Abstract

Purpose: To develop a guideline for the treatment of incompletely removed histopathologically documented ocular surface neoplasia (OSSN) with mitomycin C (MMC).

Materials & Methods: Through an interventional case series, 17 eyes of 17 patients presented with incompletely removed OSSN were treated according to a protocol using 2-3 alternate 7-day courses of MMC 0.04%. Clinical recurrence was re-treated with the same protocol. All patients had weekly follow up visits to the end of treatment course, then biweekly visits for 3 months, and monthly visits thereafter.

Results: Four patients (23.5%) experienced recurrence after the initial treatment, 3 of them responded to re-treatment and were disease-free till the end of follow up. All patients reported mild to moderate redness and irritation which was controlled with lubricants and mild corticosteroid eye drops. No serious ocular or systemic side effects were observed.

Conclusion: MMC drop 0.04% used as 2-3 alternate seven-day courses is a safe and effective treatment for OSSN. Attempting more than 2 courses of treatment (up to 4) in the initial regimen may result in lower recurrence rates.

Key words: Mitomycin C, Ocular Surface Neoplasia, Epithelial Dysplasia, Conjunctiva, Cornea, Squamous Cell Carcinoma.

Introduction

Ocular epithelial dysplasia is a relatively common ocular surface change with a wide range of clinical manifestations. These lesions represent approximately one third of all surgically excised acquired epithelial lesions of the conjunctiva. It progresses through a sequential series, increasing in severity ranging from minor superficial epithelial dysplasia [conjunctival or corneal intraepithelial neoplasia (CCIN)] to full thickness dysplasia [carcinoma in situ (CIS)] and invasive squamous cell carcinoma (SCC). Risk factors for developing CCIN and SCC are human papilloma virus (HPV), HIV infection and ultraviolet exposure.

These lesions are usually elevated, variably shaped, and sharply demarcated from the surrounding normal tissue. They can be gelatinous and velvety or leukoplakic in appearance. Less often the neoplastic process may diffusely involve the conjunctiva with indistinct border. Most of these lesions have a relatively benign course and slow progression, but malignant behaviors of SCC such as perineural invasion resulting in death have also been reported.
Although these lesions have a relatively benign course, difficulty in obtaining tumor free surgical margins may lead to recurrence rates of 25-53%.  
Cryotherapy of the tissue surrounding the site of surgical excision has been used decreasing the recurrence rate to 11% ; however, the complication rate increases with extensive freezing. Some of these complications are conjunctival scaring, symblepharon formation, deformities of the conjunctival fornices and lids.  
Mitomycin C (MMC) is a non cell cycle specific alkylating agent. Its mode of action mimics that of ionizing radiation. Recent publications have addressed the efficacy and safety of topical MMC for conjunctival and corneal SCC.  
Due to small sample sizes of the reported studies, and the variation in the medication concentration and duration, up to now there has been no approved guideline for treatment of OSSN with MMC. Another consideration is lack of information on the efficacy and safety of MMC in the Asian population affected by OSSN. In this study using the more restricted protocol suggested by Wilson and associates, we studied the efficacy and safety of MMC in Asian patients in whom previous attempts of excisional biopsy for OSSN had left surgical margins involvement in histopathologic examination.

**Materials and Methods**

The study was an interventional case series carried out as a single institution study on 17 eyes of 17 patients who referred to us after attempted excisional biopsy without cryoablation of the conjunctival border with pathologic report of SCC or CIN with surgical margin involvement. The study was approved by the ethics committee of Tehran University of Medical Science (TUMS) and an informed consent was obtained from the study subjects.

We prospectively evaluated the efficacy and toxicity of topical MMC for OSSN. MMC 0.04% was prepared by one of the authors by dissolving the powder content of a 2 mg commercially available vial for injection (Mitomycin C kyowa, kyowa Hakko kogyo Co., Ltd.) in 5 CC artificial tear (Polyvinil alcohol 1.4%, Sina Darou). The bottle was shaken several times and the medication was then put into sterile eye drop bottles. MMC 0.04 % eye drop was applied four times a day for 7 consecutive days followed by 7 consecutive days off MMC. All patients were trained to shake the eye drop bottle several times before application, to close the eye 5 minute after using the drop, and to close the punctum by applying finger pressure for at least 1 minute. Artificial tear and corticosteroid eye drops were administrated if symptoms such as redness and irritation occurred. The medication bottle was returned to the physician after each week of use. The treatment cycle (7 days on MMC and 7 days off) were repeated until all the epithelial malignancy was judged to be clinically and completely regressed using slit lamp biomicroscopy, detailed anterior segment drawings and slit lamp photography.

The clinical and histopathological data including patients’ age, gender, eye involved, tumor type and the initial management prior to referral were recorded at the time of the first visit. At the same time, detailed ocular exam and periauricular and submandibular lymph nodes palpation were performed and recorded.

All pathology reports were reviewed with one pathologist. Based on the histopathologic assessment, in situ SCC (CIN) was defined as the tumor confined to the epithelium, and invasive SCC was defined as the tumor that breached the basement membrane and exhibited stromal invasion.

During treatment, symptomatic side effects of the medication were inquired from patients at regular follow up visits. Follow-ups were scheduled as weekly visits until the end of treatment, biweekly for 3 month, and monthly thereafter. All patients could have emergency visits if needed. Evaluation of treatment side effects and tumor status were recorded at each visit. At each examination, tumor, globe and systemic status were re-assessed. The main outcome measures were tumor control and medication related toxicity.

