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Basocellular Skin Cancer about Three Patients Treated with Vismodegib Review of your Action Mechanism

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Abstract

Vismodegib (Erivedge®) is a hedgehog pathway inhibitor and is approved to treat locally advanced or metastatic basal cell carcinoma (BCC) not suitable for surgery or radiation therapy. Our main objectives were to study the intimate mechanism of action of this novel drug and to present three cases of our casuistry, the clinically evaluated objective response rate (ORR), as a contribution to the literature.

Introduction

Basal cell carcinoma (BCC) is the most common malignancy of the skin; they constitute 80% of all malignant neoplasms of the cutaneous tissue. Surgical excision is the main treatment for periocular CBC. Other treatment modalities have been reported including curettage, cryosurgery, laser treatment, surgical excision with predetermined margins of clinically normal tissue, excision under frozen section control, Moh´s micrographic surgery, radiotherapy, topical treatment, intralesional treatment, therapy. photo dynamics, immunomodulators and chemotherapy [1,2].

Until now, therapeutic recommendations for unresectable, metastatic or non-accessible tumors to radiotherapy consisted of the administration of chemotherapy based on the use of platinum, 5-fluoracil, vincristine, etoposide, bleomycin, methotrexate, cyclophosphamide and doxorubicin, alone or in combination or If this is not possible due to the existence of associated comorbidities or adverse effects, the application of palliative and supportive treatment. Although Pfeiffer et al. published that cisplatin was the most effective chemotherapeutic agent, other authors have found equally or more effective therapeutic options such as the combination of vincristine, bleomycin and prednisolone [3]. Currently, these locally advanced cases, not tributaries of surgical treatment or radiotherapy, can be controlled with vismodegib, an inhibitor of the Hedgehog (Hh) signaling pathway.

Material and Methods

In this study, we present three cases from our series with CCB, two in the nasal oculus angle and the other in the skin of the lobe of the right ear. Vismodegib was the treatment of choice in these patients because they refused to undergo surgery, resulting in damage to the tear system in two of them, and the reconstructions would require flaps or grafts. In the case of the patient with an injury to the skin of the ear lobe, she relapsed to a first surgery and chose treatment with the drug. In the three patients who preferred medical treatment for BCC, the lesion had pathological evidence. Vismodegib was administered orally in 150 mg tablets. daily.

The ages of the patients were 78 years (patient A), 83 years (patient B), and 60 (patient C). After an incisional biopsy, the reports demonstrated histopathology for BCC. Nuclear magnetic resonance imaging of the lesions of the cases revealed lesions limited to the dermis. The risk and complications of surgery and drug complications were explained in detail to the patients. Informed consents including off-label use and possible side effects of vismodegib therapy were obtained from patients in accordance with the Declaration of Helsinki. All clinical photographs that allow patient identification were taken with the approval of a consent signed by the patient.

Patients were instructed to take the 150 mg tablet. once a day, Patients were followed every fifteen days with clinical examination during the treatment period for the first 12 weeks and monthly after clearance of the lesion. Photographs were taken at each visit. The healing of the skin and the absence of any suspicious lesion with inspection and palpation were the criteria for control of the disease, since all three refused to repeat the biopsy to verify the histological response pathologically. Patient

A made a complete clinical response and remains disease-free for more than two years, patient B made a partial response of more than 50% and died of another non-tumor cause, and patient C, had stable disease and remains on treatment for more two years and rejects the indication for surgery (Figures 1-3).

Figure 1: Patient 1.

