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Original Article

Topical Mitomycin-C for Treatment of Partially-Excised Ocular Surface Squamous Neoplasia

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Background: **This study was conducted to determine the treatment outcome of incompletely removed, histopathologically documented ocular surface squamous neoplasia with mitomycin-C.**

Methods: **Through an interventional case series, 17 eyes of 17 patients presented with incompletely removed ocular surface squamous neoplasia were treated according to a protocol using two to three alternate seven-day courses of 0.04% mitomycin-C. Clinical recurrence was re-treated with the same protocol. All patients had weekly follow-up visits to the end of the treatment course, then biweekly visits for three months, and monthly visits, thereafter.**

Results: **The mean±SD follow-up period was 30.76±4.4 (range: 24.5 – 41) months. Five patients (29.4%) experienced recurrence after the initial treatment; four of them responded to retreatment and were disease-free till the end of follow-up. Survival analysis with Kaplan-Meier method was performed. Taking into account four recurrences, the 41-month nonrecurrence rate was 70.6%. However, including four of five patients with recurrence who responded to retreatment, the final outcome in survival analysis was 94.1% nonrecurrence for 41 months of follow-up.**

All patients reported mild to moderate redness and irritation which were controlled with lubricants and mild corticosteroid eye drops. No serious ocular or systemic side effects were observed.

Conclusion: **Point zero four percent (0.04%) mitomycin-C drop used as two to three alternate seven-day courses seems to be a safe and effective treatment for ocular surface squamous neoplasia.**

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Keywords: Mitomycin • ocular surface • squamous neoplasia

Introduction

Ocular epithelial dysplasia comprises one-third of all surgically-excised lesions of the conjunctiva.[1,2] Most of these lesions have a relatively benign course, but malignant behaviors have been reported.[3] Difficulty in obtaining tumor-free surgical margins may lead to recurrence rates of 25 – 53%.[2]

Mitomycin-C (MMC) is an alkylating agent.[5] Recent publications have addressed the efficacy and safety of topical MMC for ocular surface squamous neoplasia (OSSN).[1,2,4–7]

Due to variation in the protocol, up to now, there is no approved guideline for the treatment of OSSN with MMC. Using the more restricted protocol suggested by Wilson et al.,[6] we studied the efficacy and safety of MMC in patients with partially-excised OSSN.

Materials and Methods

This prospective study was an interventional case series carried out as a single institutional study from March 2004 through February 2006 on patients who were referred to Farabi Eye Hospital, affiliated to Tehran University of Medical Sciences, Tehran, Iran, in whom after attempted excisional biopsy without cryoablation of the conjunctival border, the pathology report was

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squamous cell carcinoma (SCC) or carcinoma *in situ* (CIN) with surgical margin involvement. Patients who met the inclusion criteria but would not consent to the study follow-up protocol were excluded. Finally, 17 patients (17 eyes) were included in the study.

The study was approved by the Ethics Committee of Tehran University of Medical Sciences. Informed written consent was obtained from the study subjects.

We prospectively evaluated the efficacy and toxicity of topical MMC for treatment of 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 mL artificial tear (Polyvinyl 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 seven consecutive days followed by seven consecutive days off MMC. All patients were trained to shake the eye drop bottle several times before application, to close the eye for five minutes after using the drop, and to close the punctum by applying finger pressure for at least one minute. The patients were asked to keep the drug on the bottom shelf of refrigerator between uses. Artificial tear and corticosteroid eye drops were administrated if symptoms such as redness and irritation occurred and confirmed by slit-lamp examination. The medication bottle was returned to the physician after each week of use. The treatment cycles (seven days on MMC and seven 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. No further histopathologic examinations were carried out.

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

All pathology slides were reviewed by 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 the patients at regular follow-up visits based on a comprehensive list of MMC side effects profile presented in Martindale Textbook of Pharmacology (2004). Follow-ups were scheduled as weekly visits until the end of the treatment, biweekly for three month, and monthly, thereafter. All patients could have emergency visits if needed. Evaluation of the treatment side effects and tumor status were recorded at each visit. At each examination, tumor, globe, and systemic status were reassessed. The main outcome measures were tumor control (defined as the absence of clinical recurrence detectable in slit-lamp examination) and medication-related toxicity (based on patients' reported symptoms from the list of potential complications, and also as detected on physical examination).

Results

Seventeen patients with documented histopathologic diagnosis of OSSN (CIN 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 (70.6%) were males and five (29.4%) were females. The mean±SD age of the patients was 58.7±14.9 (range: 24 – 76) years.

