Topical mitomycin chemotherapy for malignant conjunctival and corneal neoplasia

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Multicentre international cooperation would facilitate evaluations of both treatment efficacy and side effects

Atmospheric depletion of the ozone layer continues to put us at risk of ultraviolet related malignant neoplasia.¹⁻³ This problem is even worse beneath the Antarctic ozone hole that affects Australia.⁴ In this issue of *BJO* (p 819), two Australians, Khong and Muecke, report on a retrospective study of the ocular side effects of topical mitomycin chemotherapy (TMC) on 100 eyes treated for malignant ocular surface neoplasias.⁵ This single centre study employed up to three alternate 7 day TMC cycles and one concentration of mitomycin (0.04%) given four times a day. Eighty five eyes were treated for localised, diffuse, or recurrent malignant squamous conjunctival neoplasia, 12 for melanocytic conjunctival neoplasia, two with sebaceous carcinoma, and one with recurrent atypical fibroxanthoma. The most commonly reported side effects of TMC were allergic reaction (n = 31, 34%) and epiphora secondary to punctal stenosis (n = 14, 14%) at a mean follow up of 26.5 months (range 3–69 months). The authors present these complications as an acceptable risk and support the continued use of TMC for selected cases of malignant conjunctival and corneal neoplasia.

However, Khong and Muecke's report has its limitations. Their conclusions must be qualified by their methods of clinical practice. For example, their TMC study employed case selection, stopped after moderate term follow up, and paid little attention to systemic side effects. The authors' conclusions concerning safety must be limited by three specific factors: most patients were treated with only one concentration of mitomycin (0.04%) topically administered four times a day using a "week on and week off regimen," the "treatment was only commenced after complete epithelial healing was achieved," and that "punctal plugs were not used during MMC treatment in any of our cases." Let us explore these aspects of this study.

CLINICAL PRACTICE

The evolution of current clinical practice started with the first use of TMC for malignant conjunctival neoplasia as reported in the *BJO* in 1993.⁶ In that case, Finger *et al* used TMC for conjunctival melanoma arising within diffuse primary acquired melanosis with atypia. Complete regression of the superficial tumours as noted as well as chemoreduction of the nodular component.⁶ Soon after, Frucht-Pery and Rozenman reported TMC related regression of corneal intraepithelial neoplasia and, most recently, Shields *et al* reported on four patients with pagetoid conjunctival sebaceous carcinoma.⁷⁻⁸ Khong and Muecke's paper includes a table of 103 cumulative cases in 13 clinical case series.⁵ These include histopathological findings, side effects of treatment, and TMC efficacy reported from centres spanning the globe.⁹⁻¹⁶ Though few centres have staged their tumours pre-treatment and post-treatment, all have reported mitomycin related tumour regression. Clearly, TMC has come to play an integral and successful part in the treatment of malignant conjunctival and corneal neoplasia.

Nevertheless, it is important to note that Khong and Muecke investigated only one particular mitomycin concentration (0.04%) and treatment regimen.⁵ Other centres have used mitomycin 0.02% for up to 4 weeks' duration, others use TMC for chemoreduction (before surgery) and injections of mitomycin have been placed beneath the conjunctiva.^{5 9 17 18} Though the first patient was treated for 28 consecutive days, I currently prescribe TMC for two, 2 week cycles separated by a 2 week pause (with topical steroid rescue).^{6 13} We have found that lower concentrations, shorter durations of exposure, and steroid rescue are associated with fewer (or less severe) side effects. Clearly, the optimal concentration and duration of TMC treatment are yet to be determined.

CASE SELECTION

Khong and Muecke's study clearly states that some cases had been pre-treated with excision and cryotherapy and others (primarily squamous cell carcinomas) were selected out of the study.⁵ Case selection "bias" is a common confounding factor of both prospective and retrospective studies. I too "select" certain cases for TMC at the New York Eye Cancer Centre. The most common indications for topical mitomycin chemotherapy are diffuse multifocal conjunctival malignancy (primary or recurrent) that cannot be addressed by local excision with cryodestruction, radiation, or for chemoreduction (followed by excision and cryotherapy).¹⁹ Therefore, most cases not only require biopsy but often undergo or have undergone significant surgical procedures that change the architecture and cellular populations of the conjunctiva and cornea.^{12-14 20 21} Therefore, it is difficult to determine if TMC or the alternative local treatments are the cause of stem cell deficiency, inflammation, cellular atypia, cataract, conjunctival and corneal scarring.

