Chemoreduction With Topical Mitomycin C Prior to Resection of Extensive Squamous Cell Carcinoma of the Conjunctiva

Topical mitomycin C (MMC) is effective for treatment of superficial or invasive squamous cell carcinoma (SCC) of the conjunctiva. In most instances, the chemotherapeutic agent is delivered 4 times daily in topical eyedrop form directly on the affected ocular surface. The medication is continued generally for 3 or 4 weeks, at which time the tumor is usually completely regressed.

Published results have shown that thin tumors, typically those that are less than 4 mm in thickness, show complete regression with MMC. Complete regression can be found with thin tumors even if they are extensive over most of the conjunctival and corneal surface. Thick tumors (≥4 mm in thickness), however, may show only partial regression with MMC, and there is the temptation to continue the medication for a prolonged period. Nevertheless, some patients do not show a complete response despite several chemotherapeutic cycles, and in such cases, prolonged therapy with this toxic medication could lead to serious vision-threatening and globe-threatening complications. Additionally, patient intolerance of the medication generally increases with multiple treatment cycles. In these cases, the use of MMC as a neoadjuvant chemotherapy for tumor reduction (chemoreduction) prior to resection of the residual conjunctival mass. In this report, we describe 3 cases in which this strategy was used.

Following patient examination and pathologic confirmation of the diagnosis of SCC, the patients were given options for management, including the use of topical MMC 0.04%. The advantages and disadvantages of this therapy were discussed with the patient. Investigational review board approval and patient consent was obtained. Temporal punctal plugs were placed in the upper and lower ipsilateral punctum to minimize systemic absorption of the drug and prevent punctal stenosis. Mitomycin C 0.04% was delivered in cycles that consisted of medication 4 times daily for 7 consecutive days followed by 7 consecutive days of no medication. The treatment cycles were repeated until the epithelial malignancy was judged to be clinically regressed. The medication protocol was designed to be continued until complete regression of the mass was achieved. If incomplete regression was noted, the medication was used until no further regression was evident or patient intolerance or toxic effects of the medication were unacceptable. The tumor response and toxic effects on the eye were recorded. Following MMC administration, the tumor residua was treated surgically as needed with conjunctival resection using the “no touch” technique, alcohol corneal epitheliotomy, and cryotherapy to the clinically unaffected surrounding conjunctival margin. The surgery was performed at least 2 weeks or more following discontinuation of MMC to allow for recovery of the conjunctiva and adequate wound healing.

Report of Cases. A summary of these cases is provided in the Table and Figure 1. They are described below.

Case 1. A 62-year-old woman was referred to us with extensive conjunctival SCC in the left eye, confirmed on previous incisional biopsy results. Her visual acuity was 20/100 OU from myopic chorioretinal degeneration. There was a gelatinous, extensively leukoplakic conjunctival tumor involving the entire inferior bulbar and tarsal conjunctiva from medial to lateral canthus plus 4 clock hours of limbal and 1 clock hour of corneal involvement (Figure 2). The entire mass measured 40 mm × 32 mm in basal dimension and 12 mm in thickness. Following 3 weeks of chemoreduction using topical MMC, the tumor showed gradual reduction in size to 24 mm × 20 mm in basal dimension and 8 mm in thickness and the corneoscleral limbus was free of...
Chemoreduction was discontinued because of substantial toxic effects of the medication with periocular cutaneous erythema and edema and ocular irritation without punctate keratopathy. The residual mass was resected with wide surgical margins using the no touch technique, and adjuvant cryotherapy was applied to the surrounding conjunctival margins. Reconstruction of the entire inferior conjunctival fornix was achieved with alloplastic amniotic membrane graft and insertion of a temporary symblepharon ring, which was removed at 1 week because of patient intolerance. On follow-up 22 months after chemoreduction, the conjunctiva remained healed with mild nonrestrictive inferior fornical foreshortening and no tumor recurrence.

