

TO STUDY THE EFFECT OF TOPICAL MITOMYCIN-C AS AN ADJUNCT IN OCULAR SURFACE SQUAMOUS NEOPLASIA

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Abstract

Background: Ocular surface squamous neoplasia (OSSN) encompasses a range of dysplastic conditions, spanning from conjunctival-corneal intraepithelial neoplasia to the development of an invasive squamous cell carcinoma (SCC). The preferred approach for managing OSSN is surgical excision, however it is important to note that there is a somewhat significant incidence of recurrence, ranging from 33% to 56% as described in studies. Therefore, Mitomycin C, a specific inhibitor of deoxyribonucleic acid (DNA) synthesis that targets tumours, is regarded as an adjuvant therapy subsequent to the removal of primary ocular surface squamous neoplasia (OSSN). **Aim:** To Study the effect of Topical Mitomycin – C as an adjunct in ocular surface squamous neoplasia. **Materials and Methods:** This research includes a total of 20 individuals diagnosed with primary ocular surface squamous neoplasia (OSSN). A comprehensive examination of demographic information, symptomatology, and the duration of symptoms was conducted, along with an assessment of exposure to various risk factors. The researchers gained clearance from the institutional ethics committee and acquired signed consent from all patients included in the study. **Results:** The average age of the patients was 46.85±5.85 years. Out of the 20 patients seen, a significant proportion of 17 individuals, accounting for 85% of the entire sample, had temporal limbal abnormalities. Approximately 65% of individuals have visual impairment in their right eye, whereas approximately 35% experience visual impairment in their left eye. The predominant symptoms seen at the first presentation were foreign body feeling in 55% of cases, followed by the presence of a mass per eye in 35% of cases. Other less common symptoms were redness in 5% of cases, and a combination of injury and redness in another 5% of cases. The smallest mass recorded was measured at dimensions of 2 × 3 mm, whilst the highest mass was seen at dimensions of 15 × 14 mm. In 80% of the cases, the dimensions of the mass exceeded 8 mm in diameter or extended beyond 3 clock hours in 16 individuals. Corneal infiltration was seen in 50% of the cases, specifically in 10 instances. It was observed that 14 out of the total cases (70%) exhibited squamous cell carcinoma (SCC) with either good or moderate differentiation. **Conclusion:** The use of post-operative topical Mitomycin C therapy has been shown to have a synergistic effect and effectively prevents recurrence. It may be inferred that Mitomycin C demonstrates efficacy as an adjuvant in the treatment of ocular surface squamous neoplasia.

INTRODUCTION

The term "Ocular Surface Squamous Neoplasia (OSSN)" was first introduced by LEE and HIRST in 1995. The condition encompasses a range of tumours that arise from the conjunctival limbal stem cells and expand beyond the limbus to affect the surrounding cornea and conjunctiva. The spectrum of tumours

includes both mild dysplasia and more advanced squamous cell carcinoma. Ocular Surface Squamous Neoplasia (OSSN) is a confined tumour characterised by sluggish growth. While OSSN typically has a low likelihood of metastasis, it may become invasive and extend into the eyeball and orbital cavity.^[1,2] Ocular surface squamous neoplasia (OSSN) refers to a variety of epithelial squamous malignancies, which