SIDE EFFECTS

Most ophthalmic studies have noted acute TMC related ocular side effects including transient blepharitis, conjunctivitis, superficial punctate keratopathy, tearing, and discomfort.^{6 9 22} Less commonly reported and more long term (clinically apparent) ocular complications have included limbal stem cell deficiency, corneal haze, and cataract.^{21 23} In addition, mitomycin related histopathological changes have included conjunctival atrophy, inflammation, and cytological atypia.^{12 14} Most concur with Khong and Muecke's observation that treating over an intact conjunctival and corneal epithelial surface appears to limit the side effects seen in pterygium and glaucoma surgery. However, I have also found the conjunctival epithelium to be a formidable barrier to treatment of subepithelial disease warranting a modified approach in selected cases.

Khong and Muecke found allergic reaction and punctal stenosis to be the most commonly noted and statistically significant side effects of TMC.⁵ In this series 31 (34%) cases were noted to have an allergic reaction from TMC. Fourteen eyes (14%) in 14 patients were noted to develop epiphora as a result of punctal stenosis after TMC. This incidence of allergic reaction is far greater than that mentioned in previous studies. Possible reasons for this discrepancy include differing definitions of allergy, previous under-reporting, or different methods of compounding mitomycin eye drops. That the reported allergic reactions were

delayed can either support their allergic aetiology or may represent a cumulative inflammatory effect of mitomycin. I have noted that TMC related chemical conjunctivitis can be modulated by adjusting the weekly regimen (extending time off between weeks of treatment) and using topical steroid "rescue" between treatments.

The incidence of punctal stenosis could be limited by the use of punctal plugs. At the New York Eye Cancer Centre, almost all patients are requested to have plugs inserted before TMC and topical interferon chemotherapy (TIC). However, we also consider the possibility of subclinical tumour extension into the lacrimal drainage system (warranting a modified approach in selected cases). It is also reasonable to assume that punctal plugging may increase the dwell time of TMC on the tumour(s) as well as normal conjunctival and corneal tissues. Punctal plugging should decrease systemic absorption and may affect the incidence of allergic reactions.^{24, 25}

Mitomycin has been noted to cause systemic side effects (with intravenous use).⁹ Rarely mentioned in any ophthalmic series, no haematological side effects (for example, anaemia, leucopenia, thrombocytopenia) with resultant weakness, infections, and bleeding diathesis) have been reported. Other corneal side effects of systemically administered mitomycin have included pulmonary fibrosis, nausea, hepatic and renal dysfunction, as well as alopecia and diarrhoea. Despite all of these possible side effects, and with up to 12 years of reported follow up, TMC (0.02–0.04%) four times a day, for 1–4 week cycles over intact conjunctiva has not been associated with any of these findings. However, the possibility of systemic effects adds credence to the practice of punctal plugging.

SUMMARY

Over the past 14 years, topical mitomycin chemotherapy (TMC) has come to be commonly and widely used for the treatment of malignant conjunctival and corneal neoplasia. Reported methods of clinical application have varied by drug concentration (for example, 0.02% and 0.04%) as well as the number and spacing of weekly cycles. Despite these differences, no patient has been reported to lose an eye or experience a catastrophic side effect. In fact, all reported side effects are preferable to what would be expected with alternative treatments (extensive

local surgery with global cryotherapy, external beam irradiation, or orbital exenteration surgery).

Though there is no substitute for invention with subsequent evolution of clinical practice patterns, advances in new treatments (for example, TMC) could also be facilitated by the widespread adoption of standardised methods of tumour grading and treatment.²⁶ Such "staging systems" would allow multiple centres to compare and pool their results for multivariate analysis. Particularly necessary in the study of rare diseases, multicentre international cooperation would facilitate evaluations of both treatment efficacy and side effects.

Khong and Muecke should be complimented for reporting the first large scale survey of ocular complications related to TMC in treatment of malignant conjunctival neoplasia.

This study is clearly the largest retrospective, single centre evaluation of ocular complications related to TMC for malignant conjunctival neoplasia. They found allergic reaction and punctal stenosis to be the significant side effects. However, only two cases had persistent epiphora attributed to more distal obstruction of the nasolacrimal apparatus. The lack of clinically evident limbal stem cell deficiency, corneal or scleromalacia, uveitis, cataract, or glaucoma clearly supports the continued use and investigation of topical mitomycin chemotherapy for malignant conjunctival neoplasia.

Br J Ophthalmol 2006;**90**:807–808.
doi: 10.1136/bjo.2006.092734

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The research is supported by The EyeCare Foundation, Inc, New York City, NY 10021, USA.

The author has no competing interests in the product(s) mentioned in this study.

