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Review

Therapy Failure and Resistance Mechanism in Eyelid and Ocular Surface Tumors

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Key Words
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Abstract
Malignant tumors of the eyelids and ocular surface are common ocular malignancies. At present, surgical treatment is mostly the first choice for these types of tumors. However, postoperative tumor recurrence and metastasis are still regarded as failures in the treatment of such malignancies. Based on this, malignant tumors of the eyelid and ocular surface are sometimes accompanied by local adjuvant chemotherapy and systemic chemotherapy to treat patients with relapse, invasion of adjacent tissues, and systemic metastases. Still, drug resistance greatly affects the treatment effect. This review lists several mechanisms of recurrence and metastasis of ocular surface and eyelid tumors after surgery, as well as mechanisms that may lead to non-surgical treatment or drug resistance.

Introduction

Unlike most ophthalmic diseases, periocular and ocular malignancies affect vision and even threaten life. Managing periocular and ocular diseases, orbital or intracranial invasion, and metastatic lesions are challenging and often involve a multidisciplinary approach.

According to different epidemiological surveys, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most common eyelid malignancies [1]. Sebaceous gland carcinoma (SGC) and Merkel cell carcinoma (MCC) are less common but more deadly, with relatively high rates of metastasis and death [1, 2]. Conjunctival melanoma (CM) and

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ocular surface squamous neoplasia (OSSN) are the most common conjunctival malignancies [3]. Among ocular malignancies, because tumors on the eyelids or ocular surface are more likely to receive early attention, malignant tumors in this area are usually treated by surgical resection after early diagnosis [4-8]. Recurrent or large tumors, orbital, intracranial or metastatic lesions often require alternative treatment options (combination of non-surgical methods, such as targeted therapies, chemotherapy and adjuvant radiotherapy [7, 9-12]. This review summarizes several mechanisms of recurrence and metastasis of the above eyelid and ocular surface tumors after surgery, as well as mechanisms that may lead to drug resistance to non-surgical treatment.

Postoperative recurrence and metastasis

Surgical excision is undeniably the most common treatment for eyelid and ocular tumors. Although most of them are not fatal, the incidence of recurrence and postoperative metastasis is usually regarded as a therapy failure. Table 1 [13-20] shows the recurrence and metastasis rates of the postoperative periocular malignant tumors. Excision with histologic margin assessment is the standard treatment modality for periocular tumors. After successful tumor excision, a histological examination should always be carried out to confirm the diagnosis and to check the excision margin to determine the resection status. The surgical resection should always excise as much malignant tissue as necessary to achieve an R0 resection. The safety distance is difficult to define for periocular malignancies since every millimeter of healthy tissue would be decisive for later functional reconstruction [21]. Thus, intraoperative margin control (IOMC) examines the tumor and its margins before reconstruction and is increasingly commonly used. It primarily involves Mohs micrographic surgery (MMS), fast-frozen controlled (FFC), and fast paraffin (FP), and predominantly affects the effect of surgical treatment and postoperative recurrence.

A postoperative histopathological examination is essential to confirm the diagnosis and determine the resection status to identify infiltrative growing subtypes; this also influences postoperative follow-up care and the prognosis [22, 23]. Aggressive tumor subtypes significantly affect the risk of a non-radical excision, leading to a high risk of postoperative recurrence [24]. Therefore, for any patient with periocular malignancy who underwent surgery, a regular, lifelong follow-up is necessary.

Table 1. The recurrence and metastasis rates of periocular malignant tumor after different surgical excision method

Malignancies	Excision method	Follow-up recurrence rate		Follow-up metastasis rate		
		Recurrence rate	Average follow-up	Metastasis rate	Most location	Average follow-up
BCC (Basal cell carcinoma)	Mohs micrographic surgery (MMS)	1.5%-3.0% 95% CI, 1.9-4.4%	48.8±14.9 months	0.03%	Regional lymph nodes, skin, submandibular gland	Over 5 years
	Frozen section controlled (FSC)	1.9% 95% CI, 1.9-2.4%	70.7±48.0 months			
	Wide local excision (WLE)	5.9% 95% CI, 3.9-8.9%	49.2±29.3 months			
Conjunctival melanoma	Surgical resection using the "no touch" technique	26.0%-61.0%	5.0 years	25.0%	Regional lymph nodes, lungs, liver, skin, brain	5.0 years
SCC (Squamous cell carcinoma)	Mohs micrographic surgery (MMS)	2.4% - 36.9%	67.6 months	10.0% -25.0%	Regional lymph nodes,	67.6 months
SC (Sebaceous Carcinoma)	Mohs micrographic surgery (MMS)	Up to 25% (15.7%)	60.0 months	16.0%-80.0%	Regional lymph nodes, lung, brain, skull base	17.0 months
	Wide local excision (WLE)	39.6%	60.0 months	15.5%	Regional lymph nodes, lung, brain, skull base	17.0 months
Merkel cell carcinoma	Surgical resection	55.0%	2.3 years	12.4% -33.0%	Regional lymph nodes, lungs, adrenal glands, pancreas, liver, brain, and bones	5.0 years
	Surgical resection combined with radiotherapy	39.0%	2.3 years	12.4% -33.0%		5.0 years
OSSN (Ocular surface squamous neoplasia)	Partial lamellar scleroconjunctivectomy (PLSC) combined with additional treatment methods (cryotherapy, chemotherapy)	18.8% 95% CI, 17.0%-21.0%	20.1 months	2.0-3.0%	Local lymph node	15.0 months

