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Vismodegib: the Proof of Concept in Basal Cell Carcinoma

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ABSTRACT: Although basal cell carcinoma (BCC) is the most common cancer worldwide, its metastatic dissemination is exceptional. Before 2012, we had a few treatment options available for metastatic or locally advanced cases. Management of these patients was complicated due to the lack of scientific data, the deterioration of a patient's general status, the patient's advanced age, and the presence of multiple comorbidities. The hedgehog signaling pathway is dysregulated in BCC. The exploration of this signaling pathway yielded to a major milestone in the treatment of advanced BCC. Vismodegib (GDC-0449), an oral small-molecule agent that targets the Hedgehog signaling pathway, demonstrates high levels of activity in clinical trials. It was approved in January 2012 for the treatment of locally advanced or metastatic BCC. Vismodegib confirms, once again, the interest in exploring the signal transduction pathways in cancers.

KEYWORDS: basal cell carcinoma, hedgehog, vismodegib, cetuximab

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Introduction

Skin cancer is the most common malignancy in humans. Nonmelanocytic tumors are the most frequent.[1] The National Cancer Institute estimates that approximately 2 million cases of nonmelanocytic skin tumors occurred in 2012 in the USA.[2] These tumors cost more than US $400 million per year in the United States alone.[3] Basal cell carcinoma (BCC) is a nonmelanocytic skin cancer that arises from basal cells. Eighty percent of nonmelanoma skin cancers are BCC.[4] The real incidence of BCC is difficult to determine since there is no cancer registry that collects such specific data.[5] Published studies suggest that the incidence of BCC is increasing worldwide, and there is significant geographic variability.[6,7] In Caucasian individuals, the lifetime risk of developing BCC is 30%.[4,8] Australia has the highest rate of BCC in the world.[9] The prognosis for patients with BCC is excellent; it is generally considered as a curable disease.[3]

BCC occurs most frequently in Caucasian persons with environmental exposure; predisposing genetics may also play a role, such as in the case of albinism, xeroderma pigmentosum, Bazex–Dupre–Christol syndrome (follicular atrophoderma and BCC), Gorlin syndrome, and Rombo syndrome. The most important genetic factor is the presence of Gorlin syndrome. This rare, autosomal, heritable, basal-cell nevus syndrome was found to be responsible for the development of simultaneous BCC in the same patient.[10]

The clinical presentation of BCC is variable. The nodular form is the most common (70%).[11] It appears as pink pearly papule with prominent telangiectatic surface vessels. Superficial BCC occurs on 20% of cases; it appears as reddish patches on the skin that resemble eczema. The morpheaform type (10%) resembles to a yellowish ill-defined mass; it looks like localized scleroderma.[11]

BCC lesions generally grow slowly; however, in some cases, they can become highly aggressive and invade local tissue. In the head and neck region, which is the most common location, the tumor penetrates into underlying tissues (the eyelid or internal canthus) and causes local destruction and disfigurement.[4] These tumors are considered as locally advanced.

The metastatic dissemination of BCC is exceptional (range: 0.0029%–0.55%).[12] Common sites for metastases are

the lymph nodes, lung, bone, and liver.[13] The prognosis of metastatic BCC is poor, and the mean survival rates range from 8 months to 3.6 years.[14]

The majority of patients are successfully treated with cryotherapy, curettage, electrodessication, Mohs micrographic surgery, topical treatments (5-fluorouracil [5-FU], imiquimod), surgical excision, radiation therapy, or photodynamic therapy. In an advanced setting that comprises both locally advanced and metastatic disease, none of these treatments are effective, and systemic therapy remains the unique option. Before 2012, physicians had very limited effective drugs for these conditions. A better understanding of the pathogenesis of BCC has led to a revolution in the treatment of this disease. Vismodegib was approved on January 30, 2012 by the US Food and Drug Administration (FDA). It is the first available oral-targeted therapy for advanced BCC.[15] Here, we will review BCC's molecular biology, and examine the studies that have led to this major development.

