

Treating conjunctival ocular surface squamous neoplasia



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Topical MMC and 5-fluorouracil have been used to reduce recurrence rates when used as an adjunct to surgical excision and as a primary treatment; however, their use can be associated with marked ocular surface toxicity. Topical (1.000.000 IU/ml/ four times a day) or subconjunctival INF alpha 2b (3 million IU/ml/ weekly) have been employed to treat CIN. In general, topical INF alpha-2b is well tolerated. Subconjunctival administration presents more side effects as flu-like symptoms (fatigue, fever, myalgias, malaise) and mild liver disturbances[i]. Local conjunctival injection and follicular conjunctivitis are the most frequently reported side effects ¹⁷ after topical administration. Redness and increase of CIN volume without ocular discomfort have been reported in a case[ii]. Fine, diffuse, clear epithelial microcysts in the cornea after instillation of topical interferon a-2b have recently documented in other case[iii] Topical INF alpha 2-b, sometimes combined with subconjunctival INF alpha 2-b, seems to be effective as primary treatment for CIN, in recurrent cases, and also in retreatment after recurrence when INF has been used previously for a short period of time. Approximately, 9% of CIN treated with subconjunctival and/or topical INF alpha 2b showed recurrences, and 33 % of them were successfully retreated with topical IFN alpha 2b ⁹¹ . For INF alpha 2b topical treatment, the average time to complete tumor response is 11 weeks (range 2-59). For INF alpha 2b subconjunctival and topical treatment, the average time to complete tumor response is 5.5 weeks (range 2-12), ⁹¹ . Previous studies found the same observation[iv]. The time to clinical resolution using topical INF alpha 2-b was longer (11.6 weeks) than the combined intralesional and topical interferon (4.5 weeks), but that INF alpha

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2b treatment involved fewer side effects. In general, it seems that the disadvantage with topical treatment is the long duration. We must emphasize the importance of long term follow-up for CIN patients because recurrences can occur anywhere from 33 days to 11.5 years[v], although most recurrent CIN occurs within 2 years of initial excision[vi]. Many surgeons add adjunctive topical therapy to their surgical regimens for larger lesions¹⁰⁰. However, all sizes of lesions could be treated with topical INF alpha as the primary treatment because it is an effective, non-invasive treatment alternative to surgery that increases quality of life with low costs[vii]. Actually, no clear consensus on the best way to manage the disorder has been established, because long-term, well designed studies are still needed. However, two recent studies have addressed the above questions and confirmed the effectiveness of this topical therapy for CIN. The first study¹⁷ demonstrated total resolution of the tumor in 96.4% of cases treated with INF alfa 2b with a mean follow-up of 42.4 months. The second study[viii]demonstrated that topical treatment with INF and surgical excision have the same effectiveness as primary treatment for CIN for a mean follow-up of 35.6 months. The authors concluded that topical IFN alfa-2b and aggressive surgical excision can be considered equally effective as first choice for treating CIN. Topical INF alfa-2b has some advantages over conventional excision, including the reduction of risk to loose limbal stem cells secondary to surgical trauma and, thus, compromising the integrity of the ocular surface. This therapeutic mode can be recommended particularly for patients who reject any type of surgery, or mentally retarded patients in whom surgery is complicated as well as extended cases where an aggressive

excision could cause the loss of limbal stem cells⁹⁴. Topical INF or subconjunctival INF remains a controversial issue. A recent report¹⁰³ concluded that subconjunctival 0.5 ml injection of 3 million IU IFN alpha 2b is a viable medical alternative for the treatment of ocular surface squamous neoplasia (OSSN) with a mean duration of follow-up of 55 months. The authors state that the advantages of perilesional INF alpha 2b injection include more rapid tumor resolution, ensured compliance, and perhaps more direct delivery to the tumor site when compared with topical INF drops. However, some patients may be apprehensive about receiving injections around the eye and may prefer eye drops. A single weekly injection of INF may have better compliance than 4 eye-drops per day dosing for a mean of three months in many patients. Direct delivery to the tumor site may occur in well-localized lesions, while annular lesions or multifocal disease requires injection over the entire involved area, increasing the risk of conjunctival haemorrhage. By contrast, topical therapy is delivered to the entire ocular surface and has very good success rates. Topical therapy could be recommended for patients who reject any surgical procedure or those who are apprehensive about injections.. Weekly subconjunctival INF alpha 2b might be an alternative in resistant cases of CIN or recurrent conjunctival papillomatosis avoiding a mutilating surgery[ix][x]A low-molecular weight glycoprotein, produced by leukocytes, has antineoplastic and antiviral properties. It slows the cellular growth cycle and enhances the body's immune response against tumor cells. The FDA has approved IFN-a2b for the treatment of several conditions, including hairy cell leukemia. IFN-a2b therapy can be utilized as topical drops or subconjunctival injections. With

