

## Periocular Chemotherapy in Palpebral Malignancies: A Review

Nabita Aulia<sup>1\*</sup>, Halimah Pagarra<sup>2,3</sup>, Suliati P. Amir<sup>2,3</sup>, Andi Pratiwi<sup>2,3</sup>

<sup>1</sup>Ophthalmology Study Program, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

<sup>2</sup>Ophthalmology Department, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

<sup>3</sup>Ophthalmology Department, Wahidin Sudirohusodo Hospital, Makassar, Indonesia

\*Corresponding author. Email : Aulia\_nab@yahoo.com, Telp : +628114342600

### ABSTRACT

**Background:** Palpebral malignancy is still a significant health problem and consists of sebaceous gland carcinoma (SGC), basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and malignant melanoma (MM). Although total resection using the Moh micrograph method is standard therapy for these cases, periocular chemotherapy may be an alternative therapy in patients where surgery cannot be performed.

**Content:** Periocular chemotherapy in lid malignancy is recommended in cases that are inhibited or contraindicated for surgery, with obscure tumor margins, with markers of tumor invasion of vascular, lymphatic, nerve, or other orbital structures, signs of relapse after surgery, local pagetoid involvement, sizeable tumor size, and also presented an appearance of diffuse and multifocal tumor on histopathological examination. Choices of local chemotherapeutic agents based on the variety of palpebral malignancy, namely: (1) imiquimod for BCC; (2) mitomycin-C for SGC; (3) cisplatin, doxorubicin, bleomycin, peplomycin, methotrexate, and 5-fluorouracil for SCC; and (4) Imiquimod for MM. Topical chemotherapy is given to patients using an iodontoherapy method or ophthalmic cream.. More often than not, topical chemotherapy possessed a few side effects that are mild and tolerable and disappear on their own after treatment has finished.

**Conclusion:** Local/periocular chemotherapy for palpebral malignancy is an alternative adjuvant therapy that can be considered, especially in cases where surgery is not possible.

**Key words:** Malignancy, chemotherapy, palpebral, periocular



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## **Introduction**

The palpebra is an accessory visual anatomy with anterior and posterior lamellae that branch along the mucocutaneous margin of the lids and serve primarily as an orbital region protector. The lid's skin is the thinnest on the human body and lacks subcutaneous fat; it is covered in all other skin structures, including hair follicles and accessory glands like eccrine and apocrine glands.<sup>1</sup> Anywhere in these layers—the upper and lower lids, bulbar conjunctiva, fornix, and limbus—can have a lid tumor.<sup>1</sup> The most prevalent type of cancer in Europe and America is basal cell carcinoma (BCC), which accounts for 80–95% of cases. A small percentage of the palpebral malignancies in this area are squamous cell carcinomas (SCC) (5%), sebaceous gland carcinomas (SGC) (1-3%), malignant melanomas (1%), and other cancers (1%). Although BCC is infrequent (11-65%) in Asian populations, SCC (5-48%) and SGC (7-56%) are more common there than in the West.<sup>2</sup>

Wide excision biopsy via frozen surgery or more commonly known as Moh micrographic control surgery is the advised treatment modality for any kind of malignant palpebral tumors. In case of SGC, the advised modality would be conjunctival map biopsy. Further treatment in the form of topical chemotherapy, cryotherapy, and radiation should be utilized if the tumor has undefined margins or if the bulbar conjunctiva is still involved.<sup>1</sup> In general, local or periocular chemotherapy is adjunctive therapy in palpebral malignancies with partial response outcomes.<sup>3</sup> Periocular chemotherapy is administered with carboplatin, cisplatin, mitomycin-C, imiquimod, vismodegib, and other chemotherapeutic agents. Chemotherapy is often given in cases of bilateral retinoblastoma with a poor prognosis or contraindications to systemic chemotherapy. However, apart from retinoblastoma, chemotherapy can be given in cases of basal and epithelial cell malignancies in the eyelids.<sup>4,5</sup> Therefore, we will discuss periocular chemotherapy in palpebral malignancies in this article.

