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Therapy options for ocular basal cell carcinoma — possibilities and limitations

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ABSTRACT

Basal cell carcinoma (BCC) stands as one of the most prevalent malignant epithelial skin tumors worldwide, and it is characterized by diverse clinical forms with locally destructive growth and a high recurrence rate. Usually, this type of cancer is more common in individuals over the age of 60. Therefore, the current study discusses contemporary approaches to treating basal cell carcinoma, highlighting the advantages and disadvantages of potential therapeutic options.

KEY WORDS: basal cell carcinoma; subtypes; therapeutic options; Hedgehog pathway inhibitors; drug resistance

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INTRODUCTION

Epidemiology

Basal cell carcinoma (BCC) stands as one of the most prevalent malignant epithelial skin tumors and the most common type of cancer in the United States of America and Australia [1–5]. In Germany, the yearly incidence is estimated at around 200 cases per 100,000 individuals [2, 6]. In Sweden, it was 405 cases per 100,000 in 2017, rising from 308 per 100,000 individuals in 2004 [7]. In the analysis of the malignant skin tumors incidence between 2011–2018 in Russia, rate increased from 309.9 to 333.0 per 100,000 individuals. The average incidence rate in several regions of Russia was as high as 418.5 per 100,000 individuals. About 70% of these cases were BCCs [8]. In 2011 in Poland 11,439 new cases of skin cancers were registered [9]. BCC accounted for nearly 80% of these cases [10, 11]. It is estimated that approximately 110,000 adults developed BCC for the first time in 2011 alone in the United Kingdom [12, 13].

Risk factors

The emergence of BCC is influenced by a combination of environmental factors and individual characteristics, wherein exposure to ultraviolet radiation (UV) and genetics (the aberrant activation of the Hedgehog signaling pathway) are significant contributors. The primary risk factor for BCC is intermittent intense exposure to UV, although the relationship is more intricate compared to conditions such as cutaneous squamous cell carcinoma (SCC), where the risk increase correlates directly with cumulative exposure to this type of radiation. Short-wavelength UVB radiation (290–320 nm) plays a more important role than long-wavelength UVA radiation (320–400 nm). UVB radiation not only harms DNA and its repair mechanisms but

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also disrupts the immune system, leading to gradual genetic changes responsible for the formation of BCC. The augmented risk from UV radiation is additionally influenced by factors like long-term sunlight exposure, the occurrence of sunburns, a family history of other skin cancers, immunosuppression, and age. Typically, this cancer occurs more frequently in individuals over the age of 60, but recent years have witnessed a rise in incidence, particularly among younger people under 40 [3, 6, 14]. The mentioned information highlights the necessity for enhancing preventive screenings to promptly detect and provide suitable treatment for skin cancer. While both genders can be affected, men exhibit a slightly higher susceptibility to BCC [2].

Basal cell carcinoma

BCC is a slowly developing malignant epithelial tumor with diverse clinical forms. More than 75% of BCC occur in the head skin, primarily found in aesthetically significant areas such as the face and neck region. Approximately 20% of BBC appear in periocular region. It is the most common malignant eyelid tumor, and it accounts for about 85–90 % of all malignant eyelid tumors [15]. It is most frequently found in the area of the lower eyelid and medial canthus, less frequently in the area of the upper eyelid and the lateral canthus (Fig. 1) [14, 16]. Reviewing patient history, assessing clinical symptoms, and conducting a thorough examination (including inspection, palpation, and slit-lamp examination), typically enable making a working diagnosis. Numerous clinical subtypes of BCC have been detailed in the literature. Nevertheless, confirming the clinical diagnosis requires histopathological validation and identification of the specific histopathological type (Fig. 2, 3).

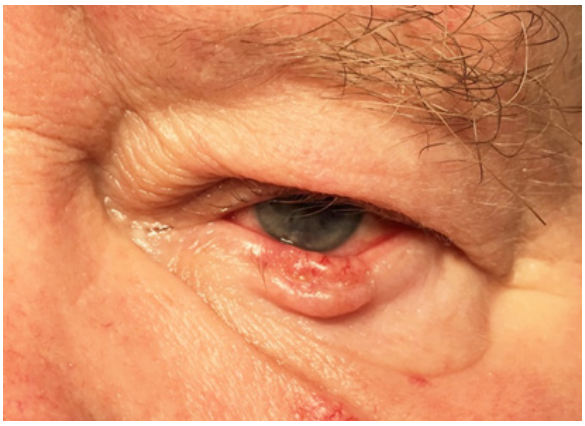

FIGURE 1. Nodular basal cell carcinoma (BCC) of the lower lid. More than 50% of the BCCs occur on the lower eyelid, 30% on the medial canthus, 15% on the upper lid and 5% on the lateral canthus [16]

Various subtypes of BCCs

The basic histopathological types of BCC include nodular, superficial, and sclerosing BCC [17]:

Nodular BCC, which upon progression may develop a central ulceration (nodulocerative basal cell carcinoma or rodent ulcer) (Fig. 2).

