

Mitomycin C in Recurrent or Extensive Ocular Surface Neoplasia

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ABSTRACT

Role of mitomycin C (MMC) is searched in recurrent cases with squamous cell carcinoma (SCC), conjunctival-corneal intraepithelial neoplasia (CCIN) or in advanced cases of ocular surface neoplasm in whom, surgical excision was impossible due to extensive involvement of ocular surface. Seventeen cases of SCC, CCIN or PAM(primary acquired melanosis) with atypia were selected. They received three cycles of MMC (0.04%) eye drop four times a day for one week. Participants were followed for 4-36 months. There were 7 females and 10 males.7 patients (41.1%) developed one time recurrence after first course of treatment but during follow up, only 3 of them (17.6%) needed surgical management while 4 others responded to another course of treatment. Six out of 17 patients (35.2%) had another systemic disease and received either chemotherapy or radiation before.We conclude that even though the trend for use of chemotherapy as a sole drug or in adjunct with surgery in the treatment of ocular surface neoplasia is rising, surgical resection still remains the first line procedure in the management of limited forms of CCIN or aggressive and invasive SCC while they are concise. Only in recurrent cases or extensive involvement of ocular surface, prescription of MMC may be reasonable.

Key Words: Conjunctiva, Mitomycin C, Neoplasia, Ocular malignancy, Squamous cell carcinoma

ÖZET

Rekürren veya Yaygın Oküler Yüzey Neoplazilerinde Mitomisin C Kullanımı

Çalışmamızda mitomisin C'nin nüks skuamöz hücreli karsinomda, konjunktivo-korneal intraepitelial neoplazide (CCIN) ve yaygın oküler yüzey tutulumu nedeniyle cerrahi eksizyon yapılamayan ileri vakalardaki rolü araştırılmıştır. Bu kriterlere uyan 17 vaka çalışmaya alınmıştır. Hastalara 1 hafta boyunca günde 4 kez 3 siklus mitomisin-C göz damlası uygulanmıştır. Vakalar 4-36 ay arasında takip edilmiştir. Toplam 7 kadın ve 10 erkek hasta çalışmada yer almıştır. Yedi vakada nüks gelişmiş, sadece 3 vakaya cerrahi gerekmiş, 4 hasta diğer tedavilere cevap vermiştir. Ko-morbid hastalığı olan 6 hastaya önceden başka kemoterapi veya radyoterapi uygulanmıştır. Sonuç olarak, adjuvan kemoterapi veya sadece kemoterapi uygulamaları gittikçe yaygınlaşsa da cerrahi rezeksiyon sınırlı CCIN veya agresif ve invaziv skuamöz hücreli kanserlerde hala ilk tedavi seçeneğidir. Sadece nüks hastalarda veya yaygın oküler yüzey tutulumunda mitomisin-C kullanımını uygundur.

Anahtar Kelimeler: Konjunktiva, Mitomisin C, Neoplazi, Oküler malignansi, Skuamöz hücreli karsinom

INTRODUCTION

Standard treatment for corneal and conjunctival intraepithelial neoplasia (CCIN) and squamous cell carcinoma (SCC) has been surgical excision of the lesion accompanying with cryotherapy (1). Although CCIN is a slowly progressive condition with a small risk of malignant transformation, even death has been reported with its peri-neural invasion (2). Reported recurrence rate is high after traditional therapy (25-53% depending on surgical approach, status of margins and length of follow up) (1,3).

When conjunctival SCC is partially excised or recurs, further surgical intervention is required to eliminate the neoplastic tissue. Several reports have suggested cryotherapy as a useful treatment for these conditions (4); however, complications including conjunctival scarring, symblepharon formation, lid or forniceal deformities and corneal edema increases with extensive freezing (5).

Topical 5-fluorouracil (6), cidofovir (7) and interferon (8) have been tried with success in the treatment of CCIN and SCC.

Mitomycin C (MMC) –which is a non cell cycle specific alkylating agent and acts like ionizing radiation (9) – has been reported for treatment of CCIN and SCC in small series of patients (10).

In this study we will evaluate the treatment with mitomycin C in partially excised or recurrent cases of SCC and CCIN or in advanced cases of ocular surface neoplasm in whom, surgical excision was impossible due to extensive involvement of ocular surface.

PATIENTS AND METHODS

The study was an interventional case series on patients with one of the following criteria who referred to Poostchi eye clinic during 2002-2006:

1- Incomplete excision of suspected lesions which then proved to be CCIN or SCC of the ocular surface without performing cryo ablation of margins or bed at the time of excision.

2- Extensive involvement of ocular surface with CCIN, SCC or primary acquired melanosis (PAM) with atypia which makes surgical excision very difficult or impossible after proving the malignant state of the condition with an incisional biopsy.