## **Classification of Palpebral Malignancy**

The tissue or cells from which an eyelid tumor develops determine whether it is benign or malignant. The majority of eyelid malignancies originate in the epidermal layer, from which epithelial and melanocytic cancers can be separated. About 85% of all eyelid malignancies are benign epithelial lesions, basal cell carcinoma (BCC), cystic lesions, and melanocytic lesions. Less frequent cancers include squamous cell carcinoma (SCC), melanoma, stromal tumors, and adnexal cancers. Other types of eyelid tumors include choristomas, hamartomas, and lymphoid tumors.<sup>3,6-8</sup>

Sebaceous gland carcinoma (SGC), basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and malignant melanoma are the most common types of eyelid malignancies in Asia, in contrast to Western populations like those in America and Europe where basal cell carcinoma and squamous cell carcinoma are the most common types of cancer. Each type of palpebral malignancy has its own response to the therapy given. In BCC, the main therapy recommended is surgery, especially in the early stages. Topical immunotherapy can be considered in advanced stages or local metastases and cases where surgery is not possible.<sup>4</sup> The preferred course of treatment for palpebral SGC is wide excisional biopsy under frozen surgery or Moh's micrographic surgical control, followed by lid reconstruction. Cryotherapy and topical chemotherapy are also beneficial when the pagetoid is localised.<sup>2</sup> The same principles of therapy are also applied in cases of SCC and malignant melanoma<sup>5,6</sup>

### **Periocular Chemotherapy in Basal Cell Carcinoma**

BCC is the most common skin malignancy, accounting for 85-95% of all malignant mole epithelial cells in non-Asian countries. Most often, the lower straps and inner frame are damaged. BCC mostly affects adults and is rare in children - children who are not predisposed. Prolonged exposure to UV light is the main risk factor.<sup>7</sup> BCC typically manifests as a single injury. Other types, such shallow BCC, are more frequently found elsewhere and are less common within the eyelid. BCC on the eyelid usually causes little pain and also results in lash loss. Clinically, the more prevalent type of nodular BCC manifests as a raised, hard, pearly nodule with irregularly spaced telangiectatic vessels. The nodule may develop an ulcer in the middle as its size increases. BCC with amelanotic pigmentation is comparable to nodular or nodulo-ulcerative BCC. A pale, indurated plaque with hazy or ill-defined edges represents the type that infiltrates. However, when the BCC is found within the inward canthus and is of the infiltrative type, local invasion into adjacent tissues, particularly the orbit, may take place. Rarely does BCC metastatically spread. An intraocular attack is uncommon.<sup>7</sup>

Most solitary BCCs with distinct margins are histopathologically associated with the nodular type variety and the morphea or sclerosing types, which match to the clinical infiltration categorization. Solitary types have oval nuclei, minimal cytoplasm, and projecting outer palisades on their epithelial cell lobules. Adnexal characteristics, known as keratolytic, cystic, or adenoid type, help identify solid BCCs. The properties of elongated basaloid strands embedded in solid fibrous stroma are used to explain the morphea patterns. The

aggressiveness of this form of BCCs causes remarkable infiltration into the nearby dermis, and at a later stage, into the orbital structures and paranasal sinuses, as well as occasionally intraocularly. The epidermis may be diffusely and multicentrically involved in the superficial type, stretching into the surface dermis. Histologically, it might be challenging to differentiate between BCCs and adnexal malignancies like sebaceous carcinoma and trichoepithelioma. An intriguing variant of BCC known as basosquamous carcinoma has morphological characteristics that are in between those of BCC and squamous cell carcinoma.<sup>7</sup>

Currently, it is believed that the pathophysiology of BCC is caused by disruption of the Hedgehog (Hh) pathway. Contrary to the underlying oncogenic mutation, the hedgehog pathway was demonstrated to be uncontrollably activated. The Hh pathway is essential for regulating cell division, proliferation, apoptosis, and self-regeneration in the growing embryo. After the embryonic stage, the Hh pathway is dormant in all normal cells, with the exception of hair, skin, and stem cells. A mutation in Ptch that causes ongoing Smo activation is the most frequent modification seen in BCC, followed by changes in p53 and cyclin-dependent kinase inhibitor 2A (CDKN2A). When used in BCC chemotherapy, vismodegib had both a full and partial response, according to reports. Vismodegib, a particular Hh pathway inhibitor, binds to Smo and blocks the activation of Hh target genes, hence blocking the Hh pathway.<sup>10</sup>