comprise varying degrees of dysplasia from moderate to severe, as well as invasive squamous cell carcinoma.^[3] The global prevalence of ocular surface squamous neoplasia (OSSN) has been shown to range from 0.02 to 3.5 instances per 100,000 individuals, with a higher occurrence seen in geographical areas in close proximity to the equator.^[4] OSSN often manifests in individuals aged between their late sixth and seventh decades, however it has been seen to manifest at an earlier age in individuals with impaired immune systems. There are several risk factors that have been associated with the development of ocular surface squamous neoplasia (OSSN). These risk factors include exposure to ultraviolet (UV) light, having an impaired immune system such as in cases of HIV infection or Human Papilloma Virus (HPV) infection, smoking, being of advanced age, and being male.^[5-7] Ocular surface squamous neoplasia (OSSN) is a very uncommon malignancy of the eye, ranking third in terms of prevalence behind melanoma and lymphoma, which are the most frequent ocular tumours. The incidence of Ocular Surface Squamous Neoplasia (OSSN) is higher in regions located closer to the equator, which may be associated with increased exposure to sunshine. The prevalence of a certain phenomenon is seen to be higher among males and individuals of Caucasian ethnicity. The prevalence of this condition is highest among those aged 50-60 years, while it is also more often seen in people under the age of 50 who reside in proximity to the equator.^[8] Surgical excision is the primary modality for the treatment of ocular surface squamous neoplasia (OSSN). Nevertheless, it has been shown that there is a significant incidence of recurrence subsequent to the exclusive use of surgical excision. Consequently, several supplementary therapy have been documented, demonstrating their efficacy in the prevention of tumour recurrence. In this research, we conducted an examination of 20 eyes belonging to 20 patients diagnosed with localised primary ocular surface squamous neoplasia (OSSN). These patients had surgical excision and were further treated with topical Mitomycin-C (MMC). We have documented the incidence of recurrence seen in these patients over a period of 24 months, as described in a previous study.^[9] The first documentation of the use of Mitomycin C in the therapeutic management of Ocular Surface Squamous Neoplasia was provided by Frucht-Pery and Rozenman in 1994. The use of topical administration of mitomycin C (MMC) in the management of ocular surface squamous neoplasia (OSSN) has been more popular in the last 16 years. This approach, known as "whole eye treatment" with MMC, has shown potential advantages compared to cryotherapy and excision in the treatment of large and subclinical instances of OSSN. The use of MMC is employed before to surgery for chemoreduction, during the surgical procedure itself, and after the operation in order to mitigate the likelihood of cancer recurrence.^[10]

MATERIALS AND METHODS

This research includes a total of 20 individuals diagnosed with primary ocular surface squamous neoplasia (OSSN). A comprehensive examination of demographic information, symptomatology, and the duration of symptoms was conducted, along with an assessment of exposure to various risk factors. The researchers gained clearance from the institutional ethics committee and acquired signed consent from all patients included in the study.

The clinical examination encompassed various assessments, such as visual acuity, refraction, examination of the anterior segment to evaluate the characteristics of the lesion (including shape, size, and extent of mobility), assessment of anterior chamber reaction, evaluation of involvement of the cornea and sclera, utilisation of fluorescein and 1% rose bengal staining under slit-lamp biomicroscopy, and examination for lymphadenopathy. These examinations were conducted to establish a clinical diagnosis. A standard laboratory analysis was conducted, which including the performance of serology assays for the detection of human immunodeficiency virus (HIV). All patients achieved physical fitness for surgery under local anaesthesia. The inclusion criteria for this study consisted of individuals who had been clinically identified with ocular surface squamous neoplasia (OSSN) using a slit-lamp biomicroscope. Additionally, those with OSSN that had involvement of less than 5 clock hours or a diameter of less than 15 mm were also included. The exclusion criteria included factors that might potentially impact the result, such as disorders related to HIV/acquired immune deficiency syndrome, weakened immunological state, xerodermapigmentosa, and ocular problems such severe dry eye and limbal stem cell deficit.

The recommended protocol for managing the condition involves surgically removing the lesion with a 3 mm margin of healthy tissue, without the use of irrigation and employing a single touch technique. Instruments are replaced after the tumour is excised. Subsequently, cryotherapy is applied to the cut end of the conjunctival undersurface for 20 seconds, as well as to the cornea and limbus for 10 seconds, utilising a double freeze thaw technique. If the ocular surface defect exceeded dimensions of 25 × 25 mm, amniotic membrane grafting was performed; otherwise, the ocular surface was allowed to heal naturally. The specimen was sent for histological analysis. It was recommended to provide topical Mitomycin C 0.04% four times daily to all postoperative patients in 3-4 cycles of alternating weekly courses, in order to confirm the healing of epithelial tissue. In instances when there was a significant mass or where surgical intervention needed to be delayed for nonmedical reasons, preoperative topical application of Mitomycin C was administered. The patients were subjected to weekly follow-up assessments after the initiation of the treatment regimen, and subsequently,

monthly follow-ups were conducted after the completion of the therapy. During each appointment, a slit-lamp examination was conducted using rose bengal 1% and sodium fluorescein 1% drops. This examination was performed in addition to the standard assessment for tumour recurrence and corneal changes such as keratitis or erosions. The effectiveness of Mitomycin C as an adjuvant treatment was assessed in terms of its impact on clinical cure rates and tumour recurrence.

RESULTS

The average age of the patients was 46.85 ± 5.85 years. Out of the sample size of 20 patients, a total of 8 individuals (40%) were found to be below the age of 40, with a notable male prevalence of 80%. Table 1 presents the relevant data. Out of the 20 patients seen, a significant proportion of 17 individuals, accounting for 85% of the entire sample, had temporal limbal abnormalities. Approximately 65% of individuals have visual impairment in their right eye, whereas approximately 35% experience visual impairment in their left eye.