3- Recurrent cases of SCC or CCIN in whom wide re excision may lead to corneal stem cell deficiency(which is a type of ocular surface disease related to difficulty in epithelium re-renewal) or production of large bare area on the ocular surface.

The study was approved by the ethics committee of Shiraz University of Medical Sciences and informed consent was obtained from participants before enrolment.

MMC 0.04% was prepared by one of the authors by dissolving the powder content of a 2 mg commercially available vial for injection of MMC (Mitomycin C, Kyowa, Hakko Kogyo Co. Ltd) in normal saline 0.9% solution and then transferred to sterile eye drop containers.

All patients were advised to shake the bottle before application, keep it refrigerated and apply finger pressure in medial canthal area for at least 2 minutes after each use.

Medication was discarded after one week. Treatment regimen includes 3-4 cycles of 7 days MMC application (4 times a day) followed by 7 days off.

Low dose corticosteroid drop and simple eye ointment were prescribed during treatment cycle if irritation symptoms occurred.

In off periods, all patients received artificial tear eye drop 4 times a day plus lubricating ointment for nights. Ocular surface photographs were obtained from all of the patients (except one) before treatment and at the last follow up visit.

All of participants were undergone complete ocular examination before, weekly during treatment and then monthly there after for 4-36 months. All of the patients' data including age, gender, initial management and pathologic reports were recorded.

At each examination, evaluation of side effects as well as the status of tumor, eye structures and whole body were done.

The main outcome measures were tumor control and treatment side effects.

RESULTS

17 patients were enrolled in the study aged between 21-75 (mean, 60.11 ± 14.68) years.

There were 7 females and 10 males. The patients' data and outcomes are shown in Table (1).

Table 1. Patients' criteria and outcomes

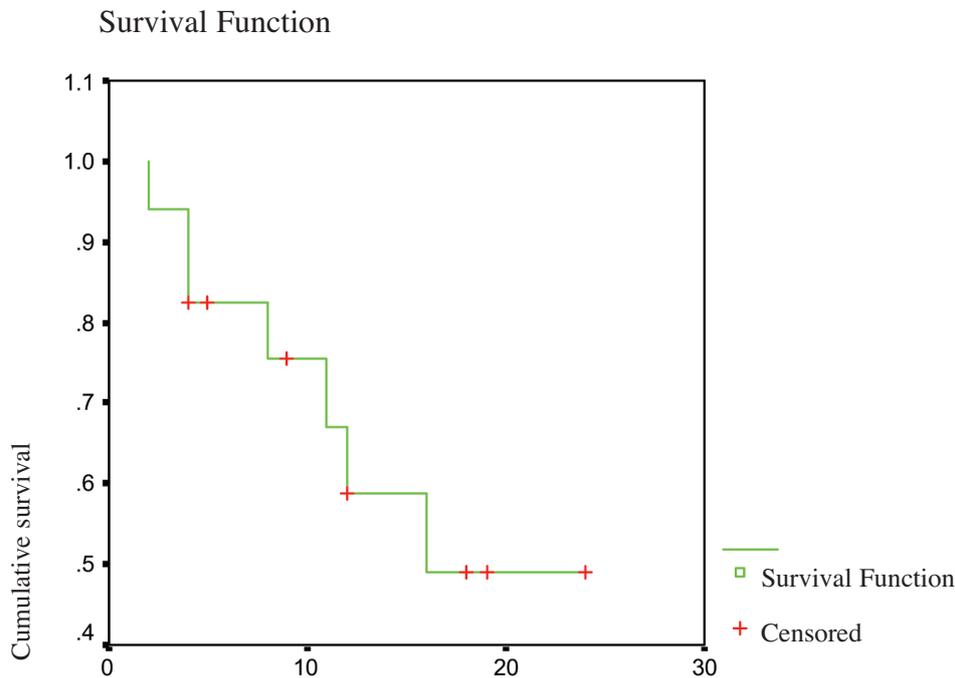
	Sex (M/F)	Age	Diagnosis	Systemic disease	Time to recurrence after treatment	Repeat of	Final results	Follow up (months)	Complications
1	F	40	R (SCC)	SLE•	16 months	+	Leads to surgery	36	Stem cell deficiency
2	F	55	IE (CIN)	Lymphoma	-	-	Successful	18	-
3	M	54	R (CIN)	BCC	12 months	+	Successful	24	-
4	F	75	IE (CIN)	-	4 months	+	Successful	24	-
5	F	75	IE (EXTENSIVE (SCC))	-	-	-	Successful	24	-
6	M	60	IE (CIN)	CLL••	-	-	Successful	9	-
7	F	71	IE (SCC)	-	11 months	+	Successful	24	Severe chemosis
8	M	21	R (SCC)	X.P•••	2 months	+	Enucleation••••	36	-
9	M	65	IE (CIN)	-	-	-	Successful	18	-
10	F	63	IE (CIN)	-	4 months	+	Leads to surgery	15	Severe irritation
11	M	70	IE (EXTENSIVE (SCC))	-	-	-	Successful	4	-
12	M	66	IE (SCC)	-	-	-	Successful	18	-
13	M	60	R (CIN)	-	8 months	+	Successful	30	-
14	M	39	IE (SCC)	-	-	-	Successful	12	-
15	M	73	IE (CIN)	-	-	-	Successful	9	-
16	F	69	PAM with atypia	-	-	-	Successful	19	-
17	M	66	IE (CIN)	Prostatic carcinoma	-	-	Successful	5	Stem cell deficiency