Superficial BCC forms as tiny clusters or lobules of malignant basaloid cells with outer palisading, situated in the upper dermis, connected to the epidermis, surrounded by a myxoid stroma, and accompanied by a lichenoid, band-like inflammatory infiltrate. They can contain micronodular, nodular, or infiltrating components (Fig. 3).

Sclerosing/fibrosing (morpheaform) BCC, which proves challenging to differentiate from surrounding tissue and tends to be more extensive upon palpation than visual inspection. Due to its aggressive invasion into deeper tissue layers and its tongue-like growth, which makes histological de-

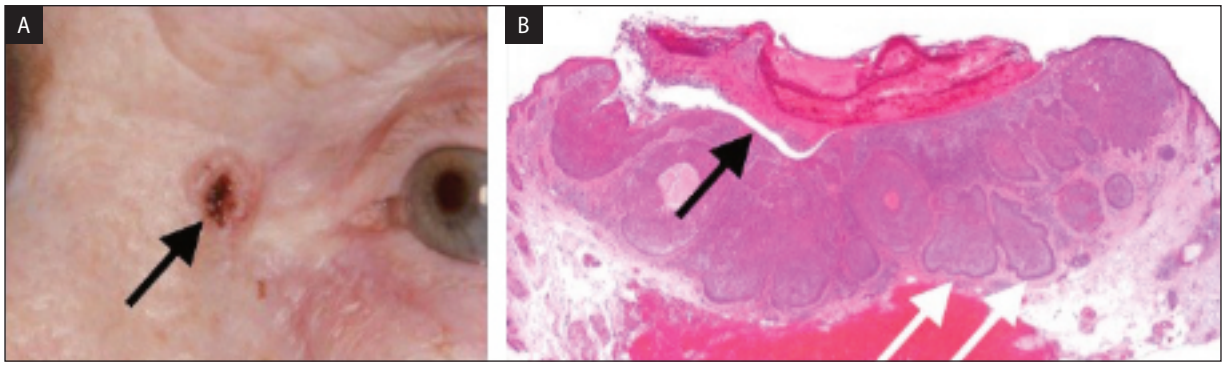

FIGURE 2A. Clinical image of a nodular basal cell carcinoma (BCC) in the medial corner of the eyelid with central ulceration surrounded by a marginal ridge (arrow); **B.** The histopathological image shows central ulceration with cell detritus (black arrow) and compact nests of tumor cells with characteristic peripheral palisading (white arrows) [2, 20]

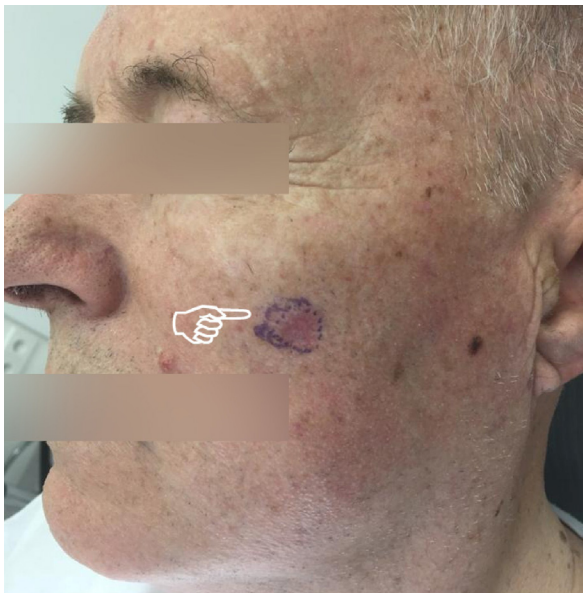

FIGURE 3. Clinical image of a superficial basal cell carcinoma (BCC)

marcation challenging, morpheaform basal cell carcinoma has a higher rate of residual positive margins after excision, and a higher risk of recurrence compared to nodular basal cell carcinoma (Fig. 4) [1, 2].

