นิพนธ์ต้นฉบับ

ประสิทธิภาพการรักษามะเร็งเยื่อบุตา Conjunctiva – Corneal Intraepithelial Neoplasia ด้วย Primary Topical 0.02% Mitomycin C

พิรุณรัตน์ เจียรักสุวรรณ, พ.บ.
กลุ่มจักษุวิทยา โรงพยาบาลสุรินทร์

Received: *May 25, 2021* **Revised:** *July 6, 2021* **Accepted:** *August 6, 2021*

บทคัดย่อ

ที่มาของปัญหา: การรักษามะเร็งเยื่อบุตา Conjunctiva - corneal intraepithelial neoplasia (CCIN) ตามมาตรฐาน ได้แก่ การผ่าตัดชิ้นเนื้อออกให้กว้างร่วมกับการจี้เย็น แต่มีข้อจำกัดในกรณีมีหลายก้อนหรือมีขนาดใหญ่แพร่กระจาย

วัตถุประสงค์: ศึกษาประสิทธิภาพ 0.02% mitomycin C ในการรักษามะเร็งเยื่อบุตา Conjunctiva - corneal intraepithelial neoplasia (CCIN) ที่ไม่เคยรักษามาก่อน

วิธีการศึกษา: การศึกษานี้เป็นการศึกษาแบบ Intervention with historical controlled case - series เพื่อดูการหายของมะเร็งเยื่อบุตา (complete resolution) ในกลุ่มผู้ป่วย CCIN ที่ได้รับการหยอดยา 0.02% mitomycin C วันละ 4 ครั้งหยอดเป็นรอบ (หยอด 7 วัน หยุดยา 7 วัน) โดยตรวจติดตามเพื่อประเมินการให้ยาในรอบต่อไปทุก 2 สัปดาห์ จนกว่าก้อนหายไป เปรียบเทียบกลุ่มผู้ป่วยในอดีตที่ได้รับการรักษาด้วยการผ่าตัด โดยใช้ตัวชี้วัดหลักคือ การหายไปของก้อนมะเร็งทั้งหมด

ผลการศึกษา: ผู้ป่วยที่ได้รับการหยอดยา 0.02% mitomycin C มีการหายของมะเร็ง 9 คน จากทั้งหมด 11 คน (ร้อยละ 81.8) ใช้เวลาในการหายไปของก้อนมะเร็งอยู่ในช่วง 7.7 สัปดาห์ มีการลดขนาดลงของก้อนมะเร็งบางส่วน 2 คน (ร้อยละ 18.2) และจำเป็นต้องเปลี่ยนวิธีการรักษาไปเป็นวิธีการผ่าตัดต่อไป ยังไม่พบการเป็นซ้ำในกลุ่มที่มีการหายไปของมะเร็ง ระยะตรวจติดตามเฉลี่ย 19.4 เดือน (อยู่ระหว่าง 6 - 40.7 เดือน) ในกลุ่มที่ผ่าตัด มีการหายของก้อนมะเร็งทั้งหมด 10 คน (ร้อยละ 100) มีการเป็นซ้ำ 2 คน จากทั้งหมด 10 คน ระยะตรวจติดตามเฉลี่ย 28.6 เดือน (อยู่ระหว่าง 3.6 - 78.2 เดือน) มีภาวะแทรกซ้อนชั่วคราวคือ ผิวกระจกตาไม่เรียบ (punctate epithelial erosion)

สรุป: การใช้ 0.02% mitomycin C ในการรักษามะเร็งเยื่อบุตา Conjunctiva - corneal intraepithelial neoplasia (CCIN) ที่ไม่เคยรักษามาก่อน ได้ผลการรักษาที่ดี

คำสำคัญ: เยื่อบุตา, มะเร็งเยื่อบุตา, mitomycin C, ยาหยอดตา, การหายของมะเร็งเยื่อบุตา

ORIGINAL ARTICLE

Efficacy of Primary Topical 0.02% Mitomycin C for The Treatment of Conjunctiva – Corneal Intraepithelial Neoplasia

Pirunrat Jiaraksuwan, M.D.

Department of Ophthalmology, Surin Hospital

ABSTRACT

BACKGROUND: The gold standard treatment for conjunctiva - corneal intraepithelial neoplasia (CCIN) is wide excision and double freeze - thaw cryotherapy. In diffuse lesions or multiple tumors, an adequately wide excision is difficult to achieve.

