Of the six patients treated within 2 weeks after primary excision and cryotherapy, there has been no tumour recurrence or symblepharon formation. Nine of the 10 study patients have maintained within one line of their pretreatment visual acuity. No retinal or optic nerve toxicity was noted.**

***Conclusion*—Since no complications which might preclude further investigation of topical MMC chemotherapy occurred, it was concluded that topical MMC chemotherapy was tolerated as a treatment for conjunctival melanoma and primary acquired melanosis with atypia.**

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Malignant melanoma of the conjunctiva is a rare ocular tumour.[1] In a Swedish population survey there was an annual incidence of 0.024 per 100 000 people.[1] Unlike uveal melanomas, malignant melanomas of the conjunctiva are usually discovered by the patient, are more accessible for treatment, and are commonly multifocal.[2–7]

Therapeutic options in the management of conjunctival melanoma have included local surgical removal (with or without cryotherapy), radiotherapy, and exenteration.[8–15] The choice of treatment has largely depended upon the availability of equipment and personnel familiar with these techniques. Other factors have included the tumour's size, distribution, and location, as well as the patient's desire to preserve vision, and the cosmetic use of the globe.

Local therapeutic success has been dependent upon the size, location, and number of tumours present when initiating definitive therapy.[13–15] Long term follow up evaluations have also shown that many "conservative" treatments exhibit a high incidence of melanoma recurrence. This is particularly ominous in that local failure may permit subepithelial tumour invasion with resultant intralymphatic, regional, and distant metastases.

Since no studies or anecdotal evidence have shown that complete extirpation of the conjunctiva and involved lids (exenteration) is better than the vision sparing alternatives, local excision with cryotherapy has become the most commonly used treatment for conjunctival melanoma and primary acquired melanosis (PAM) with atypia.[16]

Most ophthalmic oncologists would agree that local control has been improved by multimodality therapy (for example, excision and cryotherapy or excision and radiotherapy).[10 11 17] This may be (in part) due to the fact that since pathological evaluations of excised specimens commonly display patches of amelanotic melanoma extending beyond hyperpigmented areas, the visually pigmented tumour appears to offer a poor definition of the tumour's "edge".[18]

In contrast, topical chemotherapy of conjunctival tumours offers a non-surgical treatment with less dependence on surgical margins.[17 19] It can treat tumour extension onto the corneal epithelium and can easily be repeated. This approach also allows for a high concentrations of chemotherapy to be delivered directly to the tumour. We chose to investigate mitomycin C (MMC) because of its known chemotherapeutic effects against cancer and its record of few side effects reported in the treatment of pterygium and after glaucoma surgery.[20–24]

This study presents our clinical findings after MMC topical chemotherapy treatment of 10 patients with malignant melanoma of the conjunctiva and PAM with atypia.

Patients and methods

We obtained internal review board (IRB) and pharmacy committee approvals at the New York Eye and Ear Infirmary for the purpose of investigating topical chemotherapy for the treatment of conjunctival neoplasia.

MITOMYCIN C

We chose to investigate MMC instead of 5-fluorouracil (5-FU) because MMC affects cells within all phases of the cell cycle. This

Table 1 Patients and methods

No	*Age*	*Sex*	*Diffuse*	*Multifocal*	*Nodular*	*Mitomycin conc*	*Dosage*	*Treatment duration (days)*
1	68	M	yes	yes	yes	0.04%	4×daily	7
2	51	F	yes	yes	yes	0.04%	4×daily	28
3	69	F	no	no	yes	0.04%	4×daily	7
4	36	F	yes	no	yes	0.04%	4×daily	7
5	68	M	no	no	no	0.04%	4×daily	7
6	71	F	no	no	no	0.04%	4×daily	28
7	72	F	no	yes	yes	0.04%	4×daily	7
8	31	M	no	no	yes	0.04%	4×daily	7
9	54	M	yes	yes	no	0.04%	4×daily	28
10	70	F	yes	yes	no	0.04%	4×daily	28
Mean	66							

results in scission of tumour DNA even after the treatment is discontinued.[25–28] This effect should inhibit both the neoplastic tissue and the fibrovascular response after cryotherapy (symblepharon).[29]

PATIENTS

Ten patients with biopsy proved conjunctival melanoma or PAM with atypia were treated with topical MMC (0.04%) therapy (Bristol Labs, Evansville, IN, USA). The average patient age was 66 years (range 31–72). The mean time follow up observation was 29 months (range 6–46 months).