SELECTED THERAPY OPTIONS FOR BCC — POSSIBILITIES AND LIMITATIONS

Various therapeutic strategies are accessible for managing BCC. Choosing the right strategy is based on extent of disease, recurrence rate, importance of tissue preservation, cosmetic outcomes and patient's preference. The goal of treatment of BCC is to ensure the complete removal of the tumor mass while preserving both functional and cosmetic aspects, ultimately yielding optimal outcomes for the patient.

Surgery

Most commonly the first line treatment of the periocular BCC involves a thorough surgical removal including both: a) wide surgical excision followed by postoperative pathologic evaluation of margins, and b) Mohs micrographic surgery with comprehensive intraoperative margin control (frozen section margin control) [18, 19]. Complete surgical tumor excision (R0) followed with histopathological assessment of the tumor margins still represents the gold standard [20]. Determining a safety margin for periocular BCC is challenging as each millimeter of healthy tissue holds significance for subsequent functional reconstruction. Therefore, intraoperative margin control involves assessing the tumor and its borders before reconstruction. Mohs micrographic surgery is the least invasive surgical technique, involving systematic microscopic examination of tissue samples taken directly from the patient, and it enables evaluation of the entire excision margin during the surgical procedure [18–20]. Tissue is progressively excised following a specific pattern until the tumor's presence is no longer detected. The excised tissue is subjected to freezing, sectioning, and subsequent microscopic examination. This surgical technique may involve multiple successive cycles, and ensures a 96–98% cure rate for primary BCC and a 90–94% cure rate for recurrent BCC. Due

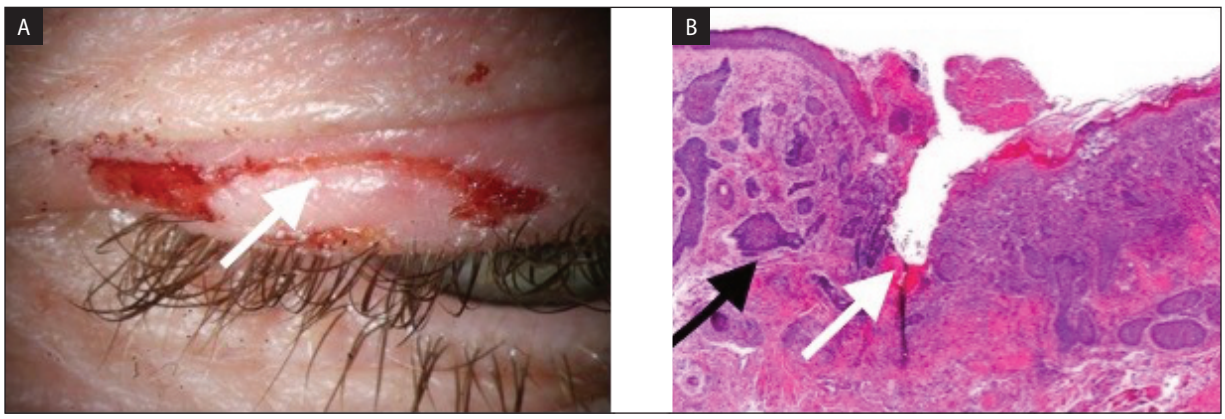

FIGURE 4. **A.** Clinical image of sclerosing basal cell carcinoma (BCC) with local extensive skin erosion (arrow) in the right upper eyelid in a 50-year-old female patient; **B.** Corresponding histopathological image shows ulceration of the skin (white arrow, consistent with skin erosion in the clinical picture) with marked accompanying inflammation surrounded by multiple disseminated tumor cell islands (black arrow) that infiltrate the surrounding tissue in a cone-like extension [2, 20]

to its considerable cost and time requirements this technique is particularly useful for addressing tumors located in aesthetically significant areas, like periocular region, as well as in morpheaform, infiltrative and recurrent BCC cases [15, 18, 19, 21, 22]. Histopathological analysis is crucial to confirm the diagnosis, assess the resection status and identify infiltrative subtypes, influencing postoperative follow-up care and prognosis. Subsequent to surgery, the recurrence rate is estimated at 1–5% annually. Recurrent, large, and infiltrative tumors affecting the orbit and intracranial region, as well as metastatic tumors, frequently require alternative therapeutic approaches (combination of non-surgical therapeutic options including adjuvant radiation therapy, chemotherapy, and targeted therapies) [23–25].