Failure and resistance of non-surgical treatment

Basal cell carcinoma

BCC is the most common eyelid malignancy worldwide, accounting for 90% of all cases [25]. It arises most frequently on the lower eyelid, followed by the inner canthus, upper eyelid and lateral canthus [26]. The tumor grows slowly and is mostly infiltrative and destructive [22, 27]. BCC is not fatal with rare distant metastases, local recurrence can be associated with about 20% of eyelid BCC cases [28]. Once metastasized, BCC is usually associated with an aggressive subtype of the primary tumor, and their overall prognosis tends to be worse than that of the primary one [29].

Hedgehog pathway inhibitor. The Hedgehog pathway is a pivotal event in the pathogenesis of BCCs, and it is reported to be activated by the PTCH1 gene, which is located on human chromosome 9q22 and encodes a transmembrane protein that negatively regulates smooth muscle (SMO), another transmembrane protein of the Hedgehog pathway [10, 30]. The mechanism of PTCH1 is binding to an extracellular ligand, such as the sonic hedgehog, then relieving the negative control on SMO, and SMO subsequently migrates in the cilia and activates the Gli transcription factor [31, 32]. Many of the genes regulated by Gli proteins are co-opted by cancer cells as they regulate several cancer-related processes, including proliferation, migration, invasion, and neovascularization [33-35].

If tumors have progressed deeply into tissues or distant metastasis, we call it locally advanced BCC (laBCC) or metastasis BCC (mBCC) [36]. In these cases, we can use Hedgehog pathway inhibitors as adjuvant therapy for patients who may suffer further disfigurement, functional loss and increased morbidity due to direct surgical treatment [36, 37].

Therefore, the occurrence of Hedgehog pathway mutations is considered a driving event in the formation of BCCs, and inactivation of the Hedgehog pathway has been a key therapeutic target for difficult-to-treat BCC [10]. Currently, two targeted hedgehog inhibitor therapies are available: Vismodegib and Sonidegib, which have different pharmacokinetics but target the same molecular SMO [38].

Vismodegib and Sonidegib play increasingly essential roles in adjuvant therapy. Still, some adverse events observed in prior studies, that include muscle spasms, dysgeusia, alopecia, fatigue, and weight loss, or serious such as fatal adverse events [35, 38]. Compared with Vismodegib, Sonidegib has the most serious and increasingly frequent side effects like CK (Creatine Kinase) elevation [34, 39]. These side effects are related to the pharmacological effects of SMO inhibitors. Even at low levels, treatment-related adverse events may lead to the therapy discontinuation in many patients [40]. Therefore, clinicians who can correctly predict and assess the treatment-related adverse events can improve patient compliance and develop treatment plans.

Another barrier in treating Hedgehog pathway inhibitors is resistance with progression and no response. It is described in a case series that regrowth of at least one tumor in 21% of patients with advanced BCCs after a mean of 56 weeks and confirmed that long-term efficacy is often mitigated by the development of tumor-acquired resistance to the medications [41]. Danial et al. showed that Sonidegib was less effective in Vismodegib-tolerant advanced BCC [42]. All patients demonstrated either progressive or stable disease with Sonidegib. The resistance mechanism is unclear, a murine model study suggests that it may be related to point mutations in SMO [35].

In the previous clinical observation of treatment of Vismodegib in advanced BCC, primary resistance occurred in 50% of patients, and secondary resistance occurred in 20% of patients [41, 43]. Primary drug resistance manifests as a mutation in SMO G497W, located in the most frequently mutated SMO region (exon 8e10) in BCC, and then a conformational rearrangement of the entire protein region, which eventually leads to a partial blockage of the protein drug entry site. This blockage leads to a significant decrease in the concentration of active Vismodegib at the SMO G497W binding site [44]. Secondary resistance showed mutations in PTCH1 and SMO D473Y after treatment. In these mutations, protein rearrangements occur, resulting in partial blockage of protein drug entry [44] (Fig. 1).