APPLICATION

For treatment, each patient was dispensed one bottle of 0.04% MMC ophthalmic solution each week (Table 1). One drop of chemotherapy was placed (by a relative or aid) into the superior conjunctival fornix, four time a day. Patient 1 also had sponge applications of MMC.[17] Patients and their families were requested to wear latex gloves if they were to handle the medication. All bottles with residual MMC was returned to our office for disposal.

Mitomycin C was used as a primary treatment for four patients. When topical MMC chemotherapy was used as a primary therapy, drops were given for 28 days (Table 1). MMC was used as an adjuvant to excision and cryotherapy for six patients. When was used as an adjuvant, drops were given for 7 days starting within 2 weeks of primary excision and cryotherapy. This treatment was given in an effort to improve long term local control.

EXCISION AND CRYOTHERAPY TECHNIQUE

All patients given adjuvant topical MMC therapy were primarily treated with excision and cryotherapy. If pigmentation was noted to extend onto the cornea, that epithelium plus 2 mm of normal appearing corneal epithelium was removed. The subjacent epicorneal tissues were "scrubbed" with absolute alcohol then quickly and copiously irrigated.[11 12] Cryotherapy was applied to all the exposed episcleral and epicorneal tissues within the bed of the excision. We use large flat oval cryotherapy tips (Cabot Medical, PA, USA) to deliver large areas of relatively uniform episcleral, epicorneal, and conjunctival cryotherapy in a double freeze thaw fashion.

FOLLOW UP EVALUATIONS

All patients were requested to be evaluated at 3 month intervals. Each examination consisted of a visual acuity determination followed by a complete ophthalmic examination. Care was taken to examine all conjunctival surfaces. Palpation for adnexal tumour formation as well as preauricular or cervical adenopathy was performed. Eyelid margins and the nasal antrum were also inspected.[6] Repeat medical evaluations for metastases and anaemia were performed or requested every 6 months.

Results

TOXICITY

After topical MMC chemotherapy, clinical evaluations of the four patients treated for 28 days revealed persistent keratoconjunctivitis which took 4–6 weeks to resolve (Table 2). One round corneal epithelial defect transiently appeared in the first case, but was thought to be due to a mechanical injury from the dropper tip. No evidence of scleral or corneal thinning was noted in any patients. Patient 6 was noted to develop a focal area of corneal haze which did not affect her vision. One cataract was noted in this series but could not be attributed to treatment. Three of the four patients who

Table 2 Results

No	*Partial response*	*Complete response*	*Local control*	*Metastasis melanoma*	*Death*	*Cryotherapy symblepharon*	*Pretreatment vision*	*Most recent vision*	*Side effects*		*Follow up (months)*
									Short term	*Long term*	
1	adjuvant	adjuvant	yes	none	No	none	20	20	KC	None	46
2	yes	no	no	yes	No	none	25	prosthesis	KC	None	42
3	adjuvant	adjuvant	yes	none	No	yes	40	30	KC	None	40
4	adjuvant	adjuvant	yes	none	No	none	20	20	KC	None	37
5	adjuvant	adjuvant	yes	none	No	none	25	25	KC	None	32
6	no	yes	yes	none	CLL	no cryotherapy	30	30	KC	Corneal haze	26
7	adjuvant	adjuvant	yes	none	No	none	20	20	KC	None	24
8	adjuvant	adjuvant	yes	none	No	none	20	20	KC	None	21
9	no	yes	no*	none	No	no cryotherapy	20	20	KC	None	12
10	yes	no	yes	none	No	no cryotherapy	32	200†	KC	None‡	6
Mean											29

*Subconjunctival recurrence; †cataract progression; ‡cataract not thought due to MMC. KC = keratoconjunctivitis.