Treatment for Advanced or Metastatic BCC

Systemic chemotherapy. BCC is the most common cancer worldwide; however, metastatic disease remains extremely rare. Limited data are available on the treatment of this condition, and there are no prospective Phase III studies. Most of the available data come from published case reports or small case series that include BCC and squamous cell carcinomas. Chemotherapeutic agents commonly used are doxorubicin, 5-FU, cisplatin, cyclophosphamide, vincristine, etoposide, bleomycin, and methotrexate. These drugs are used alone or in combination. A polychemotherapy with cisplatin seems to be the most active.[16] A significant response rate was reported with a combination of paclitaxel, 5-FU or blemomycin.[17,18] In one report, a complete regression of the tumor was observed after three cycles of combined cisplatin and 5-FU chemotherapy.[19] In another case report, the authors observed a complete response with a combination of paclitaxel and carboplatin in lung metastatic BCC.[17] The authors also reviewed the literature and found a very high response to platinum-based chemotherapy in 12 other patients; five with a complete response and four with a partial response. Although cisplatin-based regimens are effective, their use is limited by renal and hematological toxicity in a population with advanced age and multiple comorbidities.

Cetuximab. The epidermal growth factor receptor (EGFR) is a member of the tyrosine kinase growth factor receptor family. Activation of this tyrosine kinase receptor plays an important role in cell cycle progression, angiogenesis, metastasis, and reduced apoptosis.[20] A total of 57% of BCCs express EGFR.[21] Cetuximab is a monoclonal antibody that competitively inhibits EGFR.[22] It has been approved for Ras wild-type metastatic colorectal cancer and in recurrent or metastatic head and neck cancer.[23] It is a well-tolerated drug. In a Phase II study, cetuximab achieved a 69% disease control rate in patients with unresectable skin squamous cell carcinoma.[24] Concerning BCC, no prospective trials have been performed, and only isolated cases are available.[25] In a retrospective study, eight patients had received cetuximab for cutaneous carcinoma; three of the four patients who had BCC maintained remission while on treatment. This study suggested that this treatment had a beneficial role for patients that are refractory to standard therapy.[26]

Vismodegib. The hedgehog (Hh) signaling pathway was identified in 1980 through an analysis of the fruit fly, *Drosophila*. It was named after the larvae of the mutant fruit fly. The discovery was awarded the Nobel Prize in 1995.[27]

The Hh signaling pathway is a key cascade that plays a major role in cellular growth and differentiation during embryonic periods. The first demonstration of the role of the Hh signaling pathway in carcinogenesis has been done through the discovery of the genetic human mutation *(PTCH*1) in Gorlin syndrome. This mutation is responsible for the dysregulation of the Hh signaling pathway and the development of BCC. A dysregulated Hh signaling pathway was also been reported in sporadic BCC, medulloblastoma, and many other cancers, such as those of the gastrointestinal tract, brain, lung, breast, and prostate.[28]

The Hh ligand and two receptor proteins (patched 1 [PTCH1] and smoothened [SMO]) are involved in the cascade. In the physiologic condition, the Hh ligand is absent. PTCH1, a suppressor protein, forms a complex with SMO, and the Hh signaling pathway is inactive. When the Hh ligand binds with PTCH1, SMO becomes free and promotes the transcription of the different genes responsible for cellular proliferation and tumor growth. In the stratified epithelium, they cause epidermal hyperplasia with uncontrolled proliferation of the basal cells, leading to BCC.[29] PTCH mutations were found in 90% of sporadic BCC, while SMO mutations were found in 10%. These mutations were also found in other solid tumors.

In BCC, studies have suggested that the inactivation of PTCH1 or the oncogenic activation of SMO are responsible for Hh signaling pathway activation;[29] their targeting is relevant. Vismodegib (GDC-0449, Erivedge®; Genentech USA, Inc., San Francisco, CA, USA) is a synthetic, first-in-class, oral, small-molecule agent that binds selectively to SMO and inhibits its activity. Inhibiting the activation of SMO is responsible for the downstream Hh target genes, and it stops proliferation of the tumor cell. The discovery of vismodegib was made by a high throughput screening of a small molecule compound library.[30] Vismodegib was very active in preclinical studies; it was found to inhibit the growth of tumor cells without inhibiting the proliferation of the normal tissue cells.[30] In a Phase I trial testing vismodegib in refractory solid tumors, 33 of 68 patients had advanced BCC. A total of 58% of the 33 patients obtained a response (complete or partial), while 6% had a complete response and 48.5% had a partial response. The median duration of the response was

12.8 months. Vismodegib was generally well tolerated. Grade 3 adverse events included fatigue, hyponatremia, muscle spasm, and atrial fibrillation. These were reported in only six patients. The maximum tolerated dose was not reached. The choice of the dose of 150 mg/day was based on pharmacological data (maximal plasma concentration and pharmacodynamics).[31] This study confirms the role played by the Hh signaling pathway in the pathogenesis of basal cell tumors, and the importance of inhibiting this cascade.