Nine patients (52.9%) had the right eye and eight (47.1%) had the left eye involvement.

Histopathologic diagnoses were SCC *in situ* in eight (47.1%), CIN in five (29.4%), and invasive SCC in four (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 two courses of MMC and had a follow-up period of 27 months.

One patient suffered from xeroderma pigmentosum, with a history of malignant skin lesions treated with excisional biopsy. He experienced recurrence once six months after the initial treatment, and responded well to re-treatment and was disease- free until the end of the study (28 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 one week apart, and only three patients (17.6%) received three MMC courses. Three of the recurrent cases were in the first group, all of whom responded to retreatment.

The mean±SD follow-up period was 30.8±4.4 (range: 24.5 – 41) months. Twelve patients (70.6%) had no recurrences during the follow-up period; five (29.4%) experienced clinical recurrence, four of whom were managed by two additional MMC courses up to the end of the follow-up period. The mean±SD disease-free period after the initial treatment was 24.3±12 (range: 2.5 – 41) months. In four patients with recurrence who responded to retreatment, the mean±SD final disease-free follow-up period was 21.9±5.4 (range: 15 – 28) months. The fifth patient had the lesion recurrence two and a half 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 four months after cessation of the retreatment, he underwent further surgical excision. No recurrence occurred in those with invasive SCC.

Kaplan-Meier survival analysis was performed both for the initial response and the final outcome. Taking into account five recurrences, the 41-month nonrecurrence rate was 70.6% (Figure 1).

However, including four out of five cases of recurrence who responded to retreatment, the final outcome in survival analysis was 94.1% non-recurrence for 41 months of follow-up.

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

Discussion

The management of conjunctival and corneal SCC-CIN continues to evolve. Some alternative therapies to the standard surgical management include topical interferon, first described in one case by Maskin in 1994,[8] followed by some other authors, with good results and few side effects.[9,10] New modes of treatment such as disclosures photodynamic therapy (PDT)[11] are under investigation.

The classic method of excisional biopsy as defined by Shield et al.[12] is not applicable for many patients with extensive lesions. Resecting 4 mm 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[2,4] and pure alcohol is of high toxicity. A high recurrence rate (up to 53%) is also a concern.[2]

One major problem in investigations for new

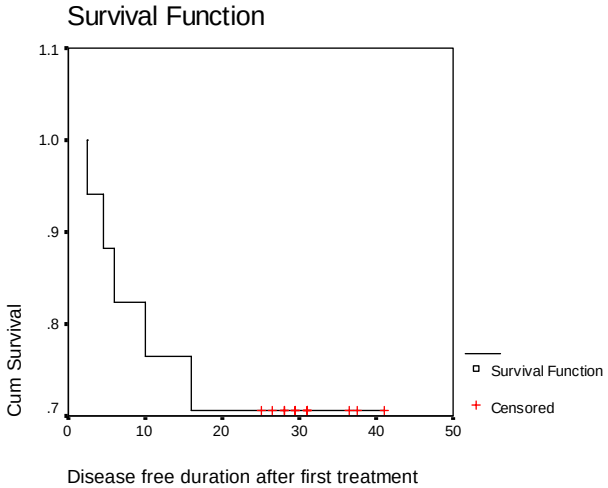

Figure 1. Survival analysis.

treatment modalities for SCC-CIN is the relatively low incidence of the tumor which makes the design of double-blind randomized clinical trials (RCT) difficult. 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.

Another important consideration in assessing the effectiveness of treatment modalities is the risk of neoplastic recurrence many years later, which mandates long-term follow-up periods. Trend of OSSN to recur in the first years may slightly decrease this concern.

Topical MMC is a well-known drug that has been used for treatment of SSC-CIN in many studies with different results.[1,2,4–7] These various results can be attributed to different drug concentrations and/or treatment durations, or solely to different follow-up periods.

Wilson et al. suggested the protocol of topical MMC 0.04% for seven days in alternate weeks.[6] Our results showed the safety and efficacy of that protocol in patients with incompletely excised SCC-CIN. The mentioned protocol had been previously used by Shield et al. on ten patients with extensive conjunctival and corneal SCC with no recurrence at six to 50 months of follow-up.[13]

Although five of our patients had recurrence with the initial protocol, four responded well to the repeated courses of MMC. One of these four patients, had xeroderma pigmentosa and the new lesion which we considered 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 examination, two alternate seven-day courses were considered sufficient. Probably, if some other objective methods such as impression cytology (to assess the histopathologic response) could have been utilized, our four recurrences would not have taken place.