**Results**

Seventeen patients with documented histopathologic diagnosis of OSSN (carcinoma in situ or SCC) with tumoral
involvement of the surgical margin were referred to our clinic after attempted surgical excision without cryoablation of the conjunctival margin or scleral bed resection. Twelve patients (75.6%) were male and 5 (29.4%) were female. The patients' age ranged from 24 to 76 years (mean=58.7, SD=14.9 yr).

Nine patients (52.9%) had the right eye involvement, and the left eye was involved in the remainder 8 (47.1%).

Histopathologic diagnoses were SCC in situ in 8 (47.1%), CIN in 5 (29.4%) and invasive SCC in 4 (23.5%) patients.

None of the patients had palpable lymph nodes in the head and neck region throughout the study. One of the patients had a prior kidney transplant. This patient was treated successfully with 2 courses of MMC and was disease free during follow up period of 9 months.

One patient suffered from xeroderma pigmentosum, with a history of malignant skin lesions treated with excisional biopsy. He experienced recurrence once 6 months after the initial treatment, and responded well to re-treatment and was disease free until the end of the study (10 months). Since the later lesion had occurred at the superior conjunctiva far from the earlier lesion that was nasal, we were not able to determine whether this was a new lesion that had risen from the genetically susceptible conjunctiva or simply a recurrence. However, we considered it as a case of recurrence in our data analysis.

Anti-HIV antibody was ordered for two patients who were under 40 years of age, which was negative in both.

Fourteen patients (82.4%) received two courses of MMC 1 week apart, and only 3 patients (17.6%) received three MMC courses. Three of the recurrent cases were in the first group, all of whom respond to re-treatment.

The follow up period ranged from 6.5 to 23 months with the mean and standard deviation (SD) of 12.76 and 4.4 months, respectively. Thirteen patients (76.5%) had no recurrences during the follow up period; 4 patients (23.5%) experienced clinical recurrence, 3 of whom were managed by 2 additional MMC courses up to the end of the follow up period. Disease free period after the initial treatment ranged from 2.5 to 23 months (mean=11.4 and SD=5.3 months). In 3 recurrent cases that responded to re-treatment, the final disease free follow up period ranged from 3 to 10 months (mean=6.2, SD=3.5 months). The fourth patient had the lesion recurred 2.5 months after the initial treatment. Even though he showed clinical response to new courses of MMC, we considered that case a treatment failure, which due to another recurrence 4 months after cessation of the re-treatment he underwent further surgical excision.

None of the recurrences occurred in the invasive SCC group.

Survival analysis with Kaplan-Meier method was performed with SPSS version 11.5 both for the initial response and the final outcome. Taking into account four recurrences, the 23 month non-recurrence rate was 74%. However, including 3 out of 4 cases of recurrence that responded to re-treatment, the final outcome in survival analysis was 94.1% non-recurrence for 23 months of follow up.

All patients reported some degree of mild to moderate eye redness and irritation that was controlled by artificial tear, mild corticosteroid drops and warm compress. None of patients developed any other ocular complications reported with MMC (such as scleral melting, etc) or any systemic complications attributable to MMC.

Discussion
The management of conjunctival and corneal SCC-CIN continues to evolve and new modes of treatment such as PDT are under investigation.

The classic method of excisional biopsy as defined by Shield is not applicable for many patients with extensive lesions. Resecting four millimeters of safety margin from the unaffected conjunctiva may cause severe ocular surface problems or may not be possible at all. Extensive partial thickness scleral bed removal may cause anterior staphyloma. Cryotherapy has its own complications and pure alcohol is of high toxicity. A high recurrence rate (up to 53%) is also a concern.

One major problem in investigations for new treatment modalities for SCC-CIN is the relatively low incidence of the tumor which makes "Randomized Double Blind Clinical Trial (RCT)" design a difficulty. To evaluate
the efficacy and safety of each mode of treatment, it seems necessary to combine the results of several interventional case series from different ethnic groups. Topical mitomycin C (MMC) is a well-known drug that has been used for SSC-CIN in many studies with different results.\textsuperscript{1,2,4-7} These variable results can be attributed to different drug concentrations and/or treatment durations. \textsuperscript{6} Wilson et al. suggested the protocol of topical MMC 0.04\% for 7 days in alternate weeks.\textsuperscript{6} Our results showed the safety and efficacy of that protocol. The mentioned protocol had been previously used by Shield et al. on ten patients with extensive conjunctival and corneal SCC with no recurrence at 6-50 months of follow up.\textsuperscript{10} Although 4 of our patients had recurrence with the initial protocol, 3 responded well to the repeat courses of MMC. One of these 3 patients (case number 4) had xeroderma pigmentosa and the new lesion which we considered it a recurrence could have been a totally new lesion irrelevant to the first one. Our decision on cessation of MMC courses was based on the clinical response. In cases without any apparent lesion on slit lamp exam, two alternate 7-day courses were considered sufficient. If some other objective methods such as impression cytology (to assess the histopathologic response) could have been utilized, our 3 recurrences would not have taken place with the recurrence rate being 6\% instead of 23.5\%.

The demographic difference between our patients and the patients treated by Wilson and Shield can also be a probable source of our slightly poorer outcomes. Further follow up of these patients is warranted for a more accurate assessment of the actual recurrence rate and long term safety of MMC.

**Conclusion**

OSSN is relatively common and a serious disease. The standard method of treatment is wide excision with cryotherapy. However, serious complications and the high recurrence rate are major concerns. MMC eye drop 0.04\% has been shown to have good clinical results and no serious side effects when used as alternate 7-day courses. We suggest 3 to 4 courses of MMC instead of 2 in all patients in the absence of an objective method for histopathologic assessments. This protocol may result in lower recurrence rates.

**References**