Radiation therapy

Radiation therapy (RT) is not exclusively used as an adjuvant therapy. Factors such as patient preference or surgery contraindications may influence the decision to opt for RT as the initial therapeutic strategy [26]. When making such a decision, it is important to take into account the studies showing that more than 50% of patients with BCC experience varying degrees of acute or late toxicity after RT [27]. RT has been documented to yield low recurrence rates for both primary BCC (7.4%) and recurrent BCC (9.5%) [28]. The 5-year recurrence rate after RT for all patients with BCC estimated by Zagrodnik et al. was 15.8%. Additionally, the studies they conducted demonstrated a strong correlation between recurrence rate and histopathological subtype. Successively, for patients with the nodular subtype the recurrence rate was 8.2%; for patients with the superficial subtype it reached 26.1%, and for patients with the sclerosing subtype it amounted to 27.7%. The sclerosing (morpheaform) subtype of BCC with high levels of p53 and low levels of Bcl-2 expression was a risk factor for recurrence after radiotherapy [29]. This subtype, which is considered to be more aggressive, occurs significantly more often in irradiated patients [30]. Factors like the clinical picture, the corresponding histopathological subtype of the tumor, and the biology of BCC play a crucial role in choosing the appropriate therapeutic strategy.

When left without treatment, BCC can become locally destructive to the point where surgical resection may be impractical, due to the tumor's considerable size or its proximity to critical or functionally important anatomical structures (significant local damage leading to disfigurement affecting extensive areas of soft tissue, cartilage, and bone) (Fig. 5). Additionally, in such cases RT might be ineffective. Until recently, there were limited options for the treatment of locally advanced BCC, infiltrative BCC and metastatic BCC. Metastasized BCC is typically linked with a more aggressive subtype of the original tumor, leading to an overall prognosis that is generally less favourable than that of the primary tumor [31]. Although metastasis of BCC is very rare, occurring in approximately 0.003% to 0.1% of cases, on January 30, 2012, the FDA granted approval to vismodegib, a small molecule inhibitor targeting the Smoothened receptor (SMO) in the Hedgehog pathway, for the management of locally advanced or metastatic BCC [32]. The approval was granted following the findings of a phase II clinical trial (ERIVANCE), which demonstrated positive responses in 43% of patients with locally advanced BCC and in 30% of individuals with metastatic BCC. The median duration of response was 7.6 months in both groups [33]. This modern therapeutical approach provides another option for treating advanced, infiltrative and metastatic BCC

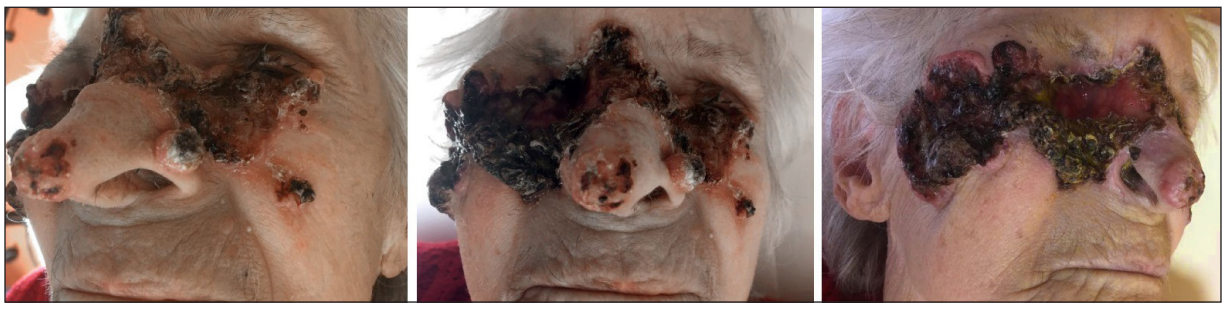

FIGURE 5. Clinical image of an elderly patient with an untreated basal cell carcinoma (BCC), whose dimensions precluded local management approaches

when surgical and radiotherapeutic treatment options have been exhausted.

Hedgehog pathway inhibitor

The Hedgehog pathway is a crucial event in the pathogenesis of BCCs, and it is documented to be activated by the PTCH1 gene. This gen is located on human chromosome 9q22. PTCH1 encodes a transmembrane protein that negatively regulates smooth muscle (SMO, transmembrane protein of the Hedgehog pathway) [34–36].