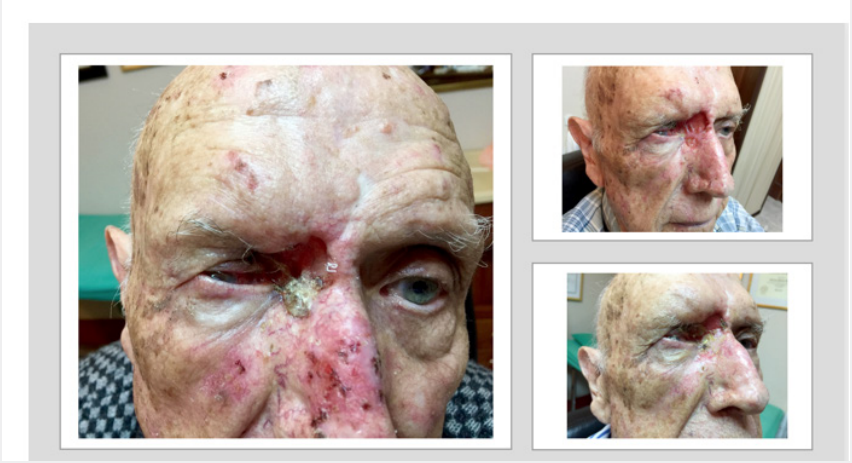

Figure 2: Patient 2.

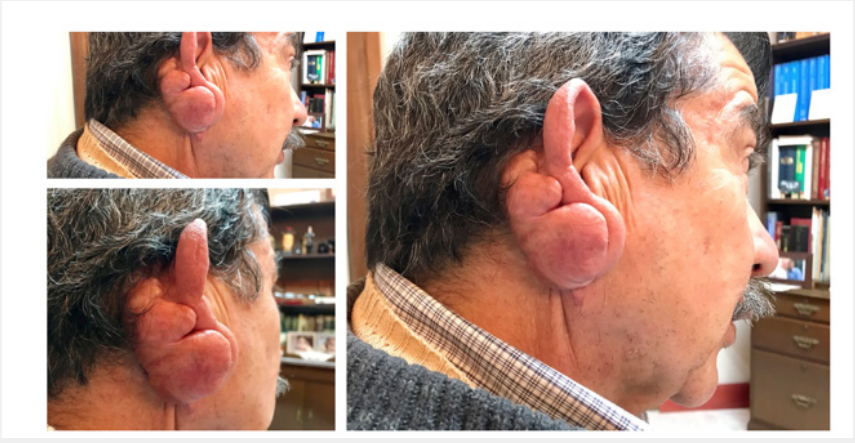

Figure 3: Patient 3.

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Discussion

Hedgehog Signaling Pathway (Figure 4)

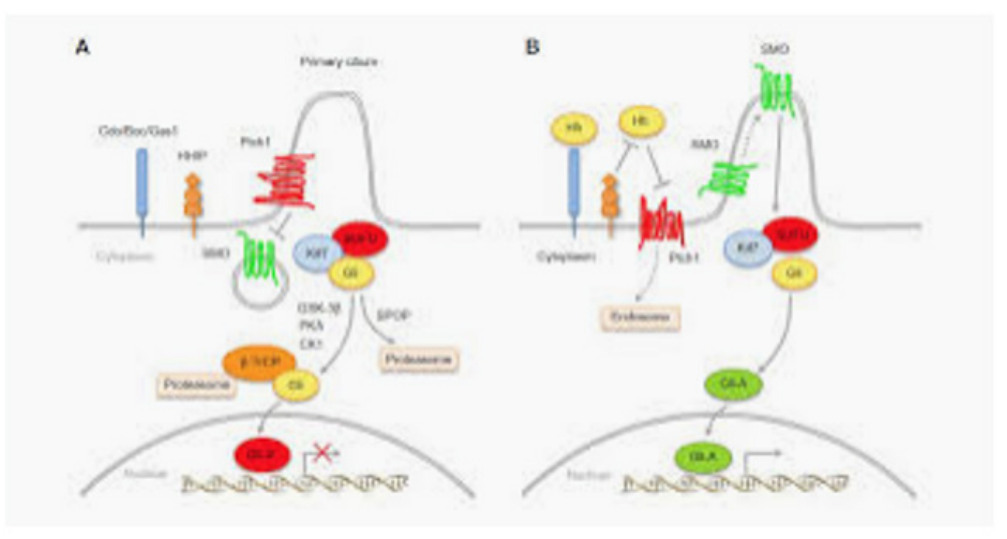

Figure 4: Hedgehog-Gli signaling basal cell.