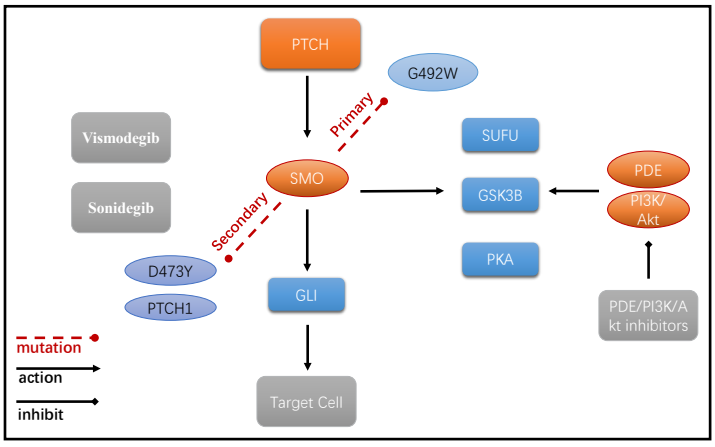

Fig. 1. Site of action and inhibit of different HPI on the hedgehog pathway. PTCH: patched: SMO: smoothened protein: SUFU: suppressor of the fused protein: GSK3B: glycogen synthetase kinase 3B; PKA: protein kinase A; GLI: transcription factor GLI; PDE: cyclin nucleotide phosphodiesterases; PI3K/Akt: phosphoinositide 3 kinase; HPI: hedgehog pathway inhibitors.

In addition, on-canonical HH pathway activation mediated by Gli, namely hedgehog-Gli (HH-GLI) signaling, also plays a key role in embryonic development, cell proliferation, differentiation and stem cell maintenance [45]. Amplification of Gli genes allows tumors to escape SMO inhibition, identity switching to more closely resembling stem cells of the isthmus, and the reduction of primary cilia, leading to a switch from the Hedgehog pathway to Ras/MAPK pathway [46]. It leads to insensitivity to conventional Hedgehog pathway inhibitors, resulting in drug resistance [47].

PD-L1. Programmed death ligand 1 (PD-L1) is a cell surface glycoprotein that is normally expressed by immune cells and binds to its receptor PD-1; it inhibits the immune response in the inflammatory response and promotes peripheral tolerance in normal physiological signaling. For many cancers, this pathway is exploited by the upregulation of PD-L1 on tumor cells and tumor-infiltrating lymphocytes (TIL), thereby evading immune surveillance [48].

Several laboratory and clinical studies suggest that PD-1 blockers should be considered salvage therapy for patients with advanced BCC whose disease has progressed after standard Hedgehog pathway inhibition [49].

The resistance mechanism to PD-1 therapy can be explained by immune escape [50]. Whereas HLA class I antigen down-regulation is widely recognized as a mechanism of tumor immune escape, both lack of HLA class I antigen expression and low numbers of activated cytotoxic T cells (CD8+/granzyme B+) can contribute to a lack of clinical response to PD-1 [51]. In BCC, HLA class I antigen down-regulation is associated with a deficiency of infiltrating CD8+ T cells [52]. In addition, β2-m expression, which plays a crucial role in HLA class I antigen expression, was not detected in BCC cells [53]. BCC tumors are infiltrated by more negative regulatory immune cells, which may also damage the activity of CD8+/granzyme B+ T cells and destroy the efficacy of PD-1 blocking [54].

Squamous cell carcinoma

Squamous cell carcinoma is the subsequent most common malignancy of the eyelid [55]. The tumor has a predilection for the lower eyelid and the lid margin. Clinically, SCC is indistinguishable from BCC, but it does not usually manifest surface vascularization and grows more rapidly. SCC most commonly occurs in fair-skinned elderly patients with a fair complexion and a history of chronic sun exposure and skin damage [10].

EGFR targeting for advanced periocular SCC. Epidermal Growth Factor Receptor (EGFR), is a transmembrane receptor protein in the ErbB receptor kinase family, also referred to as HER1 or ErbB1. EGFR is associated with various ligands, including EGF and transforming growth factor-α. Upon binding to these ligands, EGFR forms a homodimer or heterodimer

with another member of the ErbB receptor family. Activation of EGFR in keratin-forming cells leads to induction or blockade of cell proliferation, differentiation, cell migration, and increased survival and resistance to apoptosis [56].

Many clinical studies have found that in metastatic SCC, EGFR is strongly expressed in all layers of skin in all cases compared to adjacent normal skin. At the same time, the degree of overexpression of EGFR is positively correlated with the aggressiveness of the disease [55, 57]. Furthermore, conjunctival SCC specimens showed moderate to strong EGFR expression in both invasive and *in situ* components [58].

Two EGFR inhibitors, Cetuximab and Erlotinib, are currently reported to be clinically effective in patients with locally advanced periocular SCC with orbital expansion [59]. Notably, 9-13% of SCC patients stop treatment due to the side effects of EGFR inhibitors [60]. Therefore, drug side effects such as skin toxicity, mucositis, esophagitis, corneal ulceration, conjunctivitis, and ectropion caused by EGFR inhibitors will be the focus of further research [61, 62]. Since the current literature records are less, it is still uncertain whether the resistance mechanism of EGFR inhibitors in periocular SCC is the same as that in other sites.