The mechanism of PTCH1 is binding to an extracellular ligand, such as sonic Hedgehog (SHH), subsequently releasing the negative control on SMO. SMO then translocates within the cilia (composed of over 300 proteins that must work together for proper Hedgehog pathway signaling), initiating the activation of the Gli transcription factor [37, 38]. Many of the genes regulated by Gli proteins are co-opted by cancer cells, because they regulate many diverse cancer-related processes like proliferation, migration and neovascularization [35, 39]. Mutations in the Hedgehog pathway are seen as pivotal events in the development of BCCs. Targeting the inactivation of the Hedgehog pathway has been a crucial focus for treating challenging cases of BCC [23]. At present, there are two targeted therapies for the inhibition of the Hedgehog pathway: vismodegib and sonidegib. These therapies, although possessing distinct pharmacokinetics, both target the same molecular component, SMO [40]. Vismodegib and sonidegib are becoming increasingly crucial in adjuvant therapy. Alopecia, muscle spasms, fatigue, dysgeusia, weight loss are among the adverse events of therapy. In contrast to vismodegib, sonidegib exhibits more severe and increasingly common side effects, such as elevated creatine kinase levels [36, 41]. These side effects are associated with the pharmacological actions of SMO inhibitors. Even at lower concentrations, treatment-related adverse events may result in discontinuation of therapy for many patients [42]. Another barrier in the treatment with Hedgehog pathway inhibitors is the development of drug resistance, leading to lack of response and disease progression [39]. In a documented case of recurrent periocular BCC at an advanced stage, the tumor showed regression within 3 months of vismodegib therapy. However, a recurrence occurred after 9 months, leading to the ultimate treatment of orbital exenteration for the patient. The reason was the resistance to vismodegib [43]. In a published case series, regrowth of at least one tumor in 21% of patients with advanced BCCs after a mean of 56 weeks was noted. These data confirmed that long-term efficacy is often limited by the development of cancer-acquired drug resistance [44].

An Investigator-Initiated Open-Label Trial of sonidegib in advanced BCC demonstrated that sonidegib was less effective than vismodegib [45].

Although the resistance mechanism remains unclear, studies conducted on animal models suggest that it may be related to point mutations in SMO [35]. In a case series of patients treated with vismodegib in advanced BCC, primary resistance occured in 50%, and secondary resistance in 20% of patients [44, 46].

Pricl et al. present for the first time clinical, molecular and in silico evidence of primary and acquired SMO mutation-mediated resistance to vismodegib in BCC [47].

Mutation in SMO G497W, located in the most frequently mutated SMO region (exon 8e10) in BCC, leads to primary drug resistance. Consequently, a conformational rearrangement of the entire region of the protein occurs, which ultimately may lead to a partial blocking of the drug's entry site into the protein. Such partial obstruction can lead to a significant reduction in the concentration of active vismodegib at the SMO G497W binding site [48]. Mutations in PTCH1 and SMO D473Y in BCC after treatment lead to secondary drug resistance. These mutations result in a conformational rearrangement of the entire region of the protein, which ultimately may lead to making the drug's entry into the protein more difficult (Fig. 6) [48]. Amplification of Gli genes allows tumors to escape SMO inhibition, leading to a switch from the Hedgehog pathway to Ras/MAPK pathway. Kuonen et al. brought experimental evidence for the role of primary cilia as crucial regulators of the antagonistic Hedgehog signaling pathway and Ras/MAPK pathways, thereby opening perspectives for the treatment of advanced resistant BCC [48].

CONCLUSIONS

Nonsurgical forms of treatment are becoming increasingly popular for periocular malignancies. Nevertheless, surgical treatment remains the gold standard.