The first articles related to the Hh pathway appear with the identification of the Patched receptor (PTCH) during the embryogenic study of the fruit fly Drosophila melanogaster [4]. The Hh pathway appears to be crucial for the normal embryonic development of Drosophila, determining the segmental polarity and its normal morphological structure. Binns et al. several years before they published a cyclopia epidemic in sheep, which consisted of the development of congenital defects characterized by the absence of facial structures of the midline and non-divisible forebrain (holoprosencephaly) [5]. The etiology of this malformation lay in the ingestion of the liliaceous plant called Veratrum californicum during gestation, which contains an alkaloid steroid called cyclopamine [6,7]. Years later, the direct role of cyclopamine as an inhibitor of the Hh pathway was demonstrated by directly blocking one of the components of this pathway called Smoothened (SMO) [8]. However, although it was a very important agent for the study in preclinical models of the Hh signaling pathway, its low oral bioavailability and acid sensitivity has forced the development of other synthetic and semisynthetic derivatives with potential for oral administration [9].

The Hh signaling pathway plays a crucial role in organogenesis during embryogenesis in multiple species, but during adulthood it is only active in the hair follicle and stem cells, where it plays a major role in maintaining tissue homeostasis and cell repair [10]. The mechanism of the processing, secretion, and signaling of Hh pathway proteins has been more or less conserved on the phylogenetic scale, although with some differences. Drosophila has a single Hh gene, while vertebrates have 3 homologous Hh ligands: Sonic (Sh), Desert (Dh) and Indian (Ih), of which the best known is the former. Dh is involved in the development of male germ cells and Ih is an important regulator in bone growth and cartilage development [11]. Sh develops multiple other activities such as establishing left-right symmetry, CNS development, eye and muscle development.

The reception system for these proteins consists of a Patched 1 transmembrane protein receptor (PTCH1) and a SMO transmembrane protein; The latter belongs to the G protein-linked receptor family and acts as a mandatory signal transducer in the Hh pathway (Figure 1). In the absence of ligand, the PTCH1 receptor represses SMO activity; if the ligand binds the repression of SMO disappears and subsequently this results in the modulation and activation of the transcription factors GLI that are transferred to the nucleus and the transcription of genes like GLI1 [12] is induced, main marker of the Hh signaling pathway . Activation of SMO requires 2 steps for its activation in the presence of Hh: phosphorylation of its C-terminal portion by cAMP-dependent protein kinase (PKA), casein kinase 1 (CK1), casein kinase 2 (CK2) and the G protein-associated kinase 2 receptor (GRK2), and its subsequent translocation to the cell membrane by cytoplasmic vesicles. In the absence of Hh, there are multiple phosphatases that maintain low levels of SMO phosphorylation.

Within the Hh path there are 2 signaling modes, the canonical path and the non-canonical path. In the canonical pathway Hh regulates the activation of family members of GLI transcription factors. The non-canonical pathway is one that is activated independently from GLI proteins, and in turn is subdivided into 2 signaling pathways, those that do not require SMO (type 1)

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and those that do not require GLI (type 2) beyond SMO.). In the canonical Hh signaling pathway, in the absence of ligand, PTCH prevents SMO activation and translocation to the membrane, while Hh binding to the PTCH receptor results in internalization of the ligand-receptor complex and activation by phosphorylation and translocation of SMO. In vertebrates, signaling takes place in the primary cilia, regulating the processing and activation of the GLI protein. The primary cilia are non-mobile cilia that present the majority of vertebrate cells, consisting of a protrusion of the membrane in the apical zone of polarized cells. PTCH1 is found in abundant quantities in the primary cilia in the absence of Hh and is eliminated from these in the presence of Hh [13]. The fundamental role of the Hh canonical pathway is the induction of cell proliferation through the induction of genes encoding cyclin D1 and N-Myc [14].