Sebaceous gland carcinoma

Sebaceous gland carcinoma (SGC) is a very rare and slowly growing tumor. It most frequently arises from the meibomian glands. It may also arise from the gland of Zeiss or sebaceous glands. The tumor occurs most frequently on the upper eyelid, where meibomian glands are more numerous [63]. Liang et al. reports that the incidence of SGC of the eyelid has significantly increased [64]. Compared to most other malignant eyelid tumors, its prognosis is still regarded as poor, and its mortality rate is second only to that of malignant melanoma [65]. The clinical diagnosis of SGC is frequently difficult because, external signs of malignancy may be subtle in its early stage, so the tumor may resemble a less aggressive lesion. In many cases, the delayed diagnosis of meibomian gland carcinoma is due to its ability to masquerade as various other ocular diseases such as chronic conjunctivitis, superior limbic keratoconjunctivitis, cicatricial pemphigoid chalazion, basal cell carcinoma, or other eyelid tumors [66]. Definitive diagnosis is only by pathology [67].

Topical mitomycin C chemotherapy. Pagetoid spread is a common feature of periocular sebaceous carcinoma, currently documented local chemotherapy for MMC (mitomycin C) is used in the treatment of SGC with pagetoid spread [68]. The most reason for MMC treatment disturb is short- and long- complications [69]. As for recurrence after treatment, the role of adjuvant MMC for SGC without pagetoid spread is not yet established in the literature. Furthermore, the effect of adjuvant MMC upon survival time and local recurrence in cases of SGC (with or without pagetoid spread) will need to be delineated through clinical trial. Given the infrequency of the diagnosis, such a trial would need to incorporate multiple centers over a considerable time period.

Neoadjuvant systemic chemotherapy. Although surgical excision is the primary treatment for localized SGCs, more advanced tumors may suggest topical therapy and neoadjuvant systemic chemotherapy. Because of the chemosensitivity of SGC, the choice of chemotherapy combination in eyelid SGC in various case reports has been extrapolated from the standard chemotherapy agents used in the management of head-and-neck squamous cell carcinoma, including platinum-based agents (cisplatin/ carboplatin) in combination with 5-fluorouracil and taxanes [70]. The current literature records, show few cases of neoadjuvant systemic chemotherapy used for SGC, and most of them are carried out in the form of adjuvant surgery. Therefore, further clinical observation and research are needed for study its drug resistance and failure.

Merkel cell carcinoma

Merkel cell carcinoma is a rare and aggressive neuroendocrine malignancy of the skin, which affects the elderly. Although MCC may occur in any skin area, 10% of tumors involve the eyelid or periocular area [71, 72]. This tumor commonly seen in the upper eyelid, especially near the eyelid margin, and usually results in partial or complete eyelash loss [12]. MCC presents as an asymptomatic, isolated nodule that may have an ulcerated surface or overlying dilated capillaries. MCC is a fast-growing tumor associated with sun exposure, immunosuppression, and polyomavirus [73]. Its rarity may lead to difficulty in diagnosis and delay in treatment of this highly malignant tumor. MCC is often misdiagnosed as a cyst, chalazion, keratoacanthoma, or BCC. It may be associated with concurrent tumors, such as SCC, BCC, SGC, breast and ovarian adenocarcinomas, lymphomas, and may share a carcinogenic process with other cells of neural crest origin [12, 74].

PD-L1. Until now, the PD-L1 inhibitor Avelumab is the only approved treatment for advanced MCC [75]. Avelumab is a human IgG1 monoclonal antibody, which binds to PD-L1 on cancer cells and blocks its interaction with PD-1 [76]. In the treatment of metastatic MCC, immune checkpoint blockade (ICB) shows a high response rate [76, 77]. Unfortunately, the immune checkpoint inhibitors (Avelumab) are only effective in a subset of patients. Patients who respond initially show a subsequent rapid disease progression due to primary and acquired resistance to PD-1/PD-L1 inhibition [78]. According to current reports, primary resistance seems to be a more important clinical problem in MCC [79]. However, follow-up studies are still few, so that the treatment resistance of MCC is still a pivotal point to be broken through.

Other targeted therapies should be the alternatives for patients with PD-1/PD-L1 treatment failure. Apoptosis inducers such as YM155, ABT-263 have been proved to induce cell death in MCC cell lines and xenograft models [80, 81]. Aberrant activation of the PI3K pathway may be a potential therapeutic target for Merkel cell carcinoma. Some clinical data and experimental results suggest that PI3K-mTOR pathway inhibition effectively treats MCC [82, 83]. A case report has reported that the selective PI3Kδ inhibitor Idelalisib is effective in metastatic MCC [84]. Inhibition of PI3Kδ interferes with B cell signaling and shifts the balance from immune tolerance to effective anti-tumor immunity by suppressing regulatory T cells and releasing cytotoxic T cells [85]. Therefore, targeted therapy has significant research prospects for treating MCC due to PD-1/PD-L1 treatment failure or resistance.