The predominant symptoms seen at the first presentation were foreign body feeling in 55% of cases, followed by the presence of a mass per eye in 35% of cases. Other less common symptoms were redness in 5% of cases, and a combination of injury and redness in another 5% of cases, as shown in Table 3. According to Table 4, a majority of individuals

(55%) had symptoms for a period beyond six months. Sunlight exposure was seen in 14 individuals, accounting for 70% of the sample, whereas smoking habits were reported by 6 individuals, representing 30% of the sample [Table 5]. The smallest mass recorded was measured at dimensions of 2×3 mm, whilst the highest mass was seen at dimensions of 15×14 mm. In 80% of the cases, the dimensions of the mass exceeded 8 mm in diameter or extended beyond 3 clock hours in 16 individuals. Corneal infiltration was seen in 50% of the cases, specifically in 10 instances. The visual acuity of patients did not change or showed improvement after surgery when the tumour encompassed the visual axis. Clinically, ocular surface squamous neoplasia (OSSN) might present as a leukoplakic lesion or a big cauliflower-like gelatinous lesion. Histopathologically, it was observed that 14 out of the total cases (70%) exhibited squamous cell carcinoma (SCC) with either good or moderate differentiation. Additionally, 6 instances (30%) were identified as having carcinoma in situ, as shown in Table 6. Out of the total cases examined, only 4 (20%) exhibited marginal clearing, while 9 (45%) had dysplasia in at least one margin, and 7 (35%) instances exhibited dysplasia in at least two margins [Table 7]. The average duration of follow-up was 45.85 ± 5.11 months, with a range of 39-50 months. During this period, recurrence was seen in one eye, resulting in a success rate of 90%. The use of a repeated strategy for the recurrent lesion yielded a success rate of 100%.

Table 1: Demographic details

| Gender | Number of patients =20 | Percentage |
|--------------|------------------------|------------|
| Male | 16 | 80 |
| Female | 4 | 20 |
| Age in years | | |
| 20-40 | 8 | 40 |
| 40-60 | 7 | 35 |
| 60-80 | 5 | 25 |

Table 2: Eye affected

| Eye affected | Number of patients =20 | Percentage |
|--------------|------------------------|------------|
| Right eye | 13 | 65 |
| Left eye | 7 | 35 |

Table 3: Symptoms of OSSN

| Symptoms | Number of patients =20 | Percentage |
|-------------------------------------|------------------------|------------|
| Foreign body sensation | 4 | 20 |
| Foreign body sensation+mass per eye | 7 | 35 |
| Mass per eye | 7 | 35 |
| Injury+redness | 1 | 5 |
| Redness | 1 | 5 |

Table 4: Duration of presentation of OSSN

| Duration of symptoms | Number of patients =20 | Percentage |
|----------------------|------------------------|------------|
| <2 weeks | 3 | 15 |
| 2 weeks-<2 months | 2 | 10 |
| 2 months-<4 months | 2 | 10 |
| 4 months-<6 months | 2 | 10 |
| >6 months | 11 | 55 |

Table 5: Risk factors in OSSN

| Risk factors | Number of patients =20 | Percentage |
|--------------------|------------------------|------------|
| Sunlight | 11 | 55 |
| Sunlight+smoking | 3 | 15 |
| Smoking | 3 | 15 |
| Petroleum products | 3 | 15 |

Table 6: Histological findings in OSSN

| Histological findings | Number of patients =20 | Percentage |
|-------------------------------|------------------------|------------|
| Carcinoma in situ | 6 | 30 |
| Well differentiated SCC | 1 | 5 |
| Moderately differentiated SCC | 13 | 65 |

Table 7: Marginal clearance post-surgery

| Marginal clearance post-surgery | Number of patients =20 | Percentage |
|---------------------------------|------------------------|------------|
| Free margin | 4 | 20 |
| At least one margin | 9 | 45 |
| With two margin | 7 | 35 |