Therapeutic modalities generally used in managing palpebral BCC are summarized in Table 1. Surgical therapy is the main choice in this case but can be combined with radiotherapy if the tumor margins are unclear. In BCC patients who cannot undergo surgery or radiotherapy, periocular chemotherapy using vismodegib or imiquimod can be considered.<sup>4</sup>

**Table 1.** Therapeutic options for palpebral or periocular BCC.<sup>11</sup>

Therapy Options	Indications
MMS	The most effective therapy option for eliminating BCC on the palpebra
Exanteration	significant invasion of the orbit or bulbus
Radiotherapy	Exenteration of high-risk histological subtypes (morphotic/infiltrative, micronodular, or basosquamous) with perineural invasion may occur in conjunction with, when margins are uncertain, or after.
Vismodegib	For individuals who cannot tolerate surgery or radiation therapy, or who have locally advanced illness that recurs after surgery or metastatic disease.
IMQ	Periocular BCC topical immunotherapy, particularly for nodular periocular BCC.

BCC, basal cell carcinoma; MMS, Mohs micrographic surgery; IMQ, imiquimod.

### ***Vismodegib***

The majority of BCCs are treated surgically, however there is no established cure for advanced or metastatic BCC. Vismodegib, an inhibitor of the hedgehog pathway, has been used often to treat periocular and orbital BCC and lessen tumor burden. Patients with advanced-stage or metastatic BCC who are unable to undergo surgery or radiotherapy, who have additional local conditions that could return after surgery or metastatic disease, or for whom surgery could result in additional issues like loss of vision, diplopia, or the loss of structure in the eye or orbit, are advised to use this specific oral treatment. Vismodegib also treats the untreatable basal cell nevus syndrome (Gorlin syndrome), which manifests as many skin lesions on the face and periocular region. The suggested daily dosage is 150 mg. Similar to BCC, the pathophysiology of basal cell nevus syndrome involves disrupted hedgehog signaling. Since the hedgehog signal transduction system is essential for cell proliferation, alterations in the hedgehog signaling pathway could convert conjunctival intraepithelial neoplasia into an aggressive squamous cell carcinoma. In patients with basal cell nevus syndrome, vismodegib specifically blocks the G protein-coupled receptor protein, which stimulates the hedgehog pathway, to halt the evolution of BCC and lower tumor burden.<sup>11</sup>

The initial histological description of vismodegib's effects on BCC in a patient is provided by Kahana et al. After 5 months of vismodegib treatment, the residual squamous cells not only showed degenerative cytology but also failed to stain nuclear for the marker Ki-67 in surgical specimens. Muscle spasms, alopecia, dysgeusia, dysosmia, weight loss, fatigue, nausea, decreased appetite, diarrhea, keratoacanthoma, and squamous cell carcinoma are a few of the side effects of vismodegib. Generally speaking, vismodegib is well tolerated and has little adverse effects. However, some individuals stopping their treatment because of these various adverse effects. To adequately assess therapy risks and develop treatment criteria, more research will be needed.<sup>11</sup>

### ***Imiquimod (IMQ)***

Even while surgical excision remains the gold standard for treating periocular nodular basal cell carcinoma (PNBCC) and is associated to the most effective cure rate, local immunotherapy may be an alternative for patients who cannot undergo surgery. IMQ is an immune modulator that increases both innate and adaptive immunity while inducing death in tumor cells. In numerous trials, the usage of IMQ in 5% cream for nodular BCC has been documented. Depending on the patient's condition, it is often taken once daily, five times weekly, for eight to sixteen weeks. Conjunctival irritation, conjunctivitis, keratitis, foreign body sensation, weeping, poor vision, ectropion, and discomfort when blinking are common

periocular BCC symptoms that normally diminish after therapy. A clinical trial involving 19 patients evaluated the efficacy of topical immunotherapy with 5% IMQ emulsion in treating PNBCC. The histologic clearance rate was 89.5% at 3 months and 84.2% after 39.5 months. After three years, lesions larger than 10 mm receive histological clearance. Another study with 15 PNBCC patients found that after three months of IMQ treatment, all patients experienced histological remission, and after 24 months of follow-up, clinical remission. A smaller study found that 83% of those with PNBCC lesions got treatment, had clinical and histological improvement, and were symptom-free for a median of 11.7 months. In order to treat PNBCC, Garcia-Martin et al. looked at the effectiveness, aesthetic outcomes, and tolerance with 5% IMQ cream and radiation. All 15 patients in the IMQ group experienced complete clinical remission at the 24-month follow-up. Another 12 patients in the radiation group were in clinical remission at final assessment at 24 months after having therapy two or three times a week for five weeks at a dose of 300 cGy per session and a total given dose of 4,000–7,000 cGy. The cosmetic and function of the eyelid treating with IMQ were superior, despite the fact that the radiation group's treatment was more tolerable.<sup>11</sup>