drops, clinical resolution usually takes place with a mean time of about 12 weeks. Subconjunctival injection in addition topical IFN- α 2b helps to initiate non-invasive effective treatment for CCIN with faster resolution time i. e. 6 weeks. In one study, the overall response rate was 96.4 percent, and the recurrence rate was 3.7 percent after one year. The regime for topical IFN- α 2b drops with a concentration of 1 million IU/mL (1 M. I. U) or 3 million IU/mL (3 M. I. U), applied four times daily; or through subconjunctival route via injections as 3M. I. U million IU/0.5 mL, administered weekly. No significant clinical impact has been demonstrated on dose difference. When given in topical form, IFN- α 2b is generally well tolerated and has minimum side effects. However the systemic effects reported so far include, mild fever, myalgia and fatigue especially after subconjunctival injections. This s can be well managed with ibuprofen. Topical IFN- α 2b therapy is somehow gentle to ocular surface in terms of minimum drug epitheliopathy and patients have better compliance to IFN- α 2b drops when compared to other topical chemotherapeutic agents , even if used for 12 weeks or more. No punctal plugs are needed. In summary, interferon α -2b is better alternative option for topical chemotherapy that has been used in patients with CCIN . This therapy appears to provide results similar to topical chemotherapy but may be less toxic to the normal epithelium or the cornea and conjunctiva.

OTHER TREATMENT OPTIONS:

Other treatment options in the management of conjunctival OSSN include topical retinoids,

cidofovir and photodynamic therapy (PDT). Topical unguent of trans-reinoic acid (0, 01%)

showed complete resolution of CIN in 20% of cases, whereas 40% showed only partial

response[xi]. This treatment may be then only adjuvant to surgery

Regression of diffuse conjunctival CIN was demonstrated following a 6 week course of topical cidofovir eye drops (2. 5 mg/ml) with later residual lesion after surgical excision[xii]. Following PDT, using verteporfin, a complete clinical CIN regression, supported with angiographic evidence, has been reported at 1 month, without any recurrence for a mean follow-up of 8. 6 months[xiii]. Likewise, histopathological evidence showing tumor regression following treatment with PDT in a patient with in situ CIN has been reported[xiv].

MATERIALS AND METHODS:

Our study is a single centered descriptive case series and was carried out at department of ophthalmology, Lahore General Hospital, a tertiary care hospital affiliated with Post Graduate Medical Institute (PGMI) Lahore from March 2014 to August 2014. A total of 150 cases were operated upon during the study period and all the cases were reviewed for at least six months to look for signs of recurrence. All the patients were pre operatively examined on slit lamp and those patients with either a pterygium or inflamed eyes or with previously excised and treated suspicious growths were excluded from the study. The risks and benefits of the study were discussed with the

patients. Personal profile of the patient's along with the contact numbers of <https://assignbuster.com/treating-conjunctival-ocular-surface-squamous-neoplasia/>

the patients was noted. All the data was recorded on a pre-designed proforma

DISCUSSION:

Ocular surface squamous neoplasia (OSSN) is a spectrum of disease, on which few of the large series have been documented to address the role of chemotherapy and immunotherapy for the treatment of ocular surface squamous cell neoplasia, none in particular from the Pakistan, especially ; the role of interferon therapy in management of OSSN. As the CCIN is highly recurrent tumors, many researchers have made efforts to bring a treatment modality with minimum invasive therapy and side effects to treat OSSN. In our study the rate of recurrence was which is quiet similar to the results in achieved in one study ¹⁰⁵ i. e rate of recurrence was 10. 9% and and 5-year recurrence rate was 18. 5%[xv]and the most significant factors found to result recurrence were tumor size and first treatment given. However, surprisingly grading invasiveness of disease and positive margins for tumor were found less statistically significant in tumor recurrence. In contribution with ongoing research as the primary treatment therapy to treat OSSN, the interferon has proved to be most reliable drug in terms of controlling the tumor growth, preventing its recurrence and preserving the ocular surface with minimal side effects. The mitomycinC (MMC) 0. 02%-0. 04% is still being used for the treatment of OSSN as a part of topical therapy because of its role in lowering the recurrence rate. The standard treatment for CCIN is surgical. Due to the risk of recurrence and depending on the tumor free margins, adjuvant treatment like chemotherapy, cryotherapy and even