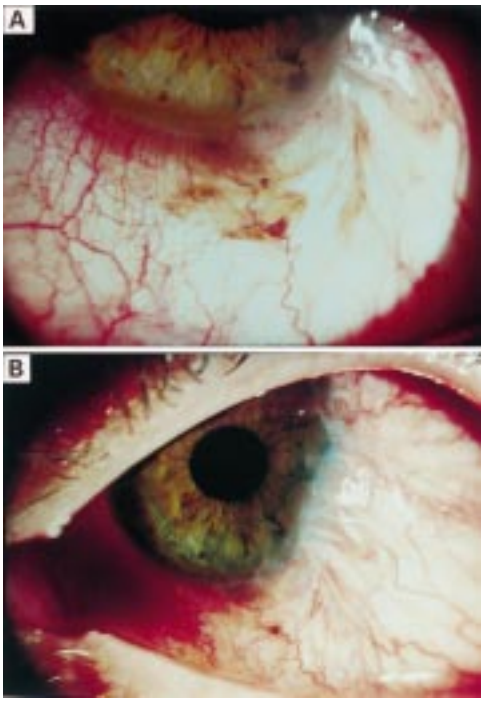

Figure 1 (A) Pretreatment photograph of patient 1 revealing perilimbal conjunctival melanoma before treatment. Note the pre-existing conjunctival scar tissue resulting from biopsy surgery. (B) 3 weeks after topical MMC therapy, a clinically subepithelial rest of melanotic tissue persists. (From Finger et al[17] with permission)

received 28 days of topical MMC are within one line of their pretreatment visual acuity (as measured before exenteration in patient 1).

The second group of six patients were given 7 days of topical MMC within 2 weeks after standard excision and cryotherapy surgery. Less keratoconjunctivitis was noted in this group (both in severity and duration). No evidence of eye wall thinning, cataract, or corneal haze was noted. Six of six patients have maintained within one line of their pretreatment visual acuity (Table 2).

TUMOUR RESPONSE

Four patients were given topical MMC chemotherapy as a primary treatment. In our first patient, nodular and subepithelial rests of melanoma appeared to be resistant to our MMC protocol (Fig 1). Therefore, this patient underwent excision and cryotherapy for residual disease, experienced a recurrence after 17 months, and was exenterated. Forty two months after topical MMC chemotherapy and 22 months after exenteration a repeat metastatic survey was positive for melanoma.

After this result, we were reluctant to use topical MMC chemotherapy as a primary treatment for any patient with melanoma nodules. The other three patients where topical MMC was used as a primary treatment, either had PAM with atypia (one), atypical PAM with focal areas of stage 1B melanoma (one), or a clinical recurrence with corneal epithelial extension (one). In these three patients with relatively superficial disease, all pigmented areas were noted to regress and all subsequent conjunctival biopsies have proved negative. The one patient with only PAM with atypia was found to develop a small subconjunctival nodular melanoma within 4 months of MMC treatment.

The second group of six patients were given 7 days of topical MMC chemotherapy treated after excision and cryotherapy (Table 2). None of these six patients have developed a recurrence with a mean follow up of 33 months (Fig 2). Postoperative MMC chemotherapy did not prevent wound closure or cause wound dehiscence.

