Treatment of Nonmelanoma Eyelid Carcinomas With Imiquimod

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Approximately 5% to 10% of all skin cancers occur in the periocular region.[1] Risk factors for eyelid neoplasms include advanced age, light skin color, family history, and chronic sun exposure.[2] The most common malignancies are basal cell carcinomas (BCCs) (90%), sebaceous carcinomas (5%), and squamous cell carcinomas (SCCs)(4%), followed by (1%) malignant melanomas, lymphomas, Kaposi sarcomas, and rarely Merkel cell carcinomas. In the periocular region, BCCs (frequency, 70%), SCCs (frequency, 70%), and melanomas (frequency, 60%) more commonly occur on the lower lid.[3-5] Sebaceous carcinomas occur on the upper eyelid the majority of the time because of the increased distribution of glands in that location.[6,7]

Studies have shown that all skin cancers of the eyelids are amenable to Mohs micrographic surgery and have lower recurrence rates when Mohs surgery is employed compared to surgical excision; however, adverse outcomes may occur whenever surgery is attempted on the eyelids, including the typical complications associated with surgical repair anywhere on the body (ie, scarring, dehiscence, flap failure or graft necrosis, hematoma, infection)[8] as well as site-specific complications (ie, ectropion, trichiasis, lagophthalmos, ptosis, keratoconjunctivitis, sicca, watery eye, webbing, entropion, orbital hemorrhage).[2,9]

Complete tumor removal, preservation of function, and cosmetic outcome are all important considerations when selecting a treatment modality for nonmelanoma skin cancers of the eyelid. Incomplete treatment can lead to recurrence; recurrent tumors tend to be more complicated to remove with higher rates of subsequent treatment failure. The periocular region is considered a high-risk area for 5-year recurrence rates, especially if the tumor's diameter is greater than 6 mm (recurrence rate, 17.5%).[10]

It has been demonstrated that nonsurgical procedures are less expensive than excision surgery in cases of BCC when considered over a 5-year period.[11] Although more aggressive neoplasms may continue to require traditional surgical procedures for definitive treatment, less-invasive topical treatment options are warranted for patients with diffuse disease, cosmetically sensitive anatomic treatment areas, and history of hypertrophic scarring, as well as in patients who are poor surgical candidates or refuse to undergo surgery.[12] Topical treatments have the advantage of assisting in the removal of eyelid tumors without collateral structural damage (eg, lacrimal point alterations, ectropion).

Topical Imiquimod Therapy

Imiquimod (IMQ) is emerging as a useful therapy in the armamentarium of topical treatment options for eyelid lesions. Imiquimod is an immune response modifier that induces cytokine production via toll-like receptor 7, subsequently inducing a cell-mediated immune response including activation of monocytes, macrophages, and antigen-presenting cells.[13,14] This member of the

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imidazoquinoline family has antiviral and antitumor properties. Topical imiquimod has been used to treat a variety of skin disorders and has been researched for skin cancers with great interest over the last decade.[15] Imiquimod is approved by the US Food and Drug Administration for the treatment of actinic keratoses, some superficial BCCs, and external genital warts.[16] It also has been successful in the treatment of other skin cancers, such as melanoma, SCC in situ, trichilemmal carcinoma, and nodular BCC, though these uses are off label.[17]

The administration protocol for IMQ is variable with application frequency ranging from once daily to once weekly and duration ranging from 6 to 16 weeks. Treatment can be tailored to individual patients to include drug holidays as needed, protection of the ocular surface from contact during applications, and ophthalmology evaluations for possible ocular surface toxicity.[12,18] A cotton swab or fingertip generally are used to apply a thin layer of cream to the target area. Although there are no definitive data on the optimal technique for protecting the ocular surface, patients should be especially cautious when using the cream on the upper eyelid because it is more likely to spread inferiorly onto the ocular surface. In case of known contact with the eye, copious irrigation should be performed to minimize surface irritation or toxicity.[17]

Studies relating to corporeal BCCs have reported that IMQ is almost as effective as surgical treatment and typically achieves good to excellent cosmetic outcomes.[19,20] Karve et al[11] compiled a summary of clinical trials evaluating the efficacy of IMQ cream 5% in the treatment of superficial BCCs, with the primary goal being clearance of the tumor as detected by clinical and/or histological examinations. Data from large randomized clinical trials demonstrated IMQ cream 5% to be statistically superior to placebo in treating superficial BCCs. The clearance rates ranged from 75% to 80.8% for patients treated 5 days per week and 73% to 87.1% for patients treated 7 days per week; however, these clearance rates were lower than those achieved by surgical methods, which were reported in the literature to exceed 95%.[11] Although case reports and small case studies describing treatment of periocular BCCs with IMQ are available, IMQ is not approved by the US Food and Drug Administration for use near the eye.

