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Vismodegib as Novel Treatment of Periocular Basal Cell Carcinoma: A Mini Review

Hendrian D. Soebagjo
Department of Ophthalmology, Faculty of Medicine-Dr. Soetomo General Hospital, Universitas Airlangga, Surabaya 60115, Indonesia

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ABSTRACT
Basal cell carcinoma (BCC) is the most common cancer in the world. This study aims to review vismodegib treatment in BCC patients. Vismodegib has been approved for the treatment of adults with mBCC, or with laBCC that has recurred after surgery or who are not eligible for surgical procedure nor radiation. Despite all advantages it possesses, this drug still has limitations such as its inevitably occurring side effects of Vismodegib which lead to a significant rate of treatment discontinuation limiting complete drug exposure as described in previous studies. Hence, long-term continuous treatment with Vismodegib might be not feasible for certain group of patients. Vismodegib had become an established treatment option for patients with locally advanced or metastatic BCC in clinical practice.

Keywords: vismodegib, basal cell carcinoma, treatment

Correspondance:
Hendrian D. Soebagjo
Department of Ophthalmology, Faculty of Medicine-Dr. Soetomo General Hospital, Universitas Airlangga
Surabaya 60115, Indonesia
E-mail: hendriands@yahoo.com

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INTRODUCTION

The world's most prevalent cancer is basal cell carcinoma (BCC). Eighty percent of BCCs occur in the area of the head and neck, 20% occur on the eyelids.(1) BCC is the leading cause of malignant eyelid tumors which can damage the surrounding tissues(2) with incidence as high as 90% of eyelid malignancies. It has a slight female predominance over male (4.53 over 4.53 per 100,000). However, the occurrence rates of women under the age of 50 are higher, and those of men over the age of 75 are higher.(3,4) BCC has a low number of orbital invasion, with only 1.6-2.5% reported incidence.(5) The epidermis emerges from a basal cell exchange, hair follicle infindibular cells or pluripotent stem cells, which may explain why BCC does not grow out of precursor lesions.(6,7)

Usually, the lifespan of the tumor is 60-80 years. Even if metastases are rare, the risk of recurrence of BCC is high. Recurrent BBCs are often correlated with primary tumors of an aggressive type (including infiltrative, micronodular, compositive, morpheaform, sclerosing, and infundibulocystic), typically with a weaker overall prognosis than the main tumor. BCC usually is not fatal. The function and appearance of the eyelid can be impaired if it is not treated for some time.(8,9) Early diagnosis and surgery also offer improved results, including functionality and aesthetic outcomes.

For more equatorial latitudes than polar latitudes the occurrence of BCC is higher.(10) One of the most significant recognized risk factors in BCC is intermittent high exposure to ultraviolet (UV) radiation. Short-wavelength UVB radiation (290-320 nm, sunburn rays) plays a greater role than long-wavelength UVA radiation (320-400 nm, tanning rays) in BCC creation.(3,11) UVB radiation destroys DNA and its mechanism of repair and changes the immune system, which results in progressive genetic modifications leading to neoplasm formation.In approximately 50% of BCC cases, mutations in the tumor-suppressor(1) gene TP53 were found caused by UV. By halting cell cycles (G1 arrests), P53 plays a role in damaged DNA in order to repair DNA or apoptosis procedure.(12) The mutations which have a significant role in cutaneous carcinogenesis activate hedgehog intercellular signaling pathway genes, including patched (Ptch), sonic hedgehog and smoothened. Ptch-1 mutations promote eyelid BCC growth.(13) A study carried out by de Gruijl et al found that long-term UV exposure can cause Ptch-1 mutations and, therefore, promote BCC development.(14) Other risk factors for the development of BCC include sun bed use, family history of skin cancers, immunosuppression, previous radiotherapy, chronic exposure to toxic substances and infections that associated with β-catenin.(10,14,15)

Last study found that a high incidence of BCC and a larger BCC size were associated with a low socioeconomic status, which corresponds to studies in the UK, Ireland, and the Netherlands showing that patients living in areas of socioeconomic deprivation are more likely to have BCC. Since early and small BCCs are usually easily managed with a good prognosis, prevention is preferable to treatment. People living in economically deprived areas should be educated that simple measures such as avoiding extensive sun exposure or long-term use of hats with visors can reduce the incidence of periocular skin cancers.(16) This study aims to review vismodegib treatment in BCC patients.