Because until the beginning of 21. century there was no effective therapy for locally advanced, infil-

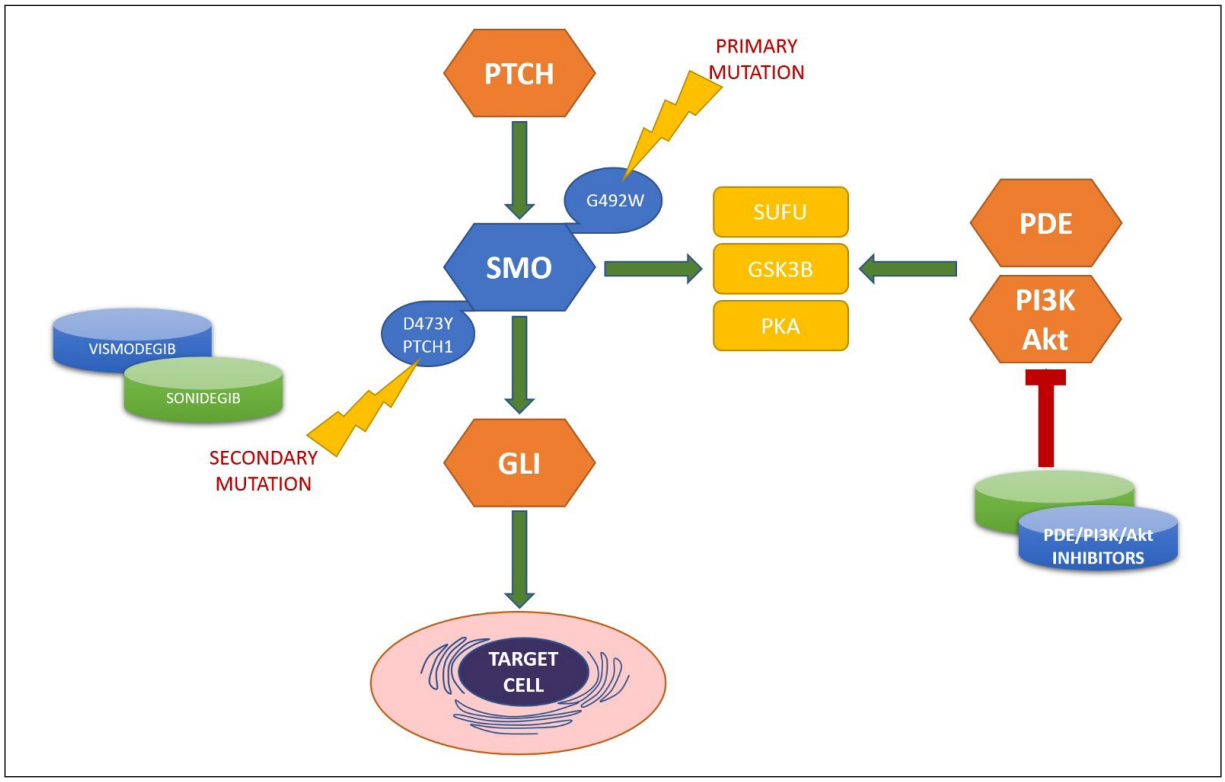

FIGURE 6. Hedgehog pathway inhibitors (HPI), such as Vismodegib and Sonidegib, are used in surgically advanced tumors as neoadjuvant therapy, prior to Mohs micrographic surgery or radiotherapy, allowing the tumor to decrease in size. Site of action and inhibition of different HPI. Patched, PTCH. PTCH1, a member of the patched gene family and the receptor for sonic Hedgehog (SHH). The PTCH1 gene product, is a transmembrane protein that suppresses the release of smoothened protein (SMO). When SHH binds PTCH1, SMO is released and signals cell proliferation. SUFU — suppressor of the fused protein; GSK3B — glycogen synthetase kinase 3B; PKA — protein kinase A; GLI — transcription factor GLI; PDE — cyclin nucleotide phosphodiesterase; PI3K/Akt — phosphoinositide 3 kinase

trative or metastatic BCC, two new drugs (vismodegib and sonidegib) have been developed to inhibit Hedgehog signaling pathway acting on SMO. They can be used as an adjuvant therapy, or in certain cases as a prior medical treatment for periocular and orbital BCC.

Understanding the complex process of drug resistance mechanisms in periocular and ocular tumors, identifying and linking signaling cascades and regulatory genes involved in it may open the way to developing new therapeutic strategies for treating BCCs. The development of innovative therapies enabling body's own regenerative processes, such as stem cell utilization, may also be a way to improve postsurgical wound healing and tissue regeneration in general. Further research is needed to explore alternative treatment options for patients for whom surgical intervention due to basal cell carcinoma (BCC) is contraindicated. Such research should also evaluate the systemic immune response, as well as the potential effect of such drugs in the treatment of other cancers.

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Conflict of interests
Authors declare no conflict of inetersts.

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