Vismodegib has a unique pharmacokinetic (PK) profile; there is nonlinearity between dose and time. A Phase Ib, randomized, open-label, multicenter study compared the effect of different dosing schedules on the safety and steady-state plasma PK profiles of vismodegib. A total of 67 patients with advanced solid tumors were included, and they received 150 mg per day for 11 days, and they were then randomized between a 150 mg maintenance dose administered every day, or one time (QW), or three time a week (TIW). The QW or TIW groups failed to maintain unbound plasma concentrations, such as daily maintenance.[32]

A pivotal multicenter, nonrandomized study was realized. This two-cohort Phase II study (ERIVANCE BCC) included 104 patients: 33 patients in the metastatic setting, and 71 with unresectable BCC that were not amenable to radiation therapy.[33] The response rate was 30% in metastatic patients. All of these responses were partial. The overall and complete response rates were 43% and 21% in locally advanced BCC. The median duration of the response was 7.6 months. The median progression-free survival was 9.5 months. The most relevant adverse events were muscle spasms, dysgeusia, weight loss, alopecia, and fatigue, which affected 30% of patients. Moreover, 25% of patients experienced serious adverse events that caused seven deaths.[33] Based on the positive results of this study, vismodegib was reviewed under the FDA's priority review program, and it was approved for use on January 30, 2012.[15]

Vismodegib was also tested in patients with Gorlin syndrome.[34] A randomized, double-blind, Phase II study compared vismodegib to placebo in basal cell nevus syndrome. Forty-one patients were included. Significant responses and few complete responses were obtained. No progress was reported during treatment. No residual disease was present in 83% of the biopsy of the clinically regressed BCC.

Chang et al.[35] performed an expanded access study testing vismodegib in 119 patients with advanced BCC. The objective responses were 46.4% and 30.8% in locally advanced and metastatic BCC, respectively. The safety monitoring duration was 6.5 months. The most common adverse events were muscle spasms (70.6%), dysgeusia (70.6%), alopecia (58.0%), and diarrhea (25.2%).

These studies (Table 1) confirm the clinical relevance of targeting Hh pathway Treatment guided by biology will change our daily practice and our way of conceiving treatment trials. Actually, several ongoing studies are continuing to investigate vismodegib in the treatment of several tumors. Active Phase II studies on sarcoma, medulloblastoma, pancreatic adenocarcinoma, glioma, and advanced head and neck BCC are currently in the recruiting stage.[36]

Conclusion

Before 2012, we had few therapeutic options in metastatic or locally advanced cases of BCC. Vismodegib confirms the important role of the Hh cascade and its direct implication on BCC pathogenesis. It has a distinct a mechanism of action, a unique PK profile, and a good tolerance profile. It has become the standard treatment of BCC, and has subsequently expanded our therapeutic arsenal.

Author Contributions

Conceived and designed the concept: NB, SL, HM, HE. Analyzed the data: NB, SL, HM, HE. Wrote the first draft: NB. Contribute to the writting of the manuscript: NB, SL. Agree with the manuscipt results and conclusion: NB, SL, HM, HE. Jointly developed the structure and arguments for the paper: NB, SL, HM, HE. Made critical revisions and approved final version: NB, SL, HM, HE. All authors reviewed and approved of the final manuscript.

DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither

Table 1. Different studies testing vismodegib.

STUDY	PHASE	PATIENTS	OR (%)	CR (%)	PR (%)	MR (MONTHS)	TOXICITY (GRADE 3 OR 4)
Lorusso et al[31]	I	33/68	58	6	48.5	12.8	6 patients
Lorusso et al[32]	Ib	67					30%
Tang et al[34]	II	41	100	Some			4%
Sekulic et al[32] (ERIVANCE)	II	104	43	21		7.9	
Chang et al[35]		119	46.4% and 30.8%				

Abbreviations: OR, overall response; CR, complete response; PR, partial response; MR, median duration of response.

under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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