Table. Summary of Clinical Findings in 3 Patients With Extensive, Thick Conjunctival Squamous Cell Carcinoma (SCC) Managed With Chemoreduction Followed by Surgical Resection of the Residua

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, y/ Race/Sex</th>
<th>Tissue Involved With SCC</th>
<th>Tumor Findings Before MMC Administration</th>
<th>Tumor Findings After MMC Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Largest Tumor Basal Dimension, mm</td>
<td>Tumor Thickness, mm</td>
</tr>
<tr>
<td>1</td>
<td>62/W/F</td>
<td>Bulbar conjunctiva; fornix; tarsal conjunctiva; cornea</td>
<td>40</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>38/W/M</td>
<td>Bulbar conjunctiva; fornix; tarsal conjunctiva; plica semilunaris</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>77/W/M</td>
<td>Bulbar conjunctiva; fornix; plica semilunaris; caruncle; cornea</td>
<td>30</td>
<td>6</td>
</tr>
</tbody>
</table>

*There were 2 tumor residua, each 7 mm in diameter (4 clock hours conjunctiva), measuring a total of 14 mm in diameter (8 clock hours conjunctiva).

Abbreviation: MMC, mitomycin C 0.04% 4 times daily.

Case 1

A 62-year-old woman with conjunctival squamous cell carcinoma measuring 40 mm in greatest basal extent and 12 mm in thickness. A, Prior to chemoreduction, the large leukoplakic mass involved the entire inferior fornix. B, Following chemoreduction with topical mitomycin C (3 cycles), the conjunctiva was edematous and injected. The leukoplakic mass reduced in size and was successfully resected. The conjunctiva was reconstructed with amniotic membrane allograft.

Figure 1. Diagram of tumor extent in 3 patients with extensive conjunctival squamous cell carcinoma before and after chemoreduction using mitomycin C (MMC) prior to surgical excision.

Figure 2. Case 1. A 62-year-old woman with conjunctival squamous cell carcinoma measuring 40 mm in greatest basal extent and 12 mm in thickness. A, Prior to chemoreduction, the large leukoplakic mass involved the entire inferior fornix. B, Following chemoreduction with topical mitomycin C (3 cycles), the conjunctiva was edematous and injected. The leukoplakic mass reduced in size and was successfully resected. The conjunctiva was reconstructed with amniotic membrane allograft.

Figure 3. Case 2. A 38-year-old man with mild ocular foreign body sensation was discovered to have a gelatinous, extensive conjunctival mass in the right eye, proven on incisional biopsy results to be SCC. On referral to us, his visual acuity was 20/20 OU. The mass measured 40 mm × 20 mm in basal dimension and 10 mm in thickness, with prominent intrinsic vascularity and surface leukoplakia. The lesion extended from the caruncle over the bulbar conjunctiva in the right eye into the inferotemporal fornix, without corneal or limbal tumor. Chemoreduction using topical MMC for a total of 4 cycles was prescribed. The tumor showed gradual reduction in size, and at completion of the last cycle, it resolved to 2 smaller lesions, each measuring 7 mm × 6 mm in basal dimension and 3 mm in thickness and each with intrinsic vascularity and leukoplakia. There were no toxic effects of MMC, but concern for long-term toxic effects prompted surgical excision of the residua. These sites were resected with wide surgical margins using the no touch technique, and adjuvant cryotherapy was applied to the surrounding conjunctival margins. Primary closure was

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achieved without the need for a graft. Nine months later, minimal fornical foreshortening was noted, and a minor focus of new tumor in the medial fornix, measuring 3 mm × 3 mm in basal dimension, was surgically resected. On last follow-up, 14 months after initial chemoreduction, there was no evidence of tumor.