Conjunctival melanoma

Conjunctival melanoma may originate from primary acquired melanosis (PAM), nevi, or de novo. CM is a subtype of mucosal melanoma that arises from atypical melanocytes in the basal layer of the conjunctival epithelium and represents 2% of ocular tumors [86]. It is the second most frequent malignant neoplasm of the conjunctiva after SCC. Compared with uveal melanoma, the incidence of conjunctival melanoma is much lower [87]. They are most frequent in the interpalpebral region of the bulbar conjunctiva, they may be observed arising from the fornix, palpebral conjunctiva, and inner canthus.

MAPK pathway inhibitor. Mitogen-activated protein kinase (MAPK) pathways are evolutionarily conserved kinase modules that can link extracellular signals to mechanisms that control essential cellular processes including growth, proliferation, differentiation, migration, and apoptosis [88]. Many studies have evaluated the importance of the mitogen-activated protein kinase (MAPK) pathway in cutaneous melanoma [89]. Mutations common in cutaneous melanoma, such as V600E in BRAF exon 15, are also found in conjunctival melanoma [90]. Some studies found, BRAF mutations in 29% to 35% of conjunctival melanomas [91, 92]. Meanwhile, NRAS (neuroblastoma rat sarcoma viral oncogene) is also a critical mutation for tumor progression, and about 15% of melanomas contain NRAS mutations [93, 94]. Both NRAS or BRAF mutated oncogenes strongly activate the MAPK (MEK/ERK) pathway. Successful inhibitor therapy with specific BRAF and MEK inhibitors targeting

the overactivated MAPK pathway driven by mutated NRAS or BRAF increases median overall survival. Therefore, specific inhibitors of these oncoproteins, MAPK pathway components or their combination have been used for tumor eradication. After a good initial response, resistant cells develop almost universally and greatly affect the drug's effectiveness, causing treatment failure [88-90, 92, 93, 95].

Resistance to Mutated BRAF Inhibitors. Most melanomas show BRAF-V600E activating mutations. Currently there are BRAF inhibitory treatments, but many mechanisms are related to resistance to BRAF inhibitors [96]. BRAF-V600E activating mutations lead to constitutive activation of the MEK-ERK signaling pathway [97]. HGF/MET signaling is involved in resistance to BRAF inhibitors, HGF prevents cell death and restores activation of the MEK/ERK and PI3K-AKT signaling pathways by preventing cell death and restoring activation of oncogenes expressing BRAF-V600E [98, 99]. HGF expression analysis in BRAF-V600E melanoma patients is identified with its expression in the tumor-associated stroma. This expression increases after BRAFi treatment, which in turn increases resistance to BRAFi treatment [100].

POU Class 4 Homeobox 1 (POU Domain, Class 4, Transcription Factor 1, POU Class 4 Homeobox 1, POU4F1), a member of the POU domain family transcription factors, is also a stem cell-associated transcription factor expressed in proliferating precursor cells in the neural crest, POU4F1 may be involved in the resistance of melanoma to BRAFi. The resistance mechanism is that elevated POU4F1 activates the MEK/ERK pathway and thus the entire MAPK pathway, rendering melanoma resistant to BRAFi. POU4F1 directly binds to the promoters of MEK and MITF (Microphthalmia-associated Transcription Factor) to promote their expressions. POU4F1 is directly bound to the promoter region of MITF and transcriptionally promotes the expression of MITF, MITF contributes to the development of melanoma resistance to BRAFi [101] (Fig. 2).

Dual activation of the pathways greatly contributes to drug resistance, as these pathways promote cell survival and proliferation. Starting from the cell surface, several receptor tyrosine kinases (RTK) converge on parallel pathways, such as the MAPK and PI3K-Akt pathways. Upregulation of RTK has been shown to activate the MAPK pathway through RAS activation directly. In addition, upregulation of specific RTKs such as insulin-like growth factor 1 receptor (IGFR1) and platelet-derived growth factor receptor (PDGFR) can activate the PI3K-Akt pathway in a non-ERK-dependent manner. Epigenetic changes affecting the epidermal growth factor receptor (EGFR) have also been shown to induce the PI3K-Akt pathway in melanoma-resistant cells [102-106].

Recently, BRAF mutant melanoma cells have adapted to the feed-forward mechanism of MAPK targeted therapy by acquiring an auto-amplified CAF-like phenotype has been reported [108]. In addition to therapy-induced tumor secretomes, therapy-induced mechanical phenotypes could endow cancer cells with unique cell-autonomous abilities to survive and differentiate within challenging tumor-associated microenvironments, thereby contributing to drug resistance and relapse [107, 108].

