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Review

Advances in Pathogenesis and Non-surgical Therapy of Cutaneous Basal Cell Carcinoma

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ABSTRACT

Basal cell carcinoma (BCC) is a low-grade malignant skin tumor originating from basal cells, which is closely related to UV radiation and tends to occur on the face. Fortunately, most of the tumors are localized and easily amenable to surgical resection. However, for those patients with specific areas of skin lesions and locally advanced as well as, in rare cases, metastatic BCC may pose a therapeutic challenge. Therefore, non-surgical treatment is needed as an important supplement or even the preferred option. In this review, we will outline the currently known pathogenesis and non-surgical therapy of BCC. With our understanding of the molecular basis of BCC, emerging targeted therapeutics such as Hedgehog pathway inhibitors, photodynamic therapy, and combined therapy are offering new avenues for the non-surgical treatment of BCC.

Keywords: Basal cell carcinoma, pathogenesis, therapy

INTRODUCTION

Basal cell carcinoma (BCC), also known as basal cell epithelioma, is the most common nonmelanoma skin cancer, accounting for 80% of cases.[1] A slowly growing tumor, BCC seldom metastasizes and has a benign evaluation, although some high-risk variants of BCC can lead to deadly results.[2] Currently, the preferred treatment plan for BCC is complete surgical resection. However, some patients are not suitable for this treatment due to age, health state, location of lesions, lesion generalization, and uncommon metastatic BCC, which can cause gradual disfigurement or even death. In recent years, many non-surgical treatments have emerged with further understanding of the pathogenesis of BCC. In this article, we discuss a brief overview of non-surgical therapies for BCC as well as emerging targeted therapeutics such as Hedgehog pathway inhibitors and immune modulators. These therapeutics have the potential to revolutionize the treatment of this common and important skin cancer.

THE PATHOGENESIS OF BCC

Hedgehog signaling pathway

During early embryonic development, the Hedgehog (HH) signaling pathway contributes to the formation of the neural tube, musculoskeletal system, hematopoietic cells, teeth, and skin. The mammalian Hedgehog family includes the Sonic Hedgehog (SHH), India Hedgehog (IHH), and Desert Hedgehog (DHH). IHH regulates chondrogenic differentiation and DHH is important for spermatogenesis and development of the neural fasciculus of peripheral nerves. Within the skin, the SHH pathway is primarily responsible for stem cell maintenance and controlling the development of hair follicles and sebaceous glands.[3] It has

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been suggested that BCC originates from stem cells permanently settled in the parietal epidermis and upper part of the hair follicle funnel.[4] Both in nevus-like basal cell carcinoma syndrome (NBCCS) or in sporadic basal cell carcinoma, aberrant activation of the SHH pathway plays a key role in tumor initiation, progression, and recurrence. Sonic Hedgehog ligands, patched 1 (PTCH1), smoothened (SMO), and GLI (glioma associated oncogene protein) are the key components of this pathway. Normally, PTCH1 acts as a regulatory molecule, reducing HH signaling by inhibiting the translocation of SMO cilia. When SHH ligand binds to PTCH1, the PTCH1-SHH complex is degraded by lysosomes which de-represses SMO, upregulating the downstream signaling cascade via several proteins, including SUFU (suppressor of fused). This ultimately leads to the release of GLI protein family members such as GLI1 (glioma associated oncogene protein-1). The GLI1 translocates to the cell nucleus and triggers the transcription of HH-dependent target genes, leading to the development of BCC.[5] Some studies have found that, somatic PTCH1 mutations can occur upto 75% of the time. It is generally well-established that heterozygous germline deletion of the PTCH1 molecular mechanism leads to NBCCS/Gorlin syndrome. Shift mutations in PTCH2 can also lead to NBCCS.[6] In addition, activating SMO mutations have been reported in approximately 10% - 20% of BCCs, demonstrating that activating mutations in SMO can induce BCC by activating the HH signaling pathway.[7]