Case 3. A 77-year-old man was referred to us with recurrent conjunctival SCC in the right eye following 3 previous corneal scrapings in an interval of 2 years for cytologic confirmation of epithelial neoplasia, 2 weeks of topical MMC used 16 months previously, and 3 weeks of topical interferon-α used 3 months previously. His visual acuity was 20/60 OD and 20/30 OS. The epithelial malignancy involved the caruncle, plica semilunaris, 3 quadrants of the bulbar conjunctiva, and 75% of the cornea, measuring 30 mm × 22 mm in basal dimension (Figure 4). The corneoscleral limbus was involved for 9 clock hours. The lesion was less than 2-mm thick, except for the superior limbal region and medial bulbar region, which each had a 6-mm thick diffuse nodule. Chemoreduction using MMC for a total of 6 cycles was prescribed. The tumor showed gradual reduction in size, and at completion of the last cycle, the tumor measured 10 mm × 10 mm in basal dimension and 4 mm in thickness with no corneal limbal tumor. There were no toxic effects of MMC, and the decision to surgically resect the residua was advised because the tumor still maintained substantial thickness with concern for deep invasion. The remaining tumor was resected with wide surgical margins using the no touch technique and adjuvant cryotherapy was applied to the surrounding conjunctival margins. Primary closure was achieved without the need for a graft.

Comment. Topical chemotherapy recently has been popularized for the management of conjunctival squamous epithelial malignancy. Initially, Fruct-Pery and Rozeman 1 used MMC 0.02% for corneal intraepithelial neoplasia. Later, several groups documented success using topical MMC 0.04% 2–8 or 5-fluorouracil15,16 for corneal as well as conjunctival squamous neoplasia. In fact, even extensive tumors involving up to 100% of the corneal surface and up to 12 clock hours of the limbus have been managed successfully with topical MMC. However, in most instances, those tumors with a complete response have been flat or minimally elevated, generally less than 4 mm in thickness.

In this report, we have introduced a novel strategy for management of extensive, thick SCC of the conjunctiva. In these cases, the tumors were 30 to 40 mm in basal dimension and 6 to 12 mm in thickness. Leukoplakia was prominent in 2 cases (cases 1 and 2), and corneal involvement was extensive in 1 case (case 3). We anticipated an incomplete response because of...
the substantial thickness of these tumors, so we used MMC as a neo-adjuvant to reduce tumor size, especially in the surrounding, less elevated portions, to allow for more limited conjunctival resection and more conservative reconstitution. With this in mind, we adapted the term chemoreduction to our use of MMC because our plan was to achieve partial reduction of the extensive mass to facilitate surgical excision.

Chemoreduction has been used for malignancies at several sites in the body, particularly brain tumors. With regard to the eye, chemoreduction has become popular in the initial management of children with bilateral retinoblastoma, and even some with unilateral disease. Additionally, chemoreduction has been used for malignancies of the lacrimal gland, allowing for more surgically amenable intraorbital process. In our 3 cases of conjunctival SCC, chemoreduction with topical MMC was effective in reducing the tumor base a mean of 57% using a mean of 4 cycles. Following MMC administration, the residual tumor was generally located at the site of the thickest tumor component or at those areas with leukoplakia. Surgery was postponed for at least 2 weeks following discontinuation of topical MMC to avoid wound healing problems. Prior to chemoreduction, we anticipated that extensive reconstruction of the conjunctiva with alloplastic amniotic membrane graft would be necessary in all 3 cases. As expected, following chemoreduction and then residual tumor excision, subsequent reconstruction was less difficult with primary closure in 2 cases and smaller amniotic membrane allograft in 1 case. Without chemoreduction, we anticipated that the corneal component would require corneal epithelial resection in 2 cases with risk for corneal pannus formation or conjunctivization from stem-cell loss. However, following chemoreduction, there was no residual corneal tumor and no need to resect the corneal epithelium in all 3 cases. Thus, chemoreduction was beneficial in sparing these patients extensive surgery, difficult tissue reconstruction, and potential complications.

The physician using topical MMC should be aware of its possible toxic effects. These include punctate keratopathy, corneal ulcer, scleral necrosis, uveitis, cutaneous erythema and edema, punctal stenosis, and others. In all cases, the medication should be returned to the physician on completion of each cycle for proper disposal. Fortunately, severe complications are not common. The only toxic effects experienced by our 3 patients included cutaneous erythema and ocular irritation in 1 patient (case 1). Importantly, wound healing following surgical resection was normal in all 3 cases. Additionally, it should be realized that MMC can alter the morphologic features of the conjunctiva, causing nuclear enlargement and chromatin smudging and hyperchromasia in the superficial epithelium, and these features can mimic malignancy on histopathologic examination.