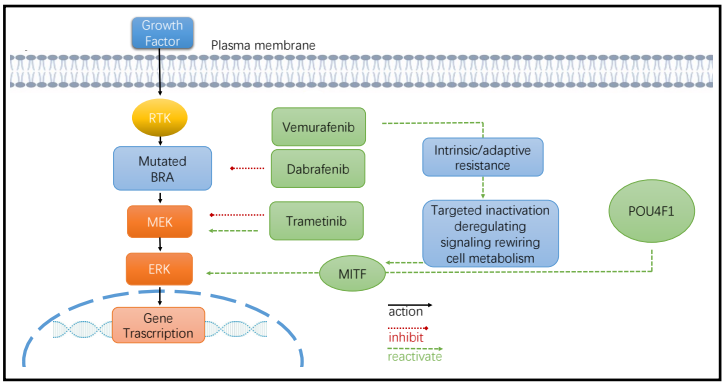

Fig. 2. BRAF mutated melanoma responds to BRAF/MEK inhibitors-targeted therapy; Development of BRAF/MEK inhibitors-targeted therapy resistance. RTK: receptor tyrosine kinases; MITF: Melanocyte Inducing Transcription Factor; POU4F1: POU Domain, Class 4, Transcription Factor 1.

Resistance to Mutated NRAS Inhibitors. Neuroblastoma RAS viral oncogene homolog (NRAS) mutations exist in 15% to 20% of melanoma patients [105]. NRAS activates multiple effector pathways, and some mutant NRAS melanoma cells may be less dependent on MEK/ERK signaling pathway [109]. The major downstream effectors of RAS are RAF (a family of protein kinases, including A-RAF, B-RAF, C-RAF), phosphatidylinositol 3-kinase (PI3K), and Ral guanine exchange factor (RalGEF) [110]. Thus, PI3K and AKT activity may be important pathways in mutant NRAS melanoma cells resistant to MEK inhibitor treatment [111].

Romano et al. have recently revealed an E545K mutation in PIK3CA, the catalytic subunit of phosphatidylinositol 3 kinase PIK3 [112]. Unlike BRAF mutant melanoma, the activation of the MAPK pathway in NRAS mutant melanoma is achieved by activating the NRAS effector C-RAF instead of BRAF. It has been confirmed that S6 is the intersection between the MAPK and PI3K pathways. At the same time, S6 phosphorylation mainly depends on S6K1 [113]. Since PIK3CA-E545K increases S6K1 and S6 phosphorylation in the AKT/mTOR pathway, resulting in resistance to MEK inhibition [112].

CDK4/6 is another important drug inhibition point in NRAS mutant melanoma, increased CDK4/6 activity can lead to early G1-S cell cycle transition and promote the progression of melanoma [114]. RB is an oncosuppressor whose primary function, is to repress the transcription of genes required for the S-phase entry, preventing the unscheduled progression through the cell cycle. RB inhibits the transcription factors of the E2F family, which regulate genes involved in cell cycle control and mitotic progression [115]. After long-term treatment with CD4/6 inhibitors, cancer cells respond to inhibitory stress and re-enter the cell cycle. At the same time, the level of cyclin D1 rises. During the early adaptation period of CDK4/6i, the activated cyclin D1 takes effect. Thereby inactivating RB through phosphorylation, inducing transcriptional E2F activity, promoting the cell cycle re-entry after CDK4/6i treatment and causing drug treatment failure [116-118] (Fig. 3).

Conjunctival intraepithelial neoplasia

Conjunctival intraepithelial neoplasia (CIN) includes a wide range of neoplastic intraepithelial changes ranging from dysplasia to full-thickness epithelial neoplasia or carcinoma *in situ*. Synonyms include mild, moderate and severe dysplasia, carcinoma *in situ*, ocular surface squamous neoplasia, intraepithelial epithelioma, and Bowenoid type of dyskeratosis [119].

Clinically, the lesions are sharply demarcated from surrounding normal epithelium and arise most typically at the corneal limbus, where corneal stem cells are located, with either or both conjunctival and corneal involvement. Most lesions are nonkeratinized, well-vascularized, pink, and have a raspberry-like configuration. The development is associated with ocular pigmentation, nonoffice and nonprofessional workers with a history of risk factors, such as sun exposure, fair skin, immunosuppression (organ transplant recipients),

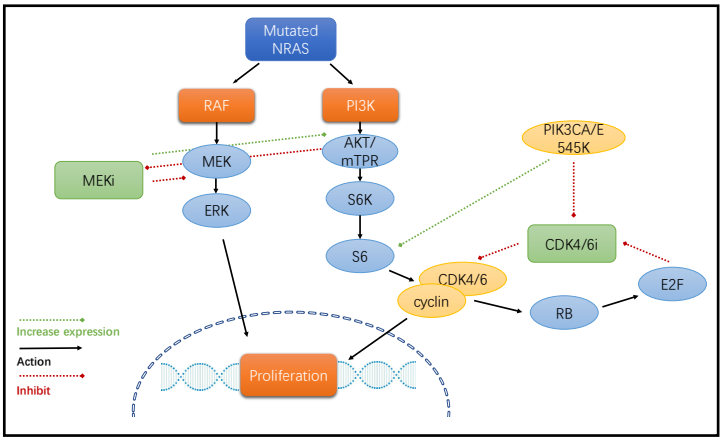

Fig. 3. NRAS mutated melanoma responds to inhibitors-targeted therapy.

and smoking [4]. In addition, there may be a correlation between OSSN and co-infection with HPV types 6 and 11 (38%), HPV type 16 (30 to 58%), HPV type 18 (50-57%), HIV, or matrix metalloproteinase upregulation [120-124].