### **Periocular Chemotherapy in Sebaceous Gland Carcinoma**

About 5% of these tumors are sebaceous gland carcinomas (SGC), a highly malignant tumor that is the second most frequent malignant eyelid tumor among Caucasians. However, it is equally prevalent as palpebral BCC in Asian nations including Japan, China, and India. This very malignant tumor, with a mortality rate of 30%, is capable of a highly aggressive local invasion, as well as metastasis to nearby lymph nodes and distant organs. But in recent years, more efficient administration has allowed the death rate to drop to 10%. SGC often affects older people, more frequently affecting women and the superior eyelid. Younger people who have had radiation to the periocular area may develop SGC.<sup>7</sup>

Clinically, a solitary nodule or a widespread disease may both be present with palpebral SGC. The solitary nodule, which is more prevalent, manifests as a hard, painless subcutaneous lesion that develops from the Zeis gland, settles on the tarsus, or shows up at the lid border. Even though SGC resembles chalazion, it causes eyelash loss as opposed to chalazion. In addition to extensive lid thickness, SGC can affect the fornix and bulbar conjunctiva. The patient may initially be identified as having conjunctivitis or persistent unilateral blepharitis because SGC has a tendency to penetrate the overlaying epithelium. The SGC caruncle appears to be a distorted yellow mass.<sup>7</sup>

SGC can be categorized histopathologically according to the level of cell differentiation. Neoplastic cells with sebaceous differentiation, displaying vacuolated foamy

cytoplasm, can be found in well-differentiated malignancies. The majority of cancerous cells in tumors with intermediate sebaceous differentiation have hyperchromatic nuclei, large nucleoli, and basophilic cytoplasm. The anaplastic tumor's poorly differentiated tumor has hyperchromatic, frequently abnormal cells, prominent pleomorphism, and strong mitotic activity. Necrosis can be seen in the tumor's center in the comedocarcinoma SGC pattern. The Oil Red O lipid stain is used to establish the diagnosis. Traditional Oil Red O staining can be substituted with immunostaining using human milk fat globulin 1 to identify SGC from BCC and SCC.<sup>7</sup>

The conjunctival epithelium and palpebral epidermis frequently show intraepithelial spread in SGC. This process is known as "pagetoid spreading." Additionally, the orbit, paranasal sinuses, and brain cavity may all be directly impacted by this invasion. Perineural infiltration and lymphatic invasion may be present in SGC with poor differentiation. Although recent medical advances have decreased mortality to less than 10%, the disease still has a mortality rate of roughly 30% and can spread to nearby lymph nodes as well as distant organs.<sup>7</sup>

Initially, the SGC therapy is frequently insufficient. Depending on the tumor's stage at the time of presentation, a number of treatments are possible, including radiation, chemotherapy, radical neck dissection, local excision, and orbital exenteration. In the beginning, wide excision is needed. A thorough examination of the patient is necessary before performing a surgical excision in order to look for any signs of pagetoid spread or multicentric origin with double eyelid eversion, as well as for any conjunctival modifications like telangiectasia, papillary changes, or malignancies. In addition to surgically removing the lid lesion, a conjunctival punch biopsy should be carried out.<sup>12</sup>