TP53

The second most frequent factor associated with BCC pathogenesis is the mutations of the *TP53* gene. The role of the vital tumor suppressor protein *p53*, encoded in the *TP53* gene, is involved in cell cycle arrest and activation of programmed death. Somatic mutations in *TP53* are common in BCC. A study has shown that *TP53* mutations were found in 17 of 42 BCCs (40%).[8] *P53* enhances apoptosis via repressing the *BCL2* and inhibiting SMO proteins in the HH pathway.[3,9] *TP53* can interact with and repress GLI though it is not a part of the Hedgehog pathway. Therefore, mutations in *TP53* further enhance Hedgehog signaling in BCC. In a mouse model studying BCC pathogenesis, *P53* loss increased SMO expression sensitizing epidermal keratinocytes to the oncogenic effects of PTCH1 deletion, which in turn led to the development of BCC.[10] In addition, *P53* could also enhance P21 protein function, inhibiting tumor formation.

DNA and histone methylation

Epigenetics plays a crucial role in transcriptional regulation. The expression of genes involved in essential cellular pathways can be altered by the aberrant epigenetic organization.[11] In addition to the *PTCH1* and *TP53*, data from both The Cancer Genome Atlas (TCGA)[12] and the Catalogue of Somatic Mutations in Cancer (COSMIC)[13] suggest that histone methyltransferases are also among the most commonly mutated genes. A recent study results showed an association between advanced BCC and the histone methyltransferase *EZH2*. They assessed the expression levels of *EZH2* in 30 less aggressive BCC subtypes and 30 more aggressive subtypes. *EZH2* expression was significantly higher in the more aggressive BCC than in the less aggressive BCC and was positively correlated with BCC aggressiveness.[14,15] This result suggests that *EZH2* could serve as a potential target for inhibiting BCC progression and that *EZH2*-associated epigenetic marker profiles could serve as histological markers of BCC aggressiveness.

Aberrant DNA methylation in association with abnormal gene expression is another hallmark of cancer. Brinkhuizen *et al.* tested the DNA methylation status, using MSP (methylation-specific polymerase) chain reaction, of 9 oncogenes and one oncogene promoter region in 112 BCC patients and 124 healthy controls. Results showed that SHH, adenomatous polyposis coli (*APC*), secreted frizzled-related protein 5 (*SFRP5*), and *RAS*-associated structural domain family 1 (*RASSF1*) genes were significantly hypermethylated in BCC.[16]

The Hippo-Yap signaling pathway

The Hippo pathway, which plays an essential role in tissue growth restriction, consists of a series of kinases. Dysfunctional regulation of the Hippo-Yap pathway has been reported in BCC from RNA sequencing research, with up-regulated YAP (Yes-associated protein) triggering proliferation of basal keratinocytes. *LATS1* gene encodes one of the kinases in the Hippo pathway. Premature stop mutations in these *LATS1* genes have been reported in 16% of BCC. Additionally, LATS2 gene (analog of *LATS*) mutations have been observed in 12% of tumors.[17]

MYCN/FBXW7 signaling

MYCN is a transcriptional activator, probably downstream of the HH pathway, involved in cell proliferation and differentiation.[17] Missense mutations have been detected in 30% of BCC, mainly within the MYC box1 region that interacts with *FBXW7*, a tumor suppressor, which triggers N-MYC ubiquitin degradation. But this is usually prevented by mutations in the box1 structural domain.[7]

TERT

The *TERT* gene encodes telomerase which is an enzyme that adds protective repeat sequences to telomeres.[18] Increasing

telomere length immortalizes cells, prevents aging and allows excessive cellular replication that are characteristic features of 90% of malignant tumors, including BCC.[19]

DPH3-OXNAD1 bidirectional promotor

Bidirectional promoters of the *DPH3* and *OXNAD1* genes are shown to be the common sites of somatic mutations in BCC, with Typical UV-signature mutations observed in most of the BCC samples.[20] The *DPH3* gene is required to produce diphthamide, a modified histidine residue in eukaryotic elongation factor 2 that helps maintain translation fidelity.[21]

Other possible driver genes

Other genes suggested as possible driver genes for BCC include *PPP6C*, *STK19*, *KRAS*, and *PIK3CA*. Additional genes found to be mutated at lower frequencies in BCC include *RB1*, *KNSTRN*, *CASP8*, *RAC1*, *ARID1A*, *CSMD1/2*, *PREX2*, *GRIN2A*, and *NOTCH1/2*.[7,22] Whether these genes are the primary drivers of BCC development or just secondary mutations remains unclear.