Although surgical resection is widely used in the treatment of OSSN, adjuvant treatments, including cryotherapy and local chemotherapy, are usually given after resection due to the high recurrence rate. The local chemotherapy drugs used for OSSN are mitomycin C (MMC), 5-fluorouracil (5-FU), anti-vascular endothelial growth factor (anti-VEGF), and interferon (IFN-α-2b) [125-127]. In recent years, antiviral drugs like cidofovir and Retinoic acid (RA) have also been used in the local treatment of OSSN [128, 129]. Currently, some of the ocular anticancer drugs used in OSSN are cytotoxic and neither specific nor targeted to cancer cells. Toxicity to healthy ocular tissues is inevitable. The ocular surface where OSSN is located is particularly susceptible to chemical toxicity because it consists of rapidly proliferating cell populations in the corneal epithelium, conjunctiva, skin and eyelid follicles. Based on the studies, the toxic effects of current topical antineoplastic drugs for OSSN are listed below (Table 2) [130, 131]. The hindrance of local chemotherapy comes from its side effects. Side effects caused by chemotherapeutic drugs often lead to treatment interruption, so treatment fails.

Adjuvant radiotherapy

Since excessive surgical excision may lead to anatomical dysfunction and poor aesthetic outcome, radiotherapy (RT) is an attractive treatment option for invasive tumors [132]. But for the side-effect of RT, has been recently reported inducing nonrepairable DNA damage and may stimulate the activation of immune system pathways [133]. Research has reported that over half of BCC patients induce various grades of acute or late toxicity after adjuvant radiotherapy [134]. By summarizing the recent literature on ocular radiotherapy, Table 3 [135-137] shows the adverse events of the RT in periocular tumors.

Recurrence after radiotherapy is still a therapy failure we should focus on. It reported overall recurrence at 5 years after the RT is 13.8% in SCC and 15.8% in BCC [138, 139]. In BCC patients, it is a strong correlation between subtype and gene expression in recurrence after radiotherapy, the sclerosing subtype and the high expression levels of p53 and Bcl-2 are the risk factor for recurrence [139]. Even in a recent single-center retrospective study, women were more likely than men to have disease progression after RT, but because of the relatively small number of patients, it remains to be seen whether gender is a real risk factor [140]. And in SCC patients, differentiation in SCCs affects the local recurrence rate [132]. For radiation treatment of conjunctival melanoma reported to date, tumor thickness and unfavorable tumor location (≥T2) are risk factors for local recurrence and metastatic disease; therefore, higher T-stage levels are associated with the risk of recurrence and metastatic disease [141]. Tumor origin is also a reported risk factor, there is a significantly higher risk for metastatic disease and death in conjunctival melanoma arising de novo [141].

Table 2. Pharmacological and toxicological effects of different topical drugs used to treat OSSN

Drug	Pharmacological mechanism	Toxicological mechanism	Side effect
Mitomycin C (MMC)	Interferes with DNA replication and cell division by alkylating and crosslinking DNA	It generates superoxide and free radicals and has a long-term effect on normal and tumor cellular proliferation.	Conjunctival hyperemia; Corneal epithelial erosions; Limbal stem cells deficient
5-fluorouracil (5-FU)	Inhibition of thymidylate synthase and incorporation of its metabolites into RNA and DNA→Induces apoptosis in cancer cells in the epithelium while relatively sparing normal epithelium	Acts on rapidly dividing ocular surface epithelial cells →Decreasing the mitotic rate of corneal and conjunctival epithelial cells →Delayed healing of the corneal epithelium.	Toxic keratoconjunctivitis; Superficial keratitis; Conjunctival hyperemia; Ectropion; Lid edema; Erythema
Interferon (IFN)-α	Inhibiting cell proliferation→Downregulating oncogene expression →Inducing tumor suppressor genes enhancing the immune recognition of cancer cells and promoting the differentiation and activation of immune cells against cancer cells	Inhibitory effects on normal epithelial cell proliferation and its immune enhancing properties	Conjunctival hyperemia; Follicular conjunctivitis; Corneal epithelial toxicity
Cidofovir	HPV is related to the etiology of OSSN, the antiviral effect of cidofovir is effective in OSS cases related to HPV infection.	Cytotoxicity produces an anti-cellular response to adjacent tissues at the same time of treatment	Conjunctivitis; Punctual stenosis
Retinoic acid (RA)	Upregulating the expression of IFN-Stimulated genes and augmenting the antiproliferative activity of IFNs	The mechanism is not clear	Papillary conjunctivitis; Corneal epithelial Microcysts; Marginal keratitis; Blepharitis
Anti-vascular endothelial growth factor (anti-VEGF)	Regulating angiogenesis→Reduce angiogenesis to support tumor growth	Prevent corneal epithelial wound healing and damage innervation	Corneal epithelial defects; Neurotrophic keratopathy