Wide excisional biopsy under freezing surgery or Moh micrographic surgical control followed by lid repair are the approved treatments for palpebral SGC. In situations where the pagetoid is localized, cryotherapy and topical chemotherapy are also beneficial. In situations of diffuse eyelid SGC, systemic chemotherapy is helpful. When a tumor has diffuse orbital and/or pagetoid involvement and is highly advanced, orbital exenteration is the advised course of treatment.<sup>13</sup> An alternate therapy for palpebral SGC is neoadjuvant chemotherapy. In enormous tumor size cases, neoadjuvant chemotherapy performed before the main operation can dramatically reduce the tumor size. This neoadjuvant therapy should be based on the findings of the histology examination. Adjuvant cryotherapy is a possibility if a map biopsy shows intraepithelial invasion in up to one quadrant. However, there are other treatment options for diffuse and multifocal involvement, including orbital exenteration,

plaque brachytherapy, surgical excision, and topical mitomycin-C. People with orbital extension and those who have lymphovascular invasion as evidenced by histopathology might wish to think about using adjuvant chemotherapy in coordination with an oncologist..<sup>13,14</sup>

In the study by Shields et al. (2004), In six (10%) cases, topical chemotherapy utilizing mitomycin C was the main course of therapy. In these situations, the initial tumor has typically been removed in its entirety from a different location, the remaining tumor is histopathologically contained to the epithelium, and based on the clinical results, no additional surgical excision is required. After the initial therapy, some patients receive ongoing care. Due to their small numbers and complexity, these types of therapies are challenging to analytically examine. Topical chemotherapy utilizing mitomycin C may be an advantageous adjuvant therapy if there is any question regarding the neoplasm's residual involvement of the bulbar conjunctiva.<sup>15</sup>

Studies on the use of topical mitomycin-C 0.04% in the treatment of sebaceous gland cancer revealed significant reductions in the invasion of the pagetoid layer of the conjunctiva. In vivo, mitomycin converts into tri- and bifunctional alkylating agents. DNA synthesis and function are impeded via binding to DNA, which leads to in cross-linking. A general cell cycle phase inhibitor is mitomycin. The chemotherapeutic medication mitomycin has been around in use for many years. It is an antibiotic with anticancer properties that has been demonstrated. The synthesis of deoxyribonucleic acid (DNA) is specifically inhibited by mitomycin. The amount of mitomycin-induced cross-linking correlates with levels of guanine and cytosine. At high levels of medication, cellular RNA and protein output may also be inhibited. The proliferation of B cells, T cells, macrophages, interferon-gamma, TNF $\alpha$ , and IL-2 production have all been demonstrated to be inhibited by mitomycin in vitro..<sup>16,17</sup>

### **Periocular Chemotherapy in Squamous Cell Carcinoma**

The squamous cell layer of the skin epithelium gives rise to squamous cell carcinoma of the lids, an aggressive malignancy that primarily affects elderly Caucasian persons. Exposure to UV radiation is the most frequent risk factor. The areas most frequently impacted are the inner canthus and inferior palpebral border. In comparison to BCC, it happens more commonly in the superior eyelid and outer canthus. SCC of the eyelid makes up just around 5% of all eyelid malignancies in comparison to BCC. Although these tumors are capable of developing on their own, they frequently do so in response to radiation therapy or pre-existing lesions such actinic keratosis, xeroderma pigmentosum, or carcinoma in situ (Bowen's disease). Clinically, SCC typically presents as a wavy-margin plaque or nodule that



is indurated but painless, frequently with core ulceration. There may be additional manifestations of these tumors, such as papillomatous lesions. The majority of eyelid SCCs have fairly favourable prognoses; nevertheless, advanced and untreated cases frequently return locally and have the potential to migrate to nearby tissues, including the orbit and lacrimal drainage system as well as the intracranial cavity. In contrast to BCC, eyelid SCC has a greater propensity to metastasize to distant organs, such as the preauricular and submandibular lymph nodes. High TNM and ACC staging have been linked to local recurrence and metastasis.<sup>7</sup>

The stage of tumor differentiation determines the histological appearance of SCC. Tumors with a high degree of differentiation are characterized by polygonal cells with a profusion of acidophilic cytoplasm, hyperchromatic nuclei of various sizes and staining characteristics, dyskeratotic cells, and plainly distinguishable intercellular bridges. Pleomorphism with anaplastic cells, aberrant mitotic features, little to no keratinization evidence, and loss of intercellular bridges are characteristics of poorly formed SCC. Adenoid and spindle SCC are the two types of SCC. A form of SCC known as keratoacanthoma has just been found.<sup>7</sup>