In the non-canonical type 1 pathway, PTCH1 acts by regulating cell survival, so that overexpression of PTCH1 induces apoptosis, as seen in multiple in vitro and ex vivo tests [15]. In vertebrates, the 3 Hh ligands have an antiapoptotic effect in cultured cells, an effect that is not blocked by SMO antagonists. Regulation of the cell cycle occurs through this signaling pathway through modulation of the subcellular localization of cyclin B1. The binding of Sh to PTCH prevents the interaction of PTCH with cyclin B1, leading to an increase in cell proliferation and cell survival [13]. In the SMO-dependent type 2 canonical signaling pathway, SMO regulates the cytoskeleton actin through GTPases, inducing migration processes, tubulogenesis, formation of dendritic spines and axons in neurons [13].

As we have previously commented, the Hh pathway is inactivated during adult life and only remains functional in stem cells, skin and hair follicle. In vitro and in vivo studies have shown how Aberrant reactivation of the Hh pathway would activate genes that promote cell proliferation, giving rise to various types of tumors such as medulloblastoma, rhabdomyosarcoma, melanoma, cancer of the pancreas, breast, lung, liver, stomach, and CBC [16,17]. Thus, inhibition of GLI transcription factors has been proposed as an emerging and promising therapeutic weapon for various types of tumors. The mechanisms through which an increase in the activation of the Hh pathway can occur are basically [2]. On the one hand, there is an increase in the expression of Hh ligand proteins, which directly leads to an increase in signage. On the other hand, genetic alterations in PTCH1 and SMO that give rise to constitutively activated receptors will also imply an increase in signal transduction through this pathway.

Molecular alterations in basal cell carcinoma

The Hh signaling pathway is constitutionally activated in CBC [18,19]. Mutations have been found in regulatory proteins of the Hh pathway independently of the presence of Hh ligand, whereas in other human tumors such as ovarian cancer or colorectal cancer, carcinogenesis is activated by an increase in the expression of the Hh ligand in tumor cells, which in turn act on stromal cells through paracrine signaling mechanisms. The identification of mutations in the PTCH1 gene in the CBC was obtained from the study of patients with basal cell nevus syndrome (SNB) or Gorlin syndrome, an inherited disease in which patients have multiple CBC and developmental disorders. Mutations in PTCH1 have been identified in most exons of the gene in patients with sporadic SNB syndrome and CBC. In the study by Aszterbaum et al. [20], the results of the analysis of 23 exons in 86 DNA samples from patients with SNB syndrome, 26 sporadic CBC and 7 CBC associated with SNB are presented. In this study, of the 26 sporadic CBCs analyzed, 11 cases presented loss of heterozygosity in one or more of the polymorph markers that were examined. This observation suggests the performance of PTCH1 as a classic tumor suppressor gene, which requires mutation in the 2 alleles to activate tumorigenesis [21].

In the case of acquired CBCs, these mutations in both alleles are produced by postnatal insults, such as UV radiation, RX, chemical carcinogenesis, or random genetic alterations. In contrast, in patients with SNB, there is a greater susceptibility to tumorigenesis, since one of the mutations is inherited in the germline and only requires an acquired mutation in the other allele for loss of heterozygosity to occur. Regarding the PTCH mutations, mutations were detected in 3 tumors, each in a different exon of the gene. In one case the mutation results in amino acid substitution, in another the appearance of a stop codon and in the third a loss of reading pattern. These mutations are not those characteristically associated with sun exposure and induced by UV. In the case of patients with SNB, mutations were identified in 8 exons in 13 of the 86 patients. The most frequently found mutations were loss of reading pattern mutations, leading to prematurely terminated gene products.

Smoothened Mutations

According to the proposed model of SMO inhibition by PTCH in the presence of Sh, SMO can only be in active form in the absence of Sh. In contrast, the presence of senseless, activating somatic mutations in the SMO gene has been identified in patients with sporadic CBC, leading to SMO acting as an oncogene. In order to verify the oncogenic potential of SMO, Xie et al. found that overexpression of mutated SMO in the epidermis of transgenic mice leads to the formation of epidermal alterations similar to that of CBC, with a similar phenotype.