OBJECTIVES: To study the efficacy of primary topical 0.02% mitomycin C for the treatment of conjunctiva - corneal intraepithelial neoplasia (CCIN).

METHODS: This is an intervention with historical controlled case - series. In this study, we compared the outcomes of patients with CCIN treated with primary topical 0.02% mitomycin C (four times daily, 7 - day on and 7 - day off regimen) and historical patients treated by excision. The primary outcome was the complete resolution of CCIN.

RESULTS: Eleven patients were treated with 0.02% topical mitomycin C, and complete resolution was achieved in nine (81.8%) patients. The median time to resolution was 7.7 weeks. Two (18.2%) patients had partial resolution and recommended for surgery. There was no recurrence in complete resolution group. The mean follow - up time of 19.4 months (range 6 – 40.7 months). In the surgical group, complete resolution was achieved in 10 (100%) patients and two out of 10 patients experienced recurrence. The mean follow - up time was 28.6 months (range, 3.6 – 78.2 months). The short - term complication was punctate epithelial erosion.

CONCLUSIONS: Primary topical 0.02% mitomycin C seemed to be effective in treating CCIN.

KEYWORDS: conjunctiva, conjunctiva - corneal intraepithelial neoplasia, mitomycin C, primary topical, complete resolution

INTRODUCTION

Ocular surface squamous neoplasia (OSSN) can manifest as simple dysplasia, conjunctiva - corneal intraepithelial neoplasia (CCIN), carcinoma in situ (CIS), and invasive squamous cell carcinoma (SCC). Incidences vary from 0.13 – 1.9 cases per 100,000 persons. Risk factors include ultraviolet exposure, human papilloma viral infection, and human immunodeficiency virus (HIV) infection. The gold standard treatment for CCIN and SCC is excision and double freeze - thaw cryotherapy. In diffuse lesions or multiple tumors, an adequately wide excision is difficult to achieve. Complications can include damage to limbal stem cells, granulation, symblepharon, and pseudopterygium.

The postsurgical recurrence rate is 15 – 52%.[1] Topical adjuvant therapies, such as mitomycin C (MMC), 5 - fluorouracil (5 - FU), and interferon alpha 2b (IFN - α2b) have been used to decrease recurrence. The advantages of topical adjuvant therapy include the prevention of injury from surgery, ability to treat the entire tumor surface, and avoidance of systemic side effects. Topical MMC has been used as a treatment for primary and recurrent CCIN. Previous studies on topical mitomycin used for primary CCINs had different concentrations and dose regimen.[2-4] The common concentrations of topical MMC were found to be 0.02% and 0.04%. For primary treatment of CCIN, it has been reported that recurrent corneal erosion was observed after using 0.02% MMC four times a day for 28 days.[3] A previous study showed that using 0.02% and 0.04% MMC in the cycle regimen (7 days on and 7 days off) had a 90% effectiveness in treating CCIN; however, in this study, most of the cases were recurrent CCIN (17 recurrent CCIN patients and three primary CCIN patients).[4]

In Thailand, a previous study reported that SCC and CIS were the most common (30%) malignant tumors of the eye and ocular adnexa in 2000 – 2005, and corneal intraepithelial neoplasia was found in 1.1% of these cases.[5] There have been few case reports of topical MMC used for primary CCIN and SCC.[2,6] Therefore, we conducted a study to evaluate the effectiveness of topical 0.02% MMC four times a day for 7 days, followed by 7 days off the cycle in primary treatment for CCIN.

METHODS

This is an intervention with historical controlled case - series conducted at Surin Hospital (tertiary care center). The study was approved by the Research Ethics Committee of Surin Hospital with the reference number of 10/2561. In a pathological report, CCINs were found in 29.3%, and SCCs were found in 7.1% of conjunctival tumors. Efficacy of topical 0.02% MMC in primary treatment for CCIN was studied. Patients newly diagnosed with CCIN from January 2012 were enrolled in the study. CCIN was diagnosed using pathological tissue from an incisional biopsy. Exclusion criteria were severe dry eye, herpes keratitis, and scleral thinning. Topical MMC was used to replace surgical treatment in all the patients with newly diagnosed CCIN since the beginning of January 2018. MMC 0.02% solution was prepared by adding 10 mL of sterile water to 2 mg of MMC. Topical 0.02% MMC was administered four times daily for 1 week, followed by 1 week off until regression of the tumor. If there was no response to medication (i.e. tumor growth, increase in mass, or no change in size) in six weeks or complications from MMC were not resolved by stopping medication and using non - preservative artificial tears, the patients were recommended for surgery. Retrospective medical charts were reviewed from 2012 to 2017. We selected CCIN patients from historical

pathological diagnoses and reviewed the data before and after surgery. From 2018, newly diagnosed CCIN patients were prescribed topical 0.02% MMC as a primary treatment. Newly diagnosed CCIN patients were treated by one ophthalmologist and followed up every two weeks. Data included visual acuity, patient's symptoms, tumor change (by slit lamp biomicroscopy), and side effects of MMC, which were collected at every visit.