DISCUSSION

Ocular surface squamous neoplasia (OSSN) has been documented as the prevailing malignant condition affecting the conjunctiva and cornea. The primary method of treating ocular surface squamous neoplasia (OSSN) has always been surgical excision. The use of surgical excision enables the reduction of tumour size and permits an expeditious histological diagnosis. The use of surgical excision as a standalone approach is associated with a significant drawback, namely a considerable recurrence rate that varies between 15% and 52%.^[11] Consequently, a number of supplementary therapies have emerged that aid in reducing the likelihood of tumour recurrence. Mitomycin-C (MMC) is an example of a chemotherapeutic drug used as an adjuvant treatment. Mitomycin C (MMC) is classified as an alkylating drug that functions as a DNA synthesis inhibitor, ultimately leading to cell necrosis and death.^[12] Multiple studies have shown the use of mitomycin C (MMC) in the treatment of both primary and recurring instances of ocular surface squamous neoplasia (OSSN), with favourable results.^[13] Although formerly regarded as a rare occurrence, OSSN has gained attention in the global literature in recent years, as shown by a growing number of reports.^[14] However, a separate investigation documented 26 instances of OSSN over a span of 7 years.^[15] The occurrence of OSSN is no longer uncommon; our study included a sample of 20 individuals diagnosed with primary OSSN. The average age of the patients was 46.85 ± 5.85 years. Out of the 20 patients included in the study, a total of 8 individuals, accounting for 40% of the sample, were found to be below the age of 40. This proportion is notably lower compared to the findings reported in previous research, where the observed ages were 64 years.^[16] and 69 years.^[17] The prevailing risk variables identified in this study were consistent with previous research, namely, exposure to sunshine and smoking. The predominant symptoms seen upon first examination were foreign body feeling in 55% of cases, followed by the presence of a mass per eye in

35% of cases. Redness was recorded in 5% of cases, while injury and redness were observed in 5% of cases. Additionally, it was found that 55% of patients presented with these symptoms after a duration of more than 6 months, which aligns with the findings published by Prabhasawatet al.^[18] At the time of presentation, it was observed that 80% of the patients had tumours with a size above 8 mm, while corneal infiltration was seen in 50% of these patients, specifically affecting 10 out of 20 eyes. In our investigation, it was observed that a significant proportion of patients (70%) had squamous cell carcinoma (SCC) comparable to the findings reported by Babar et al.^[19] This similarity in SCC presentations indicates that the patients in our study presented at an advanced stage of the disease. The primary method of therapy for ocular surface squamous neoplasia (OSSN) has traditionally been excision, since it is not feasible to definitively rule out invasive disease based only on clinical evaluation or impression cytology. The use of excision enables prompt histological detection, surgical reduction in tumour size, and the elimination of potentially fatal invasive carcinoma.^[20] According to the study conducted by Kaines et al., the research focuses on the topic of conjunctival squamous cell carcinoma with perineural invasion. According to a study published in the journal Arch Ophthalmol, one drawback of relying only on primary excision is the notable recurrence rate, which has been shown to vary between 15% and 52%. Consequently, a multitude of supplementary interventions have been documented in an effort to reduce the frequency of relapse, and the effectiveness of such supplementary therapies has been a subject of discussion. Although attempts were made to remove the tumour with a substantial margin of healthy tissue, it was found that only 4 instances (20%) achieved complete clearing at the margins, while the other cases had persisting dysplastic edges. This suggests the possibility of multifocal origin of ocular surface squamous neoplasia (OSSN) or the presence of tumour edges that were not apparent to the naked eye. In the aforementioned scenario, the implementation of a further surgical procedure aimed

at removing remaining edges with enough safety margins would result in a substantial defect in the ocular surface, as well as induce limbal stem cell shortage.^[20] Therefore, Mitomycin C, an alkylating drug that functions by impeding DNA synthesis and inducing cell death via apoptosis and necrosis, was used.^[21] Due to its selective affinity for actively proliferating cells, the medication exhibits notable antineoplastic properties. Since 1994, several research groups have shown the use of MMC in the management of both initial and recurring ocular surface squamous neoplasia (OSSN).^[22-27] Postoperative mitomycin C (MMC) administration in such circumstances not only serves to reduce the need for further surgical interventions, but also has the potential to effectively address the whole of the ocular surface, eradicate latent illness, and mitigate the development of new tumours in other areas of the ocular surface. Consequently, the use of MMC may significantly help to achieving a more favourable result.

CONCLUSION

The use of post-operative topical Mitomycin C therapy has been shown to have a synergistic effect and effectively prevents recurrence. This is particularly important in cases when patients arrive late and are less likely to adhere to follow-up appointments. Therefore, it may be inferred that Mitomycin C demonstrates efficacy as an adjuvant in the treatment of ocular surface squamous neoplasia (OSSN).

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