Mutations in the p53 gene

In addition to PTCH mutations, p53 mutations are common in CBC. In a study carried out by Ling et al. [22], micro dissected samples of tumors and adjacent healthy skin were studied in order to perform a PCR and sequencing analysis in which an allelic loss of the patched locus was found in 6/8 sporadic CBCs and 17 / 19 hereditary tumors, while mutations in p53 were found in all sporadic cases and only in 7/20 hereditary ones. Mutations

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detected in p53 in hereditary CBC cases included isolated nucleotide deletions and atypical double base substitutions compared to the pattern of nonsense mutations induced by ultraviolet light in sporadic cases. The high frequency of both mutations and their coexistence suggests that genetic alterations in the patched and p53 genes are important in the development of CBC.

Molecular expression pattern in basal cell carcinoma

In the analysis of the CBC gene expression profile carried out by Bonifas et al. [23], compared to normal skin, CBC express high levels of mRNA of PTCH1, GLI1, HIP, WNT2B and WNT5a, low levels of mRNA of c- Myc, c-fos and WNT [4]. These alterations suggest that mutations in the Hh pathway play a fundamental role in CBC carcinogenesis. At quantitative level, the PTCH1, GLI1 and HIP mRNAs appear to be the highest in this type of tumor. The HIP gene codes for a protein with the ability to bind Sh with avidity similar to PTCH1, so that high levels of its mRNA in CBCs indicate that the function of this protein may be key in the Hh signaling pathway in humans.

Clinical trials with vismodegib

Vismodegib (GDC-0449) is the first drug approved by the Food and Drug Administration (FDA) since January 2012 for the treatment of locally advanced CBC not attributable to surgery or radiotherapy and for metastatic CBC (Erivedge, Genentech, January 2012) . It is a molecule that belongs to the 2-arylpyridine family and inhibits the Hh pathway by blocking SMO3 activation. To date, one phase i clinical trial and 2 phase ii trials have been published on the use of vismodegib in patients with advanced and / or metastatic CBC (Table 1).

Phase I clinical trial

Von Hoff et al. [24] conducted a 2-stage phase I clinical trial evaluating the safety and tolerability of vismodegib in 68 patients, 33 of whom had advanced (n = 15) and metastatic (n = 18) CBC. In the first stage, which was intended to study the maximum tolerated dose, 20 patients with 3 different doses were evaluated, receiving the drug on day 1, followed by a 6-day washout period, and continuing with daily administration of the same dose at from day 8; 7 patients received 150 mg / day, 9 patients 270mg / day and 4 patients 540mg / day, without observing dose limiting toxic effects. Three of the 20 patients had CBC and each received the 3 different doses of vismodegib (150, 270, and 540 mg).

In stage 2, we intended to obtain additional information about pharmacokinetics, pharmacodynamics, and safety, and 48 patients were added, 30 of whom had CBC: 16 patients received 150mg / d and 14 patients 270mg / d. Follow-up was performed every 4 weeks by physical examination, electrocardiogram, biochemistry, and hematology. For those patients with radiologically measurable disease (especially in metastatic CBC), tumor evaluation was carried out using the response evaluation criteria for solid tumors (RECIST) (version 1.0). For non-radiologically measurable tumors, follow-up was performed by physical examination, so that a complete response was considered as the disappearance of the palpable or visible tumor, and a partial response as the reduction of more than 50% of the palpable or visible tumor diameter. Of the 18 patients with metastatic CBC, 9 obtained a partial response, 7 patients remained stable and 2 patients presented tumor progression.

The overall response rate among patients with metastatic CBC was 50%. Of the 15 patients with locally advanced CBC, 2 had complete response, 7 partial response, 4 stable disease and 2 patients had tumor progression. The overall response rate in this group of patients was 60%. The most frequently observed adverse effects were muscle cramps, dysgeusia, anorexia, and weight loss, all grade 2-3. The dose established as adequate was 150mg / d, since no plasma dose increases were observed in parallel with and proportional to the increase in orally administered dose. Vismodegib is minimally metabolized and> 98% of the drug is excreted unchanged via the bile (82% is collected in faeces and 4.4% in urine). Results of in vitro studies suggest that this drug acts as an inhibitor of CYP2C8, CYP2C9, CYP2C19 and BRCP (breast cancer resistance protein). Adverse effects can be increased if administered concomitantly with drugs that inhibit the p-glycoprotein, such as clarithromycin, erythromycin or azithromycin. The estimated half-life of vismodegib is 12 days after a single dose and 4 days after continuous daily administration [25].