THERAPEUTICS FOR BCC

Therapeutic options currently available have been divided into Surgical treatments, Systemic Therapy, Topical Therapy, and Physical Therapy. Each method is elaborated here and Table 1 lists all the methods including their advantages and disadvantages.

Surgical treatments

The main surgical treatments include surgical excision and Mohs microsurgery (MMS). Surgical excision aims to resect tumors as completely as possible based on strict adherence to the contraindications and indications for surgery. Therefore, in addition to removing the periphery of the visible tumor border, standard surgery also requires the removal of a particular area of clinically uninvolved skin tissue. Since BCC occurs mainly on the head and face, excizing excessive skin tissue hinders repair of skin defects and negatively affects the patient's appearance.[23]

MMS is used to define the degree of tumor infiltration and microscopic resection. It is not appropriate for locally advanced and metastatic BCC or eyelid BCC due to the orbital soft tissues, even though it guarantees that no tumor cells remain at the cut edge and maximizes the preservation of normal tissues. Intraoperative frozen sections are prone to false-negative results and do not ensure clean tumor resection, locally advanced and metastatic BCC requires radiation therapy or systemic therapy.[24] Recently, a Meta-analysis involving all the therapeutic options for BCC showed a recurrence rate of 3.2% at 5 years in patients treated with MMS and 5.2% with Surgical excision.[25] Surgical resection is highly invasive, especially when a local flap or implant reconstruction is recommended. Moreover, it tends to leave scars, cause hyperpigmentation and hypopigmentation, and cannot achieve the desired cosmetic results. As for small primary BCC of the trunk or extremities lacking invasive clinical or histopathological features, MMS is not indicated because other procedures have similar efficacy, whereas MMS is time-consuming, expensive, and requires higher equipment requirements.[26]

Systemic therapy

Prior treatment modalities emphasized on platinum-based therapies. Single or combination platinum-containing agents are effective in advanced BCC. Case reports of patients with BCC have shown responses to the combination of platinum-containing agents such as cisplatin and paclitaxel, cisplatin and vincristine, cisplatin and cyclophosphamide, carboplatin and paclitaxel.[27,28] In cisplatin-based treatment, the overall response rates of metastatic BCC are as high as 77%.[27] However, most patients eventually relapse and die because of this disease. Thus, some emerging small-molecule inhibitors that showed good efficacy and high security have been the focus of recent therapeutic advancements. In the following portion, we make an introduction about them in detail.[29]

Hedgehog signaling pathway inhibitors

Hedgehog signaling pathway inhibitors can effectively target the treatment of locally advanced BCC and metastatic BCC, especially small molecule-targeted SMO inhibitors, which reflect better anti-BCC effects.

Small molecule-targeted SMO inhibitors

Vismodegib and Sonidegib are currently approved for the treatment of BCC, while BMS-833923, LY2940680, Saridegib, and TAK-441 are still in clinical development.[30] Vismodegib is a small molecule drug that binds to SMO and inhibits its activity, thereby inhibiting the *GLI2* transcription factor and therefore blocking the expression of the HH signaling pathway, making it effective for the treatment of BCC. In phase III clinical study of Vismodegib in BCC,150 mg orally once daily for 28 d as a treatment cycle, in 482 patients who met the criteria for efficacy evaluation in solid tumors, 155 patients (32%) showed a complete response, 158 patients (33%) had a partial response and 128 patients (27%) with stable disease. It is shown that Vismodegib could be a novel treatment option for locally invasive and metastatic BCC.[31] According to another study by Tang *et al.* who divided 41 patients with NBCS into two groups, Vismodegib group and placebo group, Vismodegib resulted

in tumor shrinkage of BCC in NBCS and suppression of neoplastic BCC at the same time.[32]