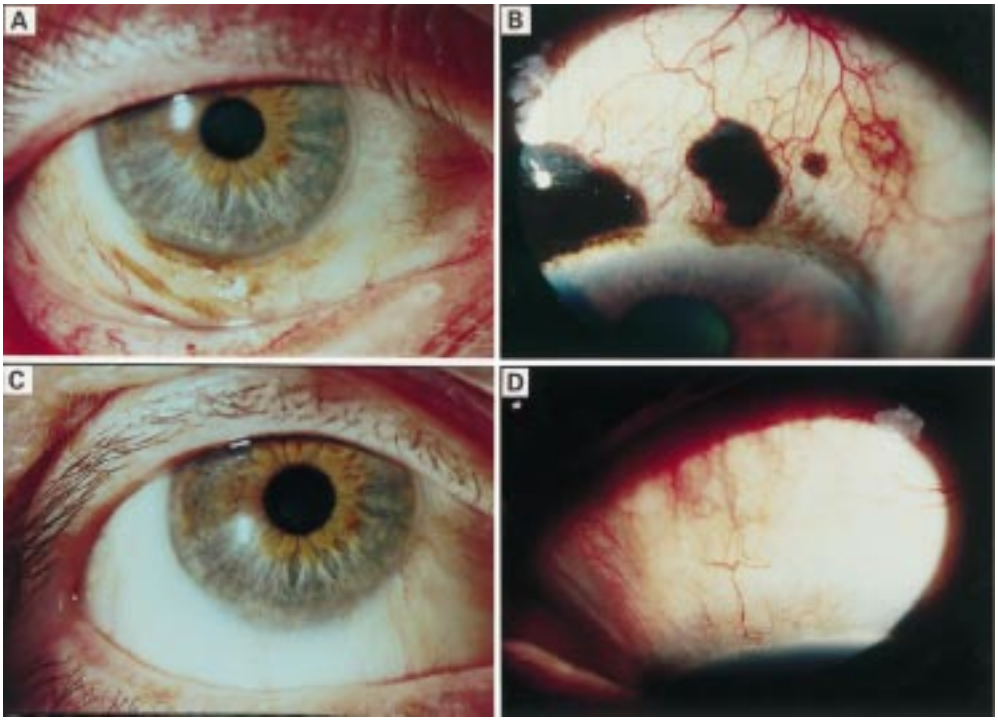

Figure 2 Left, comparison of pretreatment photograph (A) with the most recent (C) photograph of patient 3. Right, comparison of pretreatment photograph (B) with the most recent (D) photograph of patient 8.

Acute transient conjunctival injection, chemosis, and keratitis were present in all 10 MMC treated patients. No significant normal tissue toxicity could be attributed to this regimen of topical MMC chemotherapy.

Conclusion

We originally found that conjunctival melanoma and PAM with atypia responded to topical MMC chemotherapy.[17] Both cases 1 and 9 suggest that nodular rests of subepithelial melanoma were resistant to this dose regimen. In contrast, in all four cases, the areas of superficial or clinically intraepithelial tumour were noted to regress after treatment.

Topical chemotherapy is attractive because it offers a method of treating the entire conjunctiva with less dependence on defining tumour margins. In this way, topical MMC chemotherapy addresses the need to treat what is known to be an entire "conjunctiva at risk".

In this series, topical MMC chemotherapy was used both as a primary treatment and after excision and cryotherapy of the bulk of the tumour (adjuvant therapy). We investigated MMC as an adjuvant therapy because chemotherapeutic agents are known to be most effective against small tumour volumes. As an adjuvant, topical MMC chemotherapy was aimed at treating subclinical disease in order to improve local control. This approach was extremely reasonable since our phase 1 study has indicated that most all complications after MMC therapy have transient in nature. To date, we have noted no scleral or corneal melting as has been reported in treatment of pterygium and after glaucoma surgery.[30–33]

It is important to note that, in this study, we have investigated only one strength of MMC (0.04%) and two durations of treatment (7 or 28 days). Different treatment regimens (cycles) and/or chemotherapeutic agents may be found to be preferable. In this regard, we believe further research is needed.

Though this study has focused on treatment of patients who may have been candidates for surgery and/or cryotherapy, topical MMC chemotherapy should also be considered for patients who will not consent to (or cannot have) a surgical treatment for their malignant conjunctival neoplasia. Topical MMC chemotherapy should be considered as an investigational alternative for treatment of conjunctival melanoma and PAM with atypia.

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