radiotherapy has been used. Topical 5-fluorouracil and MMC have been used to minimize recurrence when used as an adjunct to surgical excision; however, their use even in the topical formulation can be associated with ocular surface toxicity. Thus, intervention with interferon alpha 2b to treat the tumor established medical regime and thus alternative to surgical procedures for the treatment of CIN with more benefits, especially in reducing tumor recurrence, and multiple surgeries can be avoided. This new chemotherapeutic drug is being used to avoid visits of the operation theatre and is useful in decreasing the potential risk of stem cell loss and scarring of limbal area. Till to date, there are no comparative studies of this topical regime combined with surgical resection, cryotherapy and additional chemotherapy in the literature. This therapy is especially recommended in conditions where patients deny undergoing any surgical procedure, patient is mentally retarded and also in patients with extensive involvement of tumor , when to perform a surgery seems difficult, and in advanced cases where a surgical procedure may result in limbal stem cell depletion. As the role of interferon in previous studies to reduce recurrence is demonstrated, it has a substantial advantage in excising new tumor. The clinician and patient should outweigh the, duration of treatment, cost of therapy and possible side effects while deciding to initiate the primary treatment of CIN with INF alpha 2b. Topical interferon is well tolerated in terms of lower epithelial toxicity. However, via Subconjunctival route, encounters more side effects. In a study, four of seven patients reported local conjunctival injection and follicular conjunctivitis but It was established, however, the folliculitis most likely resulted from vehicle, which contained glycerin benzyl alcohol 0. 09%,, and human albumin, and not the INF alpha 2b itself[xvi]. Topical INF alpha 2b, <https://assignbuster.com/treating-conjunctival-ocular-surface-squamous-neoplasia/>

added with subconjunctival INF alpha 2b, seems to be effective as primary treatment for CIN, in recurrent cases but also in recurrent cases where interferon has been used previously for a short time.

six patients out of 66 treated with subconjunctival and/or topical INF alpha 2b had recurrences. Two of them were successfully retreated with topical INF alpha 2b. Another one achieved complete remission after intra- and perioperative MMC.

For INF alpha 2b topical treatment, the average time to complete tumor response was 11 weeks (range, 2-59). The average follow-up was 13.3 months (range, 3-40), and only three patients out of 45 had recurrences. One of them was successfully retreated with topical INF alpha 2b.

For INF alpha 2b subconjunctival and topical treatment, the average time to complete tumor response was 5.5 weeks (range, 2-12). The average follow-up was 22.5 months (range, 7.2-91), and only three patients out of 21 had recurrences. One of them was successfully retreated with topical INF alpha 2b. Another one achieved complete remission after intra- and perioperative MMC.

Karp *et al.* [xvii] described the time for clinical resolution using INF alpha 2b was much longer (11.6 weeks) than in their own previous study [xviii] in which they combined intralesional and topical interferon (4.5 weeks), and also reported that INF alpha 2b treatment resulted in fewer side effects. One recurrence after treatment with 2 weeks of INF alpha 2b was newly treated with topical INF alpha 2b for 8 months with success [xix]. In general, it seems that the disadvantage of this form of treatment is the long duration. The only <https://assignbuster.com/treating-conjunctival-ocular-surface-squamous-neoplasia/>

safe method of gauging when to stop the treatment is the disappearance of the lesion in the slit lamp examination. However the latest modality to search for early recurrence is based on ultra high-resolution anterior segment optical coherence tomography in the diagnosis and management of ocular surface squamous neoplasia[xx]. Therefore, It is important to emphasize to counsel the patients for the importance of long-term follow-up for CIN patients because recurrences can occur anywhere from 33days to 11.5years[xxi], although most recurrent CIN occurs within 2years of initial excision[xxii]. The mode of onset of the tumor can even masquerade as pterygium without giving any clue of clinical suspicion and the biopsies of the recurrent pterygium have shown to be squamous cell carcinoma on histopathology. So, every specimen of pterygium should be investigated for histopathologic examination and biopsies where OSSN is found should be examined more frequently for development of clinical signs of OSSN, hence identified and treated at an early stage[xxiii]. To determine the judicious dosage of using interferon relative to the tumor size, Vann and Karp[xxiv]found efficacy relationship which was dose dependent achieved with the cumulative administration of topical therapy and subconjunctival injection for the treatment of CIN. Chen *et al.* [xxv]suggested that additive therapy with INF alpha 2b may be needed for all lesions to lower the recurrence, particularly if surgical excision seems not to ensure tumor-free margins; in large sized tumors, topical INF alpha 2b may result in limited tumor regression due to lack of insufficient drug penetration. However instead of introducing large dose of intralesional INF alpha 2b, excisional biopsy to decrease tumor mass should be performed. The larger lesions require repeated subconjunctival/perilesional injections, but it is suggested <https://assignbuster.com/treating-conjunctival-ocular-surface-squamous-neoplasia/>

that smaller or residual lesions can be managed with topical therapy alone. Other authors have described the effect of tumor size on the choice of therapy[xxvi]. Many surgeons advise additional topical therapy to their surgical regimens for larger lesions[xxvii]and the topical IFN-alpha2b plays effective role for recurrent tumors; as it avoids the risks of further destruction to stem cells around limbus as mostly other agents and surgical excision result . However, If biopsy exhibits invasiveness at any stage, topical therapy is contraindicated, surgical excision should be performed[xxviii].

However, when there is a recurrence after INF alpha 2b treatment, an alternative could be intraoperative MMC, as described by Hawkins *et al* [xxix]. In our experienceall lesion with large tumor size can be treated with topical interferon as the primary therapy because of its effectiveness, non-invasiveness, and an alternative regime avoiding surgery that enhances quality of life and is also cost effective. Today, no clear consensus on the best way to manage the disorder has been established, because long-term, well-designed studies are still needed.

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