Sample size calculation:

We calculated that seven patients would need to be enrolled for the study to have 90% power to test the hypothesis that primary topical 0.02% MMC has a reduced surgical rate from 100% to 20% at a one - sided type I error rate of 0.05.

Data collection: Data that included age, sex, underlying disease, visual acuity, slit lamp examination, size, quantity, limbal involvement of tumor, and pathological tissue were collected. Patients were followed - up every 2 weeks for evaluation before the next cycle of MMC. Tumor changes and complications were also observed. If patients experienced irritation from corneal punctate epithelial erosion (PEE), topical MMC was suspended and non - preservative artificial tears were prescribed. Clinical response, duration of treatment, and total mitomycin cycle were recorded.

Outcomes: The primary outcome was complete resolution, defined as the absence of a tumor in slit lamp examination. The secondary outcomes included tumor recurrence and treatment failure. The tumor recurrence was defined as reappear tumor after complete resolution in the previously treated areas. Treatment failure was defined as either incomplete resolution or tumor recurrence.

Statistical analysis

Demographics and clinical characteristics of patients in both groups were described and compared using Fisher's Exact test. Detail of treatment and outcome for individual patients were listed. The Kaplan - Meier survival graph was generated to determine the pattern of treatment failure over the follow - up period in both groups. A *P* - value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Eleven patients with CCIN received topical 0.02% MMC as the primary treatment (primary MMC group). The mean age of the patients was 73.3 ± 13.5 years (range 51 - 99 years). None of the patients had an HIV infection. Ten patients had limbal involvement of the tumor, and one patient had limbal and fornix involvement. The mean size of limbal involvement was 4 clock hours (range 2 – 7). Ten patients had a mass. Ten historical patients with CCIN underwent surgery (surgery group). The mean age was 52 ± 10.5 years (range, 36 – 72 years). The mean size was 2 clock hours (range, 1 – 6). All patients had limbal involvement and only one mass. The characteristics data are summarized (Table 1).

In the primary MMC group, nine (81.8%) patients had complete resolution. The mean follow - up time was 19.4 months (range, 6 – 40.7 months). The tumor regressed in size after the second MMC cycle. The mean cycle of MMC was 3.4 cycles (median = 4, range 1 – 6 cycles). The mean time to resolution was 7.7 weeks, and no one experienced recurrence.

Two patients responded partially to the treatment. One patient (case ID 6) required surgery and postoperative MMC eye drops. Recurrence was not observed within six months of surgery. Another patient (case ID 2) had a tumor involving the limbus and fornix. After five cycles of MMC, the tumor had a small decrease in size and the patient was lost to follow - up. The demographic characteristics and

results of the topical primary 0.02% MMC are summarized (Table 2).

Complications in the primary 0.02% MMC group included PEE in seven patients and corneal epitheliopathy (irregular epithelium and stromal haziness) in two patients. There have been no reports of nasolacrimal duct obstruction.

In historical patients (surgical group), all of patients had complete resolution after surgery. The mean follow - up time was 28.6 months (range, 3.6 – 78.2 months). Two patients had positive tumor margins. Five patients received postoperative mitomycin treatment. Recurrences were reported in two cases. One patient was diagnosed with CCIN, 6 clock hours of tumor size, and positive tumor margins, and recurrence was observed 11.5 months after surgery. Another case was diagnosed with CCIN, 2 clock hours of tumor size, tumor margin free, and recurrence was observed one month after surgery. PEE was found in two cases after postoperative MMC. The demographic characteristics and results of the surgical treatment are summarized (Table 3).

The Kaplan - Meier graph showed that the treatment failure in both surgery and MMC groups occurred during the first year after treatment initiation. The risk of treatment failure was not significant between the primary MMC group and the surgical group (hazard ratio for treatment failure, 1.20; 95% CI, 0.17 to 8.56; $p = 0.85$) (Figure 1). The 95% CI of the HR was relatively wide due to small size.