Abbreviations:

CIN: Conjunctival intraepithelial neoplasia; IE: Incomplete excision; PAM: Primary acquired melanosis; R: Recurrence; SCC: Squamous cell carcinoma

• : Systemic lupus erythematosus; ••: Chronic lymphocytic leukemia ;•••: Xeroderma pigmentosa;

••••: Due to intraocular penetration



Graphic 1. Survival analysis by Kaplan Meier Method (X axis: Months of follow up; Y axis: Percentages of patients who were disease free)

According to the table, 7 patients (41.1%) developed one time recurrence after first course of treatment but during 4-36 months follow up, only 3 of them (17.6%) needed surgical management while 4 others responded to another course of treatment with MMC.

Anti HIV antibody was checked in 3 cases who were younger than 40 years and none of them show positivity.

One of the patients (NO.16) had extensive ocular surface PAM with atypia with involvement of lower fornix and bulbar conjunctiva in which localized elevated focuses of malignant melanoma were existed. Patient refused extensive surgery but accepted to be enrolled in the study. Unfortunately, she didn't allow us to take any photograph but complete cure was proved in her by performing another multiple biopsy after treatment.

Follow up period of patients ranged between 4-36 months (mean, 19.11±9.64).

In recurrent cases, disease free period after the first course was between

2-16 months (mean, 8.14±5.11) and in whom cure was achieved with re-treatment, follow up period after the second course ranged between 12-22 months (mean,17.4±4.56).

Taking into account the 7 cases of recurrences, twelve months non recurrence rate was 47%; however with consideration of 4 cases of successful treatment, the final outcome was 11.35 person/months disease free period after treatment. Kaplan Meier survival analysis showed that recurrences were increased with time (Graphic 1).

In all patients mild to moderate eye congestion and chemosis was observed, but significant complications such as severe irritation, severe chemosis or signs of corneal stem cell deficiency occurred only in 4 patients. Six out of 17 patients (35.2%) had another systemic disease and received either chemotherapy or radiation before their eye problem.

DISCUSSION

Topical MMC showed variable success rates in treatment of CCIN and SCC. This may be due to differences in used regimens or variability in follow up periods (9,11,12).

The suggested protocol of Wilson et al. (13) was successful with acceptable safety and low recurrence rate, however, our similar regimen had high recurrence rate (41%) in 36 months follow up. In our study, recurrence rates seems to be higher with longer follow up periods but occurs nearly equally in SCC and CCIN cases. Kaplan Meier analysis was compatible with this fact that recurrences were increased with time. Higher recurrence rates in our study may be due to demographic differences between our population and western population or difference in environmental factors like sun exposure.

Presence of systemic disease in more than 1/3 of our patients is highly noticeable. The occurrence of ocular surface malignancy in these patients may be attributable to their systemic disease itself, immunosuppressive medication used or radiotherapy.

However, the presence of such a systemic disease seems not to be a risk factor for higher recurrence rates in our study.

Successful treatment of a widespread PAM with atypia after one course of treatment with MMC produces hope in avoidance of extensive surgery in these patients. These finding is in accordance with which was claimed by Chalasani et al. (14).

The occurrence of corneal stem cell deficiency (Limbal deficiency is a clinical entity characterized by vascularization of the corneal epithelium, chronic inflammation, persistent and recurring epithelial defects, photophobia, red eye and loss of vision (15) in two of our patients after two courses of treatment may be attributable to their previous wide limbal tumor excision; or the drug itself like what was observed by Dudeney et al (16) in an African woman. However, serious complications were not reported in mid term follow up of 100 patients treated with MMC (17). Although it was suggested that MMC should be used as the first line treatment of choice in CCIN (10); it seems that surgical resection still remains the first line procedure in the management of limited forms of CCIN or aggressive and invasive SCC while they are concise and wit-

hout extensive involvement of limbus or cornea. Only in recurrent cases or extensive involvement of ocular surface, prescription of MMC may be reasonable even though the trend for use of chemotherapy as a sole drug or in adjunct with surgery in the treatment of ocular surface neoplasia is rising (6-8,10,11,14).

Evidence based reports are needed on use and safety of MMC in ocular surface malignancies.

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