In a study of 5 patients who presented with histologically proven nodular BCCs of the eyelid and previously refused surgical treatment, IMQ cream 5% was applied at the lesion site 5 times per week for 6 consecutive weeks.[21] Complete long-term clinical clearance was obtained in 4 of 5 patients, with no tumor recurrence after 7 years of follow-up. No serious local side effects or systemic adverse events were observed following treatment. This study was the first to show the long-term outcome of IMQ for BCC in the periocular region with a 7-year follow-up period.[21]

According to the literature, BCC has a variable recurrence rate, ranging from 0.5% to 26% after any type of treatment. The recurrence rate of BCC has been shown to depend more on histology type, host-related factors, and tumor size, rather than the method used to treat the lesion.[21]

Topical application of IMQ 5% is associated with local cutaneous inflammatory reactions and less commonly conjunctival irritation or keratitis with systemic flulike symptoms. One study focused on the tolerability and safety of using IMQ cream in the periocular region.[22] Results indicated that treatment of periocular BCCs located near the margin of the eyelid often gave rise to conjunctival irritation and discomfort on blinking, even with the use of carbomer cream to protect the cornea; however, these adverse events resolved after treatment ended. None of the patients experienced chronic sequelae, and treatment was well-tolerated by all patients over the course of the study period. Additionally, each patient showed clinical and pathological resolution of lesions. The investigators noted 2 negative prognostic factors: (1) tumors that were greater than 1 cm, which required longer treatment with IMQ to promote resolution, and (2) compromised immune function, which greatly reduced the efficacy of IMQ.[22]

A number of possible strategies are available for management of ophthalmic side effects of IMQ therapy, the most common being discontinuation of treatment to provide a rest period for the patient.[23,24] In addition, lubricating drops and topical antibiotics have been used to treat ocular surface disease.[20,25] One must keep in mind that the ophthalmic side effects may be partially related to the other components of the IMQ cream, particularly the benzyl, cetyl, and stearyl alcohols. Although conjunctivitis and ocular irritation are the most frequent side effects associated with IMQ, these complications are self-limiting in the majority of patients.[26]

One prospective case study compared the efficacy, cosmesis, and tolerance of IMQ with radiotherapy as treatments of eyelid BCC.[27] Twenty-seven patients were randomly selected for treatment with either IMQ cream 5% once daily or radiotherapy 5 days per week for 6 weeks. All tumors showed histopathologic remission within 3 months of treatment, and sustained clinical remission was documented in each patient after

24 months of follow-up. Overall, treatment tolerability for IMQ was rated lower (moderate) in comparison to radiotherapy (good). However, functional results were better in patients treated with IMQ; all patients treated with radiotherapy lost their eyelashes and some presented with alterations of the eyelid skin, such as retraction or ectropion. Only 1 patient treated with IMQ showed hypopigmentation of the treatment area (<1 mm in diameter).[27]

Thus far we know of only 1 study that has evaluated the use of IMQ in combination with another modality for the treatment of eyelid skin cancers.[28] Cryotherapy, an established nonsurgical treatment modality for eyelid BCCs, was successfully combined with IMQ in 3 patients with biopsy-proven, locally advanced periocular BCCs who refused surgery. All 3 patients underwent a 9-week regimen of daily IMQ therapy with cryotherapy sessions performed at weeks 3 and 6. Pretreatment with IMQ sensitized tumor cells and the vascular bed to the apoptotic effect of cryotherapy. Furthermore, IMQ attracted naive dendritic cells that received and processed the tumor antigens released during cryosurgery and elicited a clinically evident inflammatory reaction that led to tumor elimination.[29,30]

Summary

Studies support the use of IMQ as a topical treatment in patients with eyelid carcinomas that are not amenable to treatment via surgical excision. It is the dermatologist's responsibility to inform the patient of the possible vigorous inflammatory response that can occur when IMQ is employed and take measures to protect the eye from irritation. Future research into the synergism of IMQ with other topical therapies (eg, photodynamic therapy) or the timing of initiation of IMQ when used in combination with other treatment modalities in the periocular region will only better prepare the clinician to manage and treat cancerous lesions located on this precarious area of the face.

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