UV light is the primary risk factor that initiates the pathophysiology of SCC. The most frequent genetic abnormalities in actinic keratosis, in situ squamous cell carcinoma, and invasive squamous cell carcinoma are p53 gene mutations. The three main causes of therapeutic UV exposure, ionizing radiation, and tanning bed use are the risk factors for developing squamous cell cancer. The p53 protein stops mutant cells from functioning or DNA replication. When the p53 gene is altered, the p53 protein is rendered inactive, which results in the formation of cells with DNA damage, such as those seen in squamous cell carcinoma.<sup>18,19</sup>

One other therapy also showed that chemotherapy using cisplatin and doxorubicin administered systemically and/or locally (iontophoresis) showed good resolution without any signs of therapeutic toxicity. For this investigation, the provided dose must still be altered.<sup>3</sup> The patient in a prior study with invasive Three cycles of intravenous chemotherapy (cisplatin 150 mg and 5-FU 1000 mg daily for three days during each cycle) were administered to SCC cases, with each cycle being repeated three weeks apart. With each treatment session, the orbital tumor's size is reduced. All hematological indicators were constant during the treatment cycles, and no major side effects materialized.<sup>20</sup>

Deoxyribonucleotide (FdUMP) and the folate cofactor N5-10-methylenetetrahydrofolate are thought to form a covalently bonded complex with thymidylate

synthase (TS) as fluorouracil's main mechanism of action. This hinders the conversion of uracil into thymidylate, prevents the production of DNA and RNA, and results in cell death. RNA can become fragmented when fluorouracil replaces the uridine triphosphate (UTP), which prevents both protein synthesis and RNA processing.<sup>21</sup>

Cisplatin, on the other hand, is an alkylating agent that functions in three different ways. In order to cause DNA repair enzymes to attempt to remove the alkylated base, it first binds an alkyl group to a DNA base. This slows down the target DNA's ability to produce DNA and translate it into RNA. DNA atoms are bound together by structures called cross-links, which prevent DNA from being separated for synthesis or transcription. The second creates cross-links. The third is the product of mutations brought on by nucleotide pair errors.<sup>22</sup>

In periocular SCC with microscopic stratum or perineural infiltration and/or swollen lymph nodes in unresectable, large, or multiple lesions or when the patient opposes surgery/surgical contraindications, chemotherapy may be utilized as an adjuvant therapy. Specifically, 5-fluorouracil, doxorubicin, bleomycin, peplomycin, methotrexate, and cisplatin.<sup>5</sup>

### **Periocular Chemotherapy in Malignant Melanoma**

Malignant melanocyte proliferation leads to cutaneous malignant melanoma (CMM). The cancer whose incidence has significantly increased in recent years is CMM. The chance of acquiring CMM throughout the course of one's lifetime in the United States was estimated to be 1 in 55 for males and 1 in 82 for women between 1998 and 2000. Although CMM only accounts for 5% of malignant skin tumors, it is accountable for more than 65% of skin cancer-related fatalities. 20% of cases of CMM occur in the head and neck area. 66% of these instances had facial injuries, while 3% involved eyelid injuries.<sup>6</sup>

At the time of diagnosis, histologic features and clinical criteria are used to determine the majority of CMM subtypes. The radial growth phase and the vertical growth phase are the two stages of melanomas' development. The melanoma initially forms a flat, black lesion on the skin during the radial growth phase by spreading laterally in two dimensions. The melanoma's spread into the epidermis past the three epidermal rete ridges is known as the radial growth phase, in contrast to the lesion's dermal (invasive) component. The largest melanocytic nest in the dermis must, however, be larger than the largest junctional/epidermal nest for the vertical growth phase to exist, or there must be signs of mitosis in the dermal

melanocytes. Although amelanotic melanoma can develop in the periocular and eyelid regions and present a diagnostic challenge, most melanomas are pigmented. It causes a delay in diagnosis.<sup>6</sup>

The structure of the eyelash adnexa can be used to identify malignant lentigo, which also has an aberrant pattern of melanocytes in the basal layer of the epidermis.<sup>23,24</sup> Studies have revealed that BRAF mutations were present in 40–60% of all melanoma cases. The serine/threonine protein kinase, a part of the RAS-RAF-MEK-ERK kinase pathway that encourages cell growth and proliferation, is encoded by the proto-oncogene BRAF. In response to growth signals, BRAF commonly forms homo- or heterodimers with other RAF kinases. However, BRAF mutations can lead to unchecked cell growth until malignancies develop.