Sonidegib has been approved by both the EMA and FDA for patients who experienced a relapse after surgery or radiation therapy for locally advanced BCC or were not candidates for these treatments.[33] In a multicenter, randomized, double-blind phase II trial, 230 subjects were randomized into Sonidegib 200 mg group (i.e., 79 on oral Sonidegib 200 mg daily) and the Sonidegib 800 mg group (i.e., 151 on oral Sonidegib 800 mg daily), of whom 194 were patients with locally advanced BCC and 36 were patients with metastatic BCC. Results showed that 43% of patients taking 200 mg orally and 38% of those taking 800 mg achieved an objective response, while the response rates in the metastatic BCC group were 15% and 17%, respectively.[34] Thus, compared to advanced BCC, the efficiency of Sonidegib was lower in metastatic BCC. In Phase I clinical study of Saridegib, similar results were observed.[35] Metastatic BCC cannot be treated as effectively as primary BCC due to a low *PTCH1* mutation and has a different phenotype and genotype. New therapeutic approaches are therefore needed to treat this disease.[36]

Small molecule-targeted SMO inhibitors have great promise for the treatment of BCC. But at the same time, some limitations exist as well. (I) Drug resistance. Most patients will develop resistance within a few months. (II) Metastatic BCC is relatively insensitive to Hedgehog inhibitors, and more new targets need to be identified. (III) Inhibition of the HH pathway by SMO may lead to the activation of another pathway and the creation of other tumors. In a study of 104 patients with advanced BCC treated with Vismodegib, squamous cell carcinoma occurred in 11% of patients, which may be related to this mechanism.[37] (IV) In some cases, adverse effects such as muscle spasms, rheumatic pain, alopecia, fatigue, and weight reduction may occur during treatment, which should be managed and prevented in the clinic.

Other Hedgehog signaling pathway inhibitors

Pathway inhibitors that target the SMO protein are being developed and used in the clinic. In spite of this, the development of resistance caused by point mutations in SMO limits the therapeutic application of SMO inhibitors. Moreover, different mechanisms exist which activate HH signaling in cancer cells that bypass SMO. Therefore, identifying the HH inhibitors that modulate proteins as potential targets while avoiding the problem of resistance is of great interest. Studies have focused on antagonists of GLI1, a transcription factor downstream of the HH pathway. A recent study showed that Pipinib reduces the incidence of disease by selectively inhibiting phosphatidylinositol 4-kinase IIIβ (PI4KB) and suppressing GLI-mediated transcription and expression of the HH target genes, PTCH1 and GLI1, by blocking SMO localization to cilia. Thus, inhibition of PI4KB followed by a reduction in phosphatidyl-4-phosphate levels could serve as an alternative approach to inhibit SMO function and HH signaling.[38]

Inhibition of the downstream effector GLI by arsenic trioxide and the antifungal drug itraconazole is also considered a weak HH pathway inhibitor. An open-label, exploratory phase II trial of oral itraconazole for the treatment of BCC by Kim *et al.* Found that itraconazole reduced cell proliferation by 45%, HH pathway activity by 65%, and tumor area by 24%. Another study reported the application of standard-dose or reduced dose of Vismodegib (150 mg, 1-2 times a week) in combination with itraconazole for 2 cases of recurrent facial BCC, both showing clinical remission after 16 months of follow-up.[39] Further, combination therapy may reduce the dose of HH pathway inhibitors and reduce adverse effects, which are still being explored.[40] A preliminary study of five patients with metastatic BCC treated with the combination of arsenic trioxide and itraconazole showed a reduction in GLI1 mRNA levels by 75% from baseline after 3 months of treatment. However, there was no significant reduction in tumor size.[41] In addition, Sohn *et al.* showed results from a trial of topical itraconazole for basal cell nevus syndrome that, at the maximum soluble concentration of 0.7%, itraconazole gel did not reduce GLI1 mRNA levels or the size of BCC tumors. Nevertheless, this trial did not rule out that other formulations of itraconazole at higher concentrations could be more effective. Therefore, the efficacy of topical itraconazole in BCC needs to be further investigated.[42]