Table 1 Characteristics of patients with CCIN

Characteristics	Primary MMC (n = 11)		Surgery (n = 10)		*p* - value
Sex					
Male	5		5		1.00
Female	6		5		
Age (years) mean ± SD	73.3	± 13.5	52	± 10.5	< 0.001
risk factor					
HIV	0		1		0.48
Size (clock hours)					
median	4		2		0.03
range	2 to 7		1 to 6		
Number of mass					
1	10		10		0.35
2	1				

Table 2 Demographic and results of primary 0.02% MMC treatment

ID	Age	Sex	size (clock hours)	Number of mass	No. cycle of mitomycin C	Time to Resolution (weeks)	Complication	Recurrence
1	69	male	3	1	4	14	PEE	no
2	83	female	6	1	5	failure	corneal epitheliopathy	
3	55	male	4	1	3	5.71	PEE	no
4	68	male	3	1	4	9	PEE	no
5	99	female	5	1	6	20	PEE	no
6	76	female	6	1	5	failure	PEE	
7	73	female	3	1	4	10		no
8	51	female	7	2	1	2.29	PEE	no
9	73	male	4	1	4	7.71	no	no
10	87	female	6	1	3	6.71	corneal epitheliopathy	no
11	72	male	2	1	2	5	PEE	no

PEE = punctate epithelial erosion

Table 3 Demographic and results of surgical treatment

ID	Age	Sex	Size (clock hours)	Number of mass	Positive surgical margin	Postop. MMC (cycle)	Complication	Recurrence
1	46	female	2	1	no	3	no	no
2	51	male	2	1	no	0	no	no
3	57	female	6	1	yes	3	no	yes
4	52	male	3	1	no	1	no	no
5	52	male	1	1	no	3	PEE	yes
6	39	male	1	1	no	0	no	no
7	36	male	1	1	no	0	no	no
8	62	female	3	1	no	0	no	no
9	53	female	1	1	no	0	no	no
10	72	female	6	1	yes	3	PEE	no

Postop = postoperative

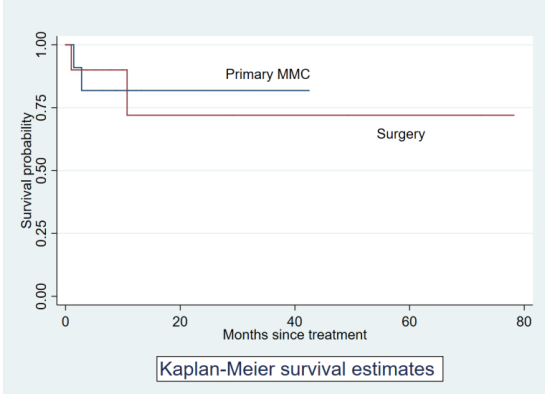

Figure 1 Kaplan – Meier Estimates of treatment failure

DISCUSSION

The standard treatments for OSSN are surgery and cryotherapy, but these procedures have limitations in treating diffuse or multifocal tumors. Performing surgical excision in enlarged or multifocal tumors requires surgical experience and carries the risk of limbal stem cell deficiency, scarring, and symblepharon. Adjunctive chemotherapy, such as topical MMC, 5 - FU, and topical IFN - α2b, is normally combined with surgery to minimize recurrence and is used as a primary treatment. MMC is an antibiotic agent isolated from *Streptomyces caespitosus*. It is an alkylating agent that inhibits DNA synthesis and induces the breakage of a single strand of DNA. A previous study reported that topical 0.02% and 0.04% MMC did not yield any differences in terms of time to resolution.[4] However, there are a variety of regimens that include continuous eye drops for 2 – 4 weeks[2,3] and cycle treatment.[4,7]

In this study, primary CCIN patients received topical 0.02% MMC on alternating weeks. Nine (81.8%) patients responded favorably to treatment with complete resolution and no one experienced recurrence. In historical surgery group, all of patients had complete resolution and two (20%) patients experienced recurrence. Difference in treatment group was not significantly associated with the risk of treatment failure.