Phase II Clinical trials

Because RECIST guidelines (version 1.07) were used for patients with metastatic CBC, and for patients with locally advanced CBC, the response was defined as a ≥30% decrease in tumor size or complete disappearance of the same. Progressive disease was defined as an increase of ≥ 20% in tumor size visible or radiologically measurable, appearance of new ulceration or new lesions. For patients with multiple lesions, the sum of the largest diameters was used to determine the response and progression. In the metastatic CBC group (n = 33), 10 partial responses (30.3%) and no complete response were obtained. The average duration of an objective response in this group of patients was 7.6 months. In the locally advanced CBC group (n = 63), 13 complete responses (20.6%) and 14 partial responses (22.2%) were obtained, with an overall response rate in this group of patients of 43%. The average duration of the response was 7.6 months. Furthermore, in 34 of the 63 patients (54%), residual CBC was not observed in subsequent biopsies. The most frequently observed adverse effects were muscle cramps, weight loss, fatigue and decreased appetite, all grade 2 and 3. The most serious adverse effects were observed in 7 patients (one with metastatic CBC and 6 with locally advanced CBC). : 3 deaths of unknown cause, myocardial infarction, meningeal disease and stroke. The relationship between deaths and the drug is unknown

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at this time. At the molecular level, they recorded and confirmed the increased expression of genes encoding factor GLI1 and the patched homologous receptor 2 (PTCH2) in tumor skin biopsies prior to treatment with vismodegib, compared to healthy skin biopsies from other subjects.

The other phase II clinical trial was developed by Tang et al. [26]; This was a randomized, double-blind, placebo-controlled trial that aimed to investigate the efficacy of vismodegib in patients with Gorlin syndrome. They collected 42 patients with this syndrome and were randomized, with a 2: 1 ratio, to receive oral vismodegib at a dose of 150 mg / d (n = 26) or placebo (n = 15) for a period of 18 months. The main indicator of efficacy was the comparative rate of appearance of new CBCs that would be tributary to surgery (those with a diameter ≥ 3 mm in the nose or in the periorbital area, ≥ 5 mm in any part of the face or ≥ 9 mm on the trunk and thighs). The secondary indicator of efficacy was the reduction in the rate of appearance of small CBC (≤ 5 mm) in the upper third of the back, reduction in the size of CBC due to surgery, duration of effect against CBC after drug discontinuation and changes in Hh gene expression in CBCs. Clinical follow-up was carried out monthly for the first 9 months and quarterly for the remaining 9 months. Only 38 patients completed the visitation regimen in the first 3 months. In addition, molecular studies were carried out to assess the degree of inhibition of the Hh pathway by analyzing the levels of mRNA encoded by GLI1 in skin biopsies, performed at the initial time and one month after starting vismodegib. The results obtained were a reduction in the appearance of new CBC tributaries to surgery in the vismodegib group compared to placebo (2 vs 29 new CBC per year, p <0.001).

Vismodegib also reduced the size of existing tumors, expressed as the percentage change in the sum of the larger diameters (-65 vs. -11%, p = 0.003). Patients in the vismodegib group underwent fewer surgeries compared to the placebo group (mean number of surgeries per patient 0.31 vs. 4.4 with placebo, p <0.001). Virtually all tumors responded to vismodegib, obtaining complete clinical remission in some patients. Regarding the study of skin biopsies and molecular studies, among the patients who received vismodegib for more than 3 months, 46% of the biopsies revealed the presence of residual tumor, and among those lesions that clinically seemed resolved, the presence of residual tumor was objectified. only in 17% of them. At the molecular level, the effect of vismodegib was also associated with a decrease in Hh signaling, with a decrease of up to 90% in the expression of GLI1 mRNA in biopsies performed at one month of treatment, a reduction in tumor proliferation, evaluated by expression of Ki67, but without observing changes in cellular apoptosis, evaluated by measuring caspase 3. The most frequent adverse effects related to treatment with vismodegib were dysgeusia, muscle cramps, alopecia and weight loss, all grade 1-3. No serious adverse effects were observed. After 8 months of treatment 7 of the 26 patients (27%) who received the drug disconti therapy ceased due to adverse effects, with resolution of the same between one and 3 months later [27-29].