Programmed cell death receptor 1 (PD-1) inhibitor

Another potential target for the treatment of BCC is immunotherapy since skin immune cells have an anti-tumor effect, and PD-1 is an immune checkpoint receptor located on lymphocytes, which, when activated by PD-1 ligands, triggers downregulation of immune function, leading to a decrease in immune tolerance. Markers predicting the effectiveness of PD-1 inhibitor therapy include programmed death factor ligand-1 (PD-L1) amplification in tumor cells and high tumor mutational burden (TMB), both of which are met in BCC. BCC has one of the highest mutational burdens of any human malignancy. In general, tumors with a high mutational burden are more responsive to PD-1 blockade.[43] Cemiplimab is a monoclonal antibody drug against the PD-1 target monoclonal antibody drug.[44] In an open-label, multi-center, single-arm, phase 2 trial, 84 patients with a

histologically confirmed diagnosis of locally advanced basal cell carcinoma (Intolerant to previous HHI therapy or having no better than stable disease after 9 months on HHI therapy) were treated with intravenous infusions of Cemiplimab 350 mg over 30 minutes every 3 weeks for up to 93 weeks or until progression or unacceptable toxicity. This study demonstrated the safety and effectiveness of Cemiplimab as systemic therapy for locally advanced BCC and is the first immunotherapy drug for patients with locally advanced BCC after HHI therapy or for whom HHIs are not appropriate.[45] The recommended dose of Cemiplimab is 350 mg intravenously over 30 minutes every 3 weeks. Other PD-1 inhibitors, such as pembrolizumab, showed an objective response rate of 38% after 18 weeks in a study of 16 patients with advanced BCC.[46]

mTOR signaling pathway inhibitor

The mammalian target of rapamycin (mTOR) is a serine/threonine-protein kinase closely associated with cell growth, metabolism, and aging. It acts through two signaling complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). Studies have shown that the mTOR pathway is highly expressed in BCC.[47] HH signals crossed over mTOR via SOX9 and showed that the SOX9-mTOR axis is a target protein downstream of SMO that enhances tumor clearance in BCC patients.[48] Therefore, drugs targeting mTOR have a therapeutic effect on progressive BCC. For example, Everolimus (mTORC1 inhibitor), an immunosuppressive agent and a proliferation signal inhibitor, targets mTOR exhibits substantial anti-neoplastic activity, principally against BCCs. Oral daily dose of 1.5 - 3 mg for 12 weeks or longer induces partial to complete BCC regression.[49]

Topical therapy

Imiquimod

Imiquimod is a non-nucleoside heterocyclic amine drug, a small molecule immunomodulator that stimulates the body's immune system to recognize viral infections and tumors by inducing the body to produce cytokines such as IFN-α, TNF-α, and IL-12, ultimately eliminating the associated lesions.[50] Williams *et al.* conducted a randomized controlled study comparing standard surgical and imiquimod treatments. The absolute response rate for topical imiquimod was 83% at 5 years. Although clearly inferior to the 98% for excisional surgery, the cosmetic effect of imiquimod was outstanding compared to the surgical approach.[51] Karabulut *et al.* reported results from three patients treating large nodular BCC at the medial canthal area with 5% imiquimod cream, applied topically once daily, five times a week for 12 weeks, with no recurrence of the tumor at 3 years of follow-up after treatment.[52] Therefore, Imiquimod could serve as an alternative to surgical treatment in some specific sites.

5-fluorouracil

5-Fluorouracil (5-FU) is a pyrimidine analogue. The 5-FU metabolites get incorporated into DNA and RNA as faulty building blocks, thus inhibiting the activity of thymidylate synthase. These mechanisms lead to the inhibition of cell growth and apoptosis. Since these mechanisms are especially effective in tissues with high proliferation rates, there is a certain "bias" against malignant cells. The FDA has approved topical 5-FU for the treatment of superficial BCC and actinic keratoses. A study in 2013 assessing the effectiveness of photodynamic therapy compared with imiquimod or fluorouracil in patients with superficial BCC, showed that the treatment success rate of 72.8% for photodynamic, 80.1% for 5% fluorouracil, and 83.4% for imiquimod at 5 years.[53] In general, this trial demonstrated that from topical imiquimod could be a viable option for the treatment of superficial BCC.