The demographic difference between our patients and the patients treated by Wilson et al.'s and Shield et al.'s protocol 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.

The long list of systemic side effects resulting from systemic administration of MMC contains bone marrow suppression, profound leukopenia and thrombocytopenia, gastrointestinal toxicity, dermatitis, alopecia, fever, malaise, and cardiotoxicity.[14] Although topical MMC at such a small dose that we used in our study was unlikely to cause systemic side effects, we tried to minimize systemic absorption of the drug by finger pressure punctual occlusion. None of our patients reported any complications attributable to systemic absorption of the drug.

OSSN is relatively common and is 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 shown good clinical results and no serious side effects when used as alternate seven-day courses.

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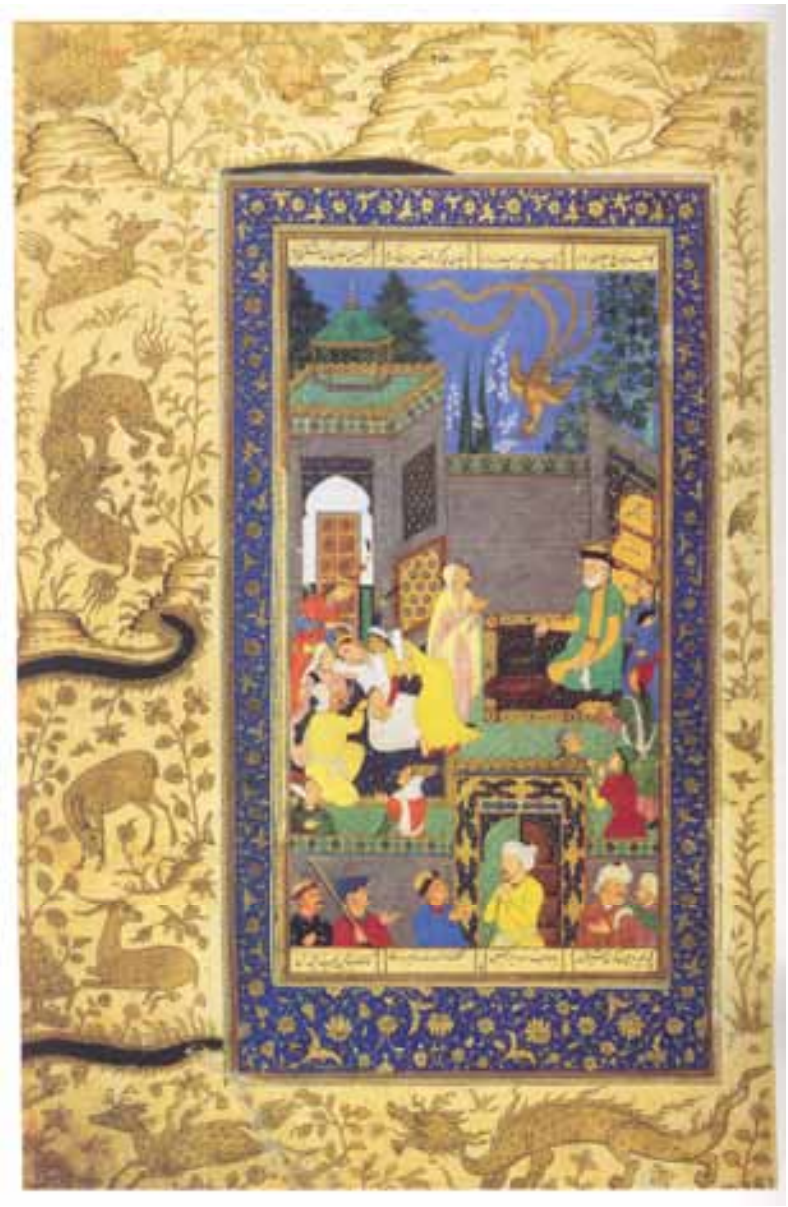

This miniature painting from a 16th century shahnameh manuscript shows the legendary birth of Rostam. Rudabeh, mother of "the Persian Hercules", undergoes a cesarean operation upon the advice of the wise Simorgh (giant mythical bird) watching from above.
Reza Abbasi Museum, Tehran
The splendour of Iran
Quoted from Vol. III, Islamic Period, P: 304–305
Originator: E. Booth-Clibborn
Booth-Clibborn Editions London, 2001