In summary, topical MMC is effective in the management of conjunctival SCC. It can be used as topical chemotherapy for relatively flat tumors or as topical chemoreduction followed by surgical resection of the residual for thicker tumors. The latter strategy allows for less extensive surgical resection and tissue reconstruction.

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21. Goldberg RA. Intra-arterial chemotherapy: a welcome new idea for the management of ad-
Occlusion of Hypotony Maculopathy Diagnosed With Optical Coherence Tomography

Three patients with hypotony had decreased vision and normal ocular examination results. Evaluation of the macula by optical coherence tomography (OCT) demonstrated hypotony maculopathy, which resolved after increasing the intraocular pressure (IOP). Several weeks after normalization of intraocular pressure, OCT showed resolution of folds in the neurosensory retina and choroid. The anatomic resolution corresponded well with the clinical findings of an increase in IOP and improved visual acuity. Optical coherence tomography is a valuable tool for diagnosing hypotony maculopathy and assessing restoration of normal anatomy following appropriate treatment to raise the IOP.

Optical coherence tomography (Zeiss Meditec, Dublin, Calif) has been shown to be helpful in diagnosing a variety of retinal conditions, including cystoid macular edema, macular hole, epiretinal membrane, and diabetic macular edema. We report 3 cases of hypotony maculopathy diagnosed using OCT that was not seen clinically as well as resolution of the maculopathy after the IOP was normalized.

Report of Cases. Case 1. A 61-year-old non-Hispanic white woman with normal-tension glaucoma underwent combined phacoemulsification cataract extraction with intraocular lens implantation and trabeculectomy with mitomycin C in the right eye. The intraocular pressure ranged from 2 to 5 mm Hg postoperatively with a best-corrected visual acuity of 20/40 OD until 3 years after surgery, when the patient developed an IOP of 1 mm Hg and best-corrected visual acuity of 20/70 OD. The ocular examination results were normal, including examination of the cornea and retina. Stratus OCT of the macula was conducted, which revealed retinal folds (Figure 2A). A trabeculectomy revision was performed to raise the IOP using direct closure of the trabeculectomy flap with 9-0 nylon sutures, which raised the IOP to 20 mm Hg. The visual acuity improved to 20/40 OD, and the retinal folds resolved on OCT (Figure 2B). Sequential laser suture lysis resulted in an IOP between 6 and 8 mm Hg, and the patient’s vision has remained stable.

Case 2. An 80-year-old Hispanic man with primary open-angle glaucoma underwent combined phacoemulsification, intraocular lens implantation, and trabeculectomy with mitomycin C in the right eye. The intraocular pressure ranged from 2 to 5 mm Hg postoperatively with a best-corrected visual acuity of 20/40 OD until 3 years after surgery, when the patient developed an IOP of 1 mm Hg and best-corrected visual acuity of 20/70 OD. The ocular examination results were normal, including examination of the cornea and retina. Stratus OCT of the macula was conducted, which revealed retinal folds (Figure 2A). A trabeculectomy revision was performed to raise the IOP using direct closure of the trabeculectomy flap with 9-0 nylon sutures, which raised the IOP to 20 mm Hg. The visual acuity improved to 20/40 OD, and the retinal folds resolved on OCT (Figure 2B). Sequential laser suture lysis resulted in an IOP between 6 and 8 mm Hg, and the patient’s vision has remained stable.

Case 3. A 61-year-old non-Hispanic white woman with primary open-angle glaucoma and cataract underwent phacoemulsification cataract extraction with intraocular lens implantation and peripheral iridectomy in the left eye. The IOP was 11 mm Hg with glaucoma medications for the first 2 years postoperatively, then dropped to 4 to 5 mm Hg for unknown reasons. Glaucoma medications were discontinu-