Physical therapy

5-aminolevulinic acid photodynamic therapy

Photodynamic therapy uses visible light to activate photosensitizers 5-aminolevulinic acid or benzoporphyrin derivatives. These photosensitizers produce cytotoxic reactive oxygen species (ROS) through protoporphyrin IX, an intracellular reactive oxygen product, that gets activated by visible light after accumulation in the organelle cell membrane, leading to tumor cell damage and death. It also exerts its effects by indirectly destroying tumor blood vessels and triggering immune responses.[54,55] Expert consensus on the clinical application of 5-aminolevulinic acid photodynamic therapy (ALA-PDT) as a clinical treatment for superficial basal cell carcinoma and nodular basal cell carcinoma that is not deeply invasive (< 2 mm). Zou *et al.* performed a meta-analysis comparing the efficacy and recurrence rates of PDT and surgery in 596 cases of nodular BCC, observing that PDT and surgery were comparable in terms of complete remission rates, however, an increased cumulative probability of recurrence was found for PDT compared to surgery.[56] Liu *et al.* divided 80 BCC into 2 groups, the control group underwent surgery alone while the observation group was treated with ALA-PDT combined with surgery.[57] The 1-year recurrence rate for the combined therapy group was 0 which also demonstrated a better long-term efficacy. In conclusion, ALA-PDT provides the advantage of specifically eliminating tumor cells while causing less damage to adjacent normal tissues, with equivalent efficacy to surgical therapy and better cosmetic

results. However, combined therapy is recommended in clinical practice for improved treatment efficacy.[58]

Radiotherapy

Clinically, radiotherapy kills BCC tumors using superficial X-rays. Where surgical excision is not an option (medically/technically inoperable), radiotherapy offers an excellent alternative. Compared with surgical treatment, its advantages lie in killing tumor cells, preserving the shape and function of surrounding normal tissues without leaving scars, and having broad clinical application prospects. However, Radiotherapy may cause skin atrophy, capillary dilation, and depigmentation or pigmentation in the radiated field.[59] The 5-year cure rates according to a meta-analysis were 83% - 95% for radiation therapy.[60] Shan *et al.* treated 14 BCC patients with superficial X-rays, at a total dose of 45.6 - 53.2 Gy. The results showed that fourteen lesions in 14 patients disappeared, with no relapse after 2 years of follow-up. The main adverse effects were radiodermatitis and ulceration of the lesions, which disappeared within 1 month.[61] Superficial X-ray radiation therapy for BCC has a low recurrence rate, which is an ideal method for patients who are not suitable for surgical treatment. Furthermore, the efficacy of radiotherapy is linked to the extent of radiation and therefore the scope of radiotherapy should be strictly controlled. It is reported that small, low-risk BCC should be treated with a radiation field margin of 0.5 cm beyond the clinically apparent tumor, while high-risk BCC should be treated with a wider margin of 1 to 1.5 cm.[62] Therefore, radiotherapy boundaries should be evaluated and paid attention to prevent side effects. For patients with advanced, aggressive facial BCC, radiation therapy may be given priority. Radiation therapy is contraindicated in Gorlin-Goltz syndrome since it induces secondary tumors. Different radiotherapy techniques have been developed to date, such as external beam radiotherapy and superficial brachytherapy. The choice between them has to consider many factors: tumor size, location, and infiltration depth.[63]

Electrochemotherapy

Electrochemotherapy (ECT) is a technique used to ablate malignant tumors by temporarily permeabilizing cells after exposing them to a brief pulsed electric field in combination with low doses of chemotherapeutics. The cell membrane gets temporarily destabilized by the local application of the electrical pulse leading to pore formation on the cell surface and allowing passive diffusion of drugs that are present locally to enter the cell. The National Institute for Health and Clinical Excellence in the United Kingdom deemed that ECT was a relatively safe treatment for primary BCC due to its simplicity of operation and less damage to surrounding normal tissues. A prospective randomized controlled trial was conducted by Clover *et al.* to compare the effectiveness of electrochemotherapy in combination with surgery for primary BCC.[64] After 60 days of treatment, all the lesions treated with ECT responded except for 8/69 (12%) who needed a second treatment to ensure a complete response. All patients who underwent surgical treatment showed complete histological clearance after primary excision, except two patients requiring a further wider excision. Five years after surgery, there were 5 recurrences in the ECT group and one recurrence in the surgery group. The overall complete response rate in the surgical group was 39/40 (97.5%). Another clinical trial evaluating the effectiveness of ECT in head and neck tumors, including BCC, showed that it was the best choice for small, primary, and early-stage tumors.[65] In conclusion, ECT can be an effective adjunct to surgical treatment of BCC, with reasonable durable response rates.