Vismodegib resistance mechanisms

The issue of acquired drug resistance is especially prevalent in the context of kinase inhibitors. The recent introduction into the clinic of vismodegib as an inhibitor of the Hh signaling pathway has provided the appearance of the first record of resistance to the group of therapies directed against the SMO receptor and, by extension, has favored the consideration of the phenomenon of acquired resistance to drugs. directed against molecules related to the G29 protein-coupled receptor. Specifically, Rudin et al. published the first case of medulloblastoma treated with vismodegib with good initial response, but with loss of efficacy at 3 months. This was a 26-year-old male patient with a metastatic medulloblastoma in whom treatment with vismodegib was started at a dose of 150mg / d with a rapid and notable initial tumor regression; Molecular analysis of the primary tumor and metastases prior to treatment revealed the existence of a mutation in PTCH1 (PTCH1-W844C), as well as an upregulation of different genes involved in the Hh pathway, confirming the premise that the disease was induced by an overactivation of this signaling pathway [30]. Yauch et al. They attempted to elucidate the nature of the drug resistance mechanism in this patient, so they collected a biopsy of a tumor lesion and identified, by genetic sequencing, a heterozygous GC nonsense mutation at position 1497 of SMO, which predicts change. of amino acid at codon 473 of aspartic acid (Asp) by histidine (His) (D473H). This mutation was not detected in pretreatment biopsies, although it is possible that it was present at a lower frequency than detectable levels [31]. For their part, Dijkgraaf et al. Based on in vitro studies, published a new mutation in SMO by inducing mutations in SMO regions important for interaction with vismodegib.

Most of the 21 new mutations showing deficiency for vismodegib binding were either inactive with regard to signaling or were not expressed on the cell surface. However, the SMO-E518A mutation did show significant activity and demonstrated partial resistance to the presence of 1 micromole / l vismodegib [32]. One way to approximate the resistance generated by specific mutations is the development of second-generation inhibitors that retain activity in the presence of mutations. This strategy has been used successfully in the case of drug resistance directed against the epidermal growth factor receptor (EGFR), for example nilotinib, a second-generation inhibitor that showed clinical activity in patients with imatinib-resistant chronic myeloid leukemia [33]. A valid alternative could be the use of antagonists of the Hh signaling pathway with a different mechanism of action than vismodegib. For example, itraconazole has recently been found to inhibit the Hh pathway through a different mechanism than cyclopamine and is currently pending determination [34]. On the other hand, the use of antagonists of the Hh pathway beyond SMO, such as GANT61, which blocks GLI function, could be considered as a strategy in the context of resistance against vismodegib [35].

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Conclusion

In the last twenty years, there have been important advances in understanding the functions and mechanisms of action of Hh proteins in the development of cancer [36,37]. Although not all the mechanisms of the Hh signaling pathway have been fully studied, it is evident that an aberrant Hh pathway favors tumor growth and proliferation, also increasing its aggressiveness and the frequency of metastasis. Inhibition of the Hh pathway is, therefore, a promising and selective new approach for the treatment of certain advanced malignancies, such as CBC and medulloblastoma, among others. Initial clinical trials conducted with the oral SMO antagonist GDC-0449 show good efficacy and safety in CBC and medulloblastoma. These preliminary studies have laid the foundations for the use of these inhibitors in other cancers, for which we have some clinical trial published in the literature with promising results; however, more experience is needed to be able to truly assess its long-term efficacy, administration time and the possible appearance of new adverse effects.

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