Table 3. Toxicological effects of radiotherapy in periocular malignancies

Toxic site	Toxicity	Period of occurrence	Toxicological process
Lacrimal gland	Dry-eye syndrome; Lacrimal duct stenosis	(Acute) During a course of ocular RT (Late) 4-11 years	Lacrimal gland toxicity/Blepharitis - Reduction of the tear film lipid layer stenosis of the lacrimal Puncta/ Canaliculi/ Nasolacrimal ducts – Secondary dry eye
Eyelashes/Eyelid	Dermatitis; Eyelid malposition; Trichiasis; Epilation; Skin erythema; Madarosis; Wound healing delay	(Acute) During a course of ocular RT (Late) 4-11 years	Cutaneous telangiectasis and atrophy – Fibrosis/ Cicatrization - Lid deformity - Ectropion/ Entropion Regrowth of eyelashes – Trichiasis/ Distichiasis
Iris	Iritis; Neovascular glaucoma	-	Iris atrophy - Neovascular glaucoma Recurrent inflammation - Fibrin, keratic precipitates, synechiae
Ocular surface	Acute conjunctivitis; Keratitis; Edema; Stromal ulceration	(Acute) 6-8 weeks (Late) 9-10 months	Lacrimal gland toxicity/Blepharitis - Chronic corneal abrasion -Corneal vascularization/ Corneal opacification Conjunctiva scar – Symblepharon - Restriction of ocular movements
Lens	Cataract	36.0 months	Damage to the germinative zone of the lens epithelium/ Disruption of membrane channels, protein crosslinks, ion pumps-cell death - Compensatory mitosis/ Generation of "Wedl" cells – Lens opacity
Retinopathy	Occlusive micro-angiopathy; Retinal neovascularization	18.0-24.0months	Endothelial cell loss/capillary closure - Hypoxic changes - Persistent ischemia in the retina – Neovascularization - Intraocular Hemorrhage
Optic	Optic Neuropathy (RION)	18.0months-3 years	Optic nerve radiation-related vasculopathy and neuroglial cell degeneration- Dose-dependent endothelial cell loss Vascular inflammation/ hyalinization/ Vessel wall fibrosis-Obliterative endarteritis –Infarction/Areas of necrosis Somatic mutations in glial cells – Demyelination/ Neuronal degeneration

Meanwhile, a retrospective study of 100 patients with eyelid sebaceous carcinoma showed that T categories (≥T2) and tumor size (>2 mm) were associated with an increased risk of local recurrence, lymph node metastasis, and distant metastasis after radiotherapy [142].

Conclusion

Considering that recurrent malignancies are more aggressive and express higher metastatic potential, patients with eyelid and ocular surface malignancies require postoperative regular tumor long-term follow-up. The frequency and duration of follow-up depend on the type of malignancy. A minimum of 5 years of follow-up is recommended for primary BCC or recurrent BCC of the scleroderma subtype, as well as SebCa, MCC, and SCC [5].

The complex mechanisms of recurrence and metastasis make it difficult to develop effective, safe and cost-effective therapies as well as convenient surveillance strategies for ocular malignancies. Given the recommendations in the regulation of uveal melanoma, we also advocate a data-driven surveillance program in eyelid and ocular surface malignancies with the ultimate goal of enrolling patients with oligometastatic and advanced disease in clinical trials to help develop effective regulatory and therapeutic approaches [143].

Meanwhile, to summarize the treatment of malignant eyelid and ocular surface tumors, single surgical treatment has a high recurrence rate. In contrast, recurrent malignant tumors are often associated with aggressive and multiple metastases. Local adjuvant therapy and systemic chemotherapy are essential. The side effects of local adjuvant therapy are also the reason that the current treatment interruption cannot be ignored. The response and outcome of systemic chemotherapy depends on multiple redundant and diverse biological processes and molecular mechanisms that affect the sensitivity of cancer cells to chemotherapeutic agents. There is a need to develop novel targeted cancer therapies that target cellular resistance, particularly "pivotal" genes. Understanding this multidimensional process of resistance mechanism in eyelid and ocular surface tumors, identifying and linking signaling cascades and regulatory genes involved, may pave the way for advanced molecular diagnostics, developing minimally invasive interventions, and the use of progenitor/stem cell and even regenerative therapy.

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Author Contributions

(I) Conception and design: Xiaojun Ju, Ludwig M. Heindl; (II) Administrative support: Ludwig M. Heindl; (III) Provision of study materials: Ludwig M. Heindl, Alexander C. Rokohl, Xiaojun Ju; (IV) Collection and assembly of data: Alexander C. Rokohl, Xiaojun Ju, Wanlin Fan; (V) Data analysis and interpretation: Ludwig M. Heindl, Vinodh Kakkassery, Xiaojun Ju; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Statement of Ethics

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure Statement

The authors have no conflicts of interest to declare.

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