Combined therapy

Commonly used combination therapies include photodynamic combined with imiquimod, surgical combined with drug, radiation therapy, or ALA-PDT.[66,67] The laser immunotherapy (LIT), a combination of laser and immunotherapeutic agents, has recently been reported to have multiple potential advantages, including enabling topical delivery of immunological agents, as well as laser-based amplification of immunotherapeutic agents. Studies on LIT show direct anti-tumor effects as well as systemic adaptive immunity which is characterized by the prevention of tumor recurrence and regression in distant untreated tumors. These findings imply that LIT can be used as adjuvant therapy for BCC patients who have failed to respond to single laser therapy or immunotherapy. Nevertheless, LIT remains an experimental strategy and further research in the field is warranted.[68] In addition, radiation combined with herbal medicine has also achieved progress. Zhang *et al.* showed that the Integrated Chinese and Western medicine, where they combined CO_2 with Chinese herbal medicine to treat BCC, was superior to laser treatment alone.[69] External use of traditional Chinese medicine on laser wounds accelerates wound healing and reduces the proliferation of scarring since they are known to resolve decay and regenerate muscle, clear heat and detoxification, and acts as anti-cancer agents. It enables to kill residual tumor cells, even improves the healing rate, and reduces the recurrence rate.[70]

Others

Include gene therapy: gene therapy aims to correct or compensate for genetic defects by introducing an exogenous gene with the corresponding function to a cell with a

Table 1. *Summary of therapies of Cutaneous Basal Cell Carcinoma and their advantages and disadvantages*

	Therapies	Advantages	Disadvantages
Surgical treatments	Surgical excision Mohs microsurgery	resect tumors as completely as possible and have a low recurrence rate	expensive, affect the patient's appearance, cannot achieve the desired cosmetic results and high risk of infection
Systemic therapy	Chemotherapy	it is a systemic treatment with high response rate, and it's effective in metastatic lesions,	although it has good efficacy, it can harm the body's immune system and lead to severe side effects such as recurrence, vomit and even death
	Hedgehog signaling pathway inhibitors	effective, convenient, prolong patient survival, wide range of applications, non-invasive, provide alternative treatment for locally invasive and metastatic BCC	drug resistance, adverse effects may occur during treatment, activate other pathways and lead to tumorigenesis
	PD- 1 inhibitor	provide alternative treatment for locally advanced BCC patients who are intolerant to HHI therapy, effective, long-time remission	long-term treatment, adverse effects and toxic effects may occur during treatment, low drug safety
	mTOR signaling pathway inhibitor	safe, prolong patient survival	expensive, long- term treatment, lack of clinical research in BCC
Topical therapy	Imiquimod 5-fluorouracil	affordable,safe,convenient, outstanding cosmetic effect, good compliance	may lead contact dermatitis, not suitable for invasive tumors, poor efficacy when used alone and needs to be used in combination with surgery or photodynamic therapy
Physical therapy	5-aminolevulinic acid photodynamic therapy Radiotherapy Electrochemotherapy	effective, better cosmetic results, specifically eliminating tumor cells and less damage to normal tissues, improve the quality of patients' life	not suitable for deep and advanced tumors, may cause skin atrophy, depigmentation or pigmentation

functional defect. The occurrence of BCC is associated with multiple mutations, including *K-ras*, *H-ras*, *N-myc*, *nm-23*, and *C-erb2*. Numerous experimental studies have been conducted on gene therapy for BCC, and further research progress is expected. In addition, there are many other treatments like nanopulse therapy, cryotherapy, EGFR inhibitor Cetuximab, VEGFR inhibitor pazopanib, PI3K inhibitor Buparlisib (BKM120), and so on.

CONCLUSION

The molecular basis of BCC is complex, including genetic susceptibility and multiple somatic mutations. Recent advances in sequencing technology have allowed us to better understand the mutated genes and implicated molecular pathways. The non-surgical treatments discussed in this article are also based on these insights gained over the past decade into the molecular pathogenesis of BCC. As our

knowledge of the disease continues to improve, we look forward to more innovative treatments emerging.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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