In primary MMC group had two cases of failure, one patient had a thick tumor and 6 clock hours of limbal involvement, and another patient had limbal and fornix tumor involvement. This result was consistent with that of Kusumesh et al.[8] who reported that 8% of patients responded poorly to

MMC. One patient with xeroderma pigmentosum had bilateral CCIN and failed to respond to both MMC and IFN - α2b. Both eyes underwent surgery, and the pathological tissue was found to be SCC. Another patient had a pedunculated mass from the superior fornix. We thought that the thickness and location of the tumor might have influenced the tumor resolution. Manoher et al.[9] reported that primary CCIN was achieved with treatment with topical 0.02% MMC for two weeks, followed by two weeks without treatment, and that CCIN did not recur. Similarly, no recurrence was observed in the MMC group of the present study. Switching to other topical therapies has been reported in cases of resistance to MMC. Recurrent CCIN with MMC resistance has been successfully treated with 1% 5 - FU[10] and IFN - α2b.[11] However, the costs and benefits should be considered. Recurrences were not found in the primary MMC group with the mean follow - up was 19.4 months. The observation of recurrence needs longer follow up period when compare with surgical group.

The mean cycle of treatment was similar to that in prior studies that used a high concentration of treatment (0.04% MMC).[7,12] It requires a longer time to resolve than a continuous regimen.[2,3] We observed two patients with a smaller, persistent tumor after receiving three cycles of MMC and had PEE. We planned an ongoing surgery. When the MMC was discontinued and the ocular surface was treated, the tumor sizes decreased and disappeared after 6 weeks. Thick tumors responded slowly to MMC. Therefore, it requires observation time. The results of previous studies are summarized (Table 4).

The ocular side effects of MMC were PEE, as was similar to previous studies.[3,4,7,12,13] It was resolved by pausing MMC treatment and applying non - preservative artificial tears. PEE occurred after three cycles of MMC.[7] In previous studies, punctal stenosis was the second most common complication (14%) after two to three cycles of MMC.[14] This was resolved by performing punctal dilatation and irrigation. Punctal stenosis was not observed in any of our cases. This may be due to the low concentration, cycle therapy, and short duration of MMC. Two patients had corneal epitheliopathies, which manifested as irregular epithelium and stromal haziness, due to limbal toxicity. Case ID 2 was treated with five - cycle MMC as in the Dudney BW study[15] and case ID 10 was treated with three - cycle MMC. However, we did not find this condition in case ID 5, which was treated with six cycles of non - continuous MMC. After three cycles of MMC, case ID 5 experienced PEE and stopped MMC for 3 weeks, after which, MMC was restarted. This finding indicates that limbal toxicity is dose - continuously related.

Patients in the MMC group had an older average age than that of the surgical group and two patients each had one relative eye. Most of the patients refused surgery. Therefore, topical primary mitomycin was a suitable treatment for these patients. We suggest topical primary 0.02% MMC treatment for diffuse, multiple tumors, elderly age, and patients with multiple medical comorbidities.

The limitations of our study include a small sample size, and further studies are required to assess whether primary topical MMC versus gold standard surgery is more effective.

In conclusion, CCIN was successfully treated with topical primary 0.02% MMC. It is an alternative therapy, especially for patients who refuse surgery. However, this treatment requires cooperation and long - term follow - ups.

Table 4 Summary of results of studies using topical mitomycin for the treatment of OSSN

Study	No. of patients	Regimen	Duration	Mean time resolution	Follow up time	Recurrence
Continuous regimen						
Prabhasawat, et al[2]	6 recurrent (5 CCIN, 1 SCC) 1 primary (CIS)	Topical 0.002% QID 4 – 8 week on and 2 - 3 week off	2 - 14 weeks	5.2 weeks	29.6 months (2 - 52 months)	14% recurrence
Ballalai, et al[3]	18 primary CCIN 5 recurrent CCIN	Topical 0.02% QID for 2 weeks	4 weeks	4 weeks	46 months in primary group, 54 months in recurrent group	4.3% recurrence
Cycle regimen						
Daniell, et al[4]	17 recurrent CCIN 3 primary CCIN	Topical 0.02 – 0.04% QID 1 week on – 1 week off	1 - 5 cycles	4.5 weeks (4 - 8 weeks)	13 months (3 - 26 months)	20% recurrence, 10% persistent
Russell, et al[14]	8 CCIN	Topical 0.04% QID 3 week on – 3 week off	2 cycles	N/A	20 months (1 - 49 months)	0% recurrence, 12.5% persistent
Gupta, et al[7]	73 localized CCIN 8 recurrent CCIN 10 diffuse CCIN (≥ 5clock hours)	Excision + cryotherapy + Topical 0.04% QID 1 week on - 1week off (for localized and recurrent group), Topical 0.04% QID 1 week on – 1 week off (for diffuse group)	2 - 3 cycles	N/A	56.8 months (5.8 - 119.8 months)	0% recurrence in localized, 12.5% in recurrent group, 30% recurrence/ persistence in diffuse group
Manoher, et al[9]	6 primary CCIN	Topical 0.02% QID 2 week on – 2 week off	3 cycles	N/A	24 months	No recurrence
Kusumesh et al[8]	25 OSSN diagnosed by clinical	Topical 0.04% QID 1 week on - 1 week off	2 cycles	1.4 months	23.6 months	0% recurrence, 8% persistent
Current study	11 primary CCIN	Topical 0.02% QID 1 week on - 1 week off	2 - 6 cycle	7.7 weeks	19.4 months (6 - 40.67 months)	0% recurrence, 18% persistent