BRAF mutations were found in 60–70% of melanoma lesions and metastatic vertical growth, according to another study, raising the possibility that these oncogenic alterations play a role in the formation of cancer. This gene is then targeted for therapy in malignant melanoma.<sup>25–27</sup>

In addition to BRAF activation, NRAS, which shares the same activation pathway as BRAF, is one of the molecules that is known to contribute to the development of malignant melanoma. Then come mutations in p53, CDK4 / CDKN2A, c-KIT, MC1R, and Cadherin, which affect melanoma cells' ability to proliferate and remain alive. BRAF activation is currently the primary target of melanoma treatment.<sup>28</sup>

Depending on the clinical stage at the time of diagnosis, CMM is treated surgically. Treatment of main lesions and close-by lymph nodes should be considered when evaluating CMM. CMM of the palpebral and periocular region requires collaborative diagnosis and treatment, as with all malignant eye tumors, to provide patients with the best care available.<sup>6</sup>

In administering additional therapy of periocular chemotherapy, imiquimod has an important role. An immune response modulator called imiquimod increases cell-mediated immunity. The Food and Drug Administration (FDA) has given the topical 5% imiquimod its approval to treat superficial basal cell carcinoma. However, in situ melanoma has also been successfully treated with it. Surface malignant lentigo of the palpebral skin with diffuse involvement of considerable portions of the palpebral skin may be treated with topical imiquimod. Surgery to remove malignant lentigo that has frequently returned is not recommended due to the size of the lesion or the challenges of attaining negative surgical margins on older individuals with extensive sun damage.<sup>6</sup>

Recently, the imiquimod 5% immune modulator has been successfully used to treat

malignant lentigo. This may affect future LMM events. Borucki and Metze published case reports showing imiquimod's efficacy in the treatment of LMM; nevertheless, more research is required to determine its function in the management of MFIs and MMs.<sup>29</sup>

The FDA has given the drugs dacarbazine and temozolomide permission to be used. Drugs that introduce alkyl groups into guanine bases, such as dacarbazine and its analog temozolomide, damage DNA damage can cause apoptosis and other processes that result in cell death. Following ingestion, dacarbazine undergoes hepatic demethylation to produce 3-methyl-(triazine-1-yl)imidazole-4-carboxamide (MTIC), which is further transformed into diazomethane and its active metabolite. The "standard of care" in the treatment of metastatic melanoma is dacarbazine, the gold standard. Usually, dacarbazine has a 10–20% response rate and three–6 month cancer-free intervals. Leukopenia, anemia, and nausea—all indications of bone marrow suppression—as well as vomiting and nausea are among dacarbazine's most frequent side effects. When taking temozolomide, antiemetics can be used to treat nausea and vomiting. Temozolomide (TMZ), an analog of dacarbazine and a derivative of triazene, was found similar with dacarbazine in a phase III trial comprising 305 patients.<sup>13,30</sup>

## **Conclusion**

The most common type of palpebral malignancy, particularly among Asian populations, is sebaceous gland carcinoma (SGC), which is followed by basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and malignant melanoma (MM). Another therapeutic approach that has the potential to result in a partial remission of the tumor is local chemotherapy. This therapy is indicated in cases of surgical rejection/contraindications, unclear tumor boundaries, signs of tumor invasion into the vascular, lymphatic, nerve, or other orbital structures, chances of recurrence after surgery, local pagetoid involvement, large tumor size, and if there are diffuse and multifocal tumor features on histopathological examination. Choice of local chemotherapeutic agents based on the type of palpebral malignancy, namely: (1) imiquimod for BCC; (2) mitomycin-C for SGC; (3) bleomycin, peplomycin, doxorubicin, cisplatin, 5-fluorouracil, and methotrexate for SCC; and (4) Imiquimod for MM. Giving topical chemotherapy can use the iodontoherapy method or ophthalmic cream. In general, topical chemotherapy has side effects that are mild and tolerable and go away on their own after treatment is finished. Thus, local/periocular chemotherapy for lid malignancy is an alternative adjuvant therapy that can be considered.

### Conflicts of Interest

Nothing to declare

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