REFERENCES

- 1 McMichael AJ, Woodruff RE, Hales S. Climate change and human health: present and future risks. *Lancet* 2006;**367**:859–69.
- 2 Yu GP, Hu DN, McCormick S, et al. Conjunctival melanoma: is it increasing in the United States? *Am J Ophthalmol* 2003;**135**:800–6.
- 3 Bergmanson JP, Sheldon TM. Ultraviolet radiation revisited. *CLAO J* 1997;**23**:196–204.
- 4 McCarthy WH. The Australian experience in sun protection and screening for melanoma. *J Surg Oncol* 2004;**86**:236–45.
- 5 Khong J, Muecke J. Complications of mitomycin C therapy in 100 eyes with ocular surface neoplasia. *Br J Ophthalmol* 2006;**90**:819–22.

- 6 Finger PT, Milner MS, McCormick SA. Topical chemotherapy for conjunctival melanoma. *Br J Ophthalmol* 1993;**77**:751–3.
- 7 Frucht-Pery J, Rozenman Y. Mitomycin C therapy for corneal intraepithelial neoplasia. *Am J Ophthalmol* 1994;**117**:164–8.
- 8 Shields CL, Naseripour M, Shields JA, et al. Topical mitomycin-C for pagetoid invasion of the conjunctiva by eyelid sebaceous gland carcinoma. *Ophthalmology* 2002;**109**:2129–33.
- 9 Wilson MW, Czechonska G, Finger PT, et al. Chemotherapy for eye cancer. *Surv Ophthalmol* 2001;**45**:416–44.
- 10 Heigle TJ, Stulting RD, Palay DA. Treatment of recurrent conjunctival epithelial neoplasia with topical mitomycin C. *Am J Ophthalmol* 1997;**124**:397–9.
- 11 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.
- 12 Demirci H, McCormick SA, Finger PT. Topical mitomycin chemotherapy for conjunctival malignant melanoma and primary acquired melanosis with atypia: clinical experience with histopathologic observations. *Arch Ophthalmol* 2000;**118**:885–91.
- 13 Kurli M, Finger PT. Topical mitomycin chemotherapy for conjunctival malignant melanoma and primary acquired melanosis with atypia: 12 years' experience. *Graefes Arch Clin Exp Ophthalmol* 2005;**243**:1108–14.
- 14 Salomao DR, Mathers WD, Sutphin JE, et al. Cytologic changes in the conjunctiva mimicking malignancy after topical mitomycin C chemotherapy. *Ophthalmology* 1999;**106**:1756–60; discussion, 1761.
- 15 Finger PT, Czechonska G, Liarikos S. Topical mitomycin C chemotherapy for conjunctival melanoma and PAM with atypia. *Br J Ophthalmol* 1998;**82**:476–9.
- 16 Pe'er J, Frucht-Pery J. The treatment of primary acquired melanosis (PAM) with atypia by topical mitomycin C. *Am J Ophthalmol* 2005;**139**:229–34.
- 17 Donnenfeld ED, Perry HD, Wallerstein A, et al. Subconjunctival mitomycin C for the treatment of ocular cicatricial pemphigoid. *Ophthalmology* 1999;**106**:72–8; discussion 79.
- 18 Donnenfeld ED, Perry HD, Fromer S, et al. Subconjunctival mitomycin C as adjuvant therapy before pterygium excision. *Ophthalmology* 2003;**110**:1012–16.
- 19 Finger PT. "Finger-tip" cryotherapy probes: treatment of squamous and melanocytic conjunctival neoplasia. *Br J Ophthalmol* 2005;**89**:942–5.
- 20 Daniell M, Maini R, Tole D. Use of mitomycin C in the treatment of corneal conjunctival intraepithelial neoplasia. *Clin Experiment Ophthalmol* 2002;**30**:94–8.
- 21 Dudley BW, Malecha MA. Limbal stem cell deficiency following topical mitomycin C treatment of conjunctival-corneal intraepithelial neoplasia. *Am J Ophthalmol* 2004;**137**:950–1.
- 22 Kopp ED, Seregard S. Epiphora as a side effect of topical mitomycin C. *Br J Ophthalmol* 2004;**88**:1422–4.
- 23 Sacu S, Segur-Eltz N, Horvat R, et al. Intumescent cataract after topical mitomycin-C for conjunctival malignant melanoma. *Am J Ophthalmol* 2003;**136**:375–7.
- 24 Bartlett JD, Boan K, Corliss D, et al. Efficacy of silicone punctal plugs as adjuncts to topical pharmacotherapy of glaucoma—a pilot study. Punctal Plugs in Glaucoma Study Group. *J Am Optom Assoc* 1996;**67**:664–8.
- 25 Sakamoto A, Kitagawa K, Tatami A. Efficacy and retention rate of two types of silicone punctal plugs in patients with and without Sjögren syndrome. *Cornea* 2004;**23**:249–54.
- 26 Finger PT. Do you speak ocular tumor? *Ophthalmology* 2003;**110**:13–4.