N/A = not available

Conflicting Interest: none

Financial support: none

Acknowledgements

We wish to acknowledge Associate Professor Dr. Saranath Lawpoolsri and Associate Professor Dr. Kosol Kampitak for their valuable advices.

Reference

1. Tananuvat N, Lertprasertsuke N. Ocular surface squamous neoplasia. In: Srivastava S,editor. Intraepithelial Neoplasia. London: IntechOpen; 2012. p 35-62.
2. Prabhasawat P, Tarinvorakup P, Tesavibul N, Uiprasertkul M, Kosrirukvongs P, Booranapong W, et al. Topical 0.002% mitomycin C for the treatment of conjunctival-corneal intraepithelial neoplasia and squamous cell carcinoma. Cornea 2005 ;24:443-8.
3. Ballalai PL, Erwenne CM, Martins MC, Lowen MS, Barros JN. Long-term results of topical mitomycin C 0.02% for primary and recurrent conjunctival-corneal intraepithelial neoplasia. Ophthalmic Plast Reconstr Surg 2009;25:296-9.
4. Daniell M, Maini R, Tole D. Use of mitomycin C in the treatment of corneal conjunctival intraepithelial neoplasia. Clin Exp Ophthalmol 2002;30:94-8.
5. Pombejara NF, Tulvatana W, Pungpapong K. Malignant tumors of the eye and ocular adnexa in Thailand: a six - year review at King Chulalongkorn Memorial Hospital. Asian Biomedicine 2009;3:551-5.
6. Tangpakasit W, Reanpinyawat T, Bhornmata A. A case report: squamous cell carcinoma of conjunctiva. Thammasat Thai Journal of Ophthalmology 2014;9(2):1-5.

7. Gupta A, Muecke J. Treatment of ocular surface squamous neoplasia with mitomycin C. Br J Ophthalmol 2010;94:555-8.
8. Kusumesh R, Ambastha A, Kumar S, Sinha BP, Imam N. Retrospective comparative study of topical interferon α2b Versus Mitomycin C for primary ocular surface squamous neoplasia. Cornea 2017;36:327-31.
9. Manoher JM, Kochar A, Chauhan A. Topical 0.02% Mitomycin C for management of primary corneal - conjunctival intraepithelial neoplasia as primary therapy: a long term follow up. IAIM 2016;3(8):16-22.
10. Yamamoto N, Ohmura T, Suzuki H, Shirasawa H. Successful treatment with 5-fluorouracil of conjunctival intraepithelial neoplasia refractive to mitomycin-C. Ophthalmology 2002;109: 249-52.
11. Kaliki S, Singh S, Iram S, Tripuraneni D. Recombinant interferon alpha 2b for ocular surface squamous neoplasia: an efficient and cost-effective treatment modality in Asian Indian patients. Indian J Ophthalmol 2016;64:702-9.
12. Besley J, Pappalardo J, Lee GA, Hirst LW, Vincent SJ. Risk factors for ocular surface squamous neoplasia recurrence after treatment with topical mitomycin C and interferon alpha-2b. Am J Ophthalmol 2014;157:287-93.
13. Moon J, Choi SH, Lee MJ, Jo DH, Park UC, Yoon SO, et al. Ocular surface complications of local anticancer drugs for treatment of ocular tumors. Ocul Surf 2021;19:16-30.
14. Russell HC, Chadha V, Lockington D, Kemp EG. Topical mitomycin C chemotherapy in the management of ocular surface neoplasia: a 10-year review of treatment outcomes and complications. Br J Ophthalmol 2010; 94:1316-21.
15. Dudney BW, Malecha MA. Limbal stem cell deficiency following topical mitomycin C treatment of conjunctival-corneal intraepithelial neoplasia. Am J Ophthalmol 2004 ;137: 950-1.