LITERATURE REVIEW

Current Treatment Options in Periocular Basal Cell Carcinoma

Surgical Therapy

Over decades, the standard BCC procedure has been surgeries to remove tumors with wide safety margins.The most common technique of vertical section (bread-loaf) is for histological analysis in laboratories of specimens taken from the operation.(17) This procedure, however, has some limitations in which only about 1% of the tissue margins are investigated. Thus, tumor recurrence can still occur although the histology report has shown a tumor-free margin.In a large meta-analysis study involving more than 16,000 BCC specimens, the incidence of tumor recurrence following conventional surgical excision was analyzed.(18) Primary BCC recurrent rates range from 2–5 mm (0.39% to 3.96%) depending on the size of the surgical margin.

Their study also showed that tumor recurrence in 27 percent of the cases had a positive margin.

In turn, conventional surgical removal of recurrent BCCs leads to higher rates of recurrence, from 11.6% to 17.4%.(19) In recurrent BCCs, the majority of international recommendations therefore suggest Mohs micrographic surgery(20), at least where there are additional chances in recurrence. The surgeon is allowed to conduct targeted re-excision of the remaining tumor tissue in Mohs micrographic procedure in an intraoperative evaluation on frozen areas during the same surgical session. For primary BCC, a randomized prospective trial comparing Mohs' excision with conventional excision and histological work-up resulted in 2 and 4 percent recurrence rates, respectively.(21) For recurrent tumors, Mohs and conventional surgery have been documented respectively by the same authors as 2.4% vs 12.1%. In general, after Mohs surgery recurrence rates range from 1% to 3% for primary and 2% to 7% for recurrent BCCs following a 3–5 year follow-up period.(22) Therefore, Mohs micrographic operation in the high-risk region, for example, in the nasal or periorific area of the head/neck may especially be recommended for recurring tumors.

Nonsurgical Therapy

For low-risk subtype of BCC, such as superficial BCC, several nonsurgical approaches are frequently used, either physically ablative or medical. These alternatives are widely used in patients who have contraindicated or unfeasible surgery because of their age or comorbidity, and for those who decline surgery.

Curettage with subsequent electrodessication and cryotherapy are local ablative therapies. Depending on the anatomic location, tumor form and therapist experience, recurrence rates with these therapies are somewhat different because there have been no specific protocols. Recurrence may follow within 5 years after treatment of primary BCC with curettage or cryotherapy in 3-19 percent and 8-40 percent cases, respectively.(23,24) For low-risk primary BCC after careful patient selection, both procedures are recommended.(22) In general, ablative treatment of recurring BCC is not recommended due to its high recurrence rates.Topical treatments such as imiquimode may be considered as a alternative to ablative therapies and, especially, in patients suffering from multiple concurrent low-risk BCCs.

Treatment using topical imiquimode 5% cream has been proven to be effective, although not as effective as surgical excision, in several case series.(25) Imiquimode (IMQ) 5% cream works by stimulating both innate and cellular immune pathways to activate the antigenic cells via toll-like receptor 7, and promote the production of apoptosis-induced cytotoxic cells, Langerhans cells and natural killers' cells.(26) The use of IMQ is particularly useful when patients suffer from carcinoma of the eyelid near medial canthal region where reconstruction of the defect may need grafts or flaps in other periocular tissues. Tinelli et al. showed that the health effects and adverse conditions that could affect their chances for clearances and expense were generally more of concern to patients.(27)

Systemic Treatment in Advanced Basal Cell Carcinoma

As mentioned above, most common BCCs can be treated by surgical or nonsurgical procedures with a fairly low risk of recurrence. However, BCC may be considered unresectable by the treating physicians, especially after many recurrences involving underlying structures, such as bones, cartilages or muscles. An unresectable or metastatic BCC is known as advanced BCC. The incidence of unresectable locally advanced BCC (laBCC) is hard to estimate as the definition itself mostly relies on the respective health center expertise and is also somewhat subjective. The incidence of metastatic BCC (mBCC) has been estimated around 0.0028-0.55% in patients previously diagnosed with BCC, as described by study conducted in Denmark collecting 14-year data from 1997 to 2010.(28)

BCC is the most common form of malignancy followed by squamous cell carcinoma.(1) Locally advanced or metastatic BCC used to be treated by chemotherapy after exhaustion of surgical and radiotherapeutic treatment options.(29) Monotherapy based on Cisplatin or combination regimens is most widely used. With records of partial or complete responses to various treatments, in prospective randomised research, the therapeutic value of chemotherapy has never been identified.(30,31) The removal of cancer tissue is normally performed and can often not remove cancer entirely since the tissue stays behind and can turn into new cancer tissue.(32) Therefore, today's chemotherapy as advanced BCC therapy in international guidelines is no longer recommended.

As mentioned briefly above, the Ptch-1 or p53 mutations represent the most common genetic changes leading to the BCC and can be found in about 70% and 60% of BCCs, respectively.(33) The pivotal inactivating Ptch-1 mutations were initially described in families with Gorlin syndrome, a rare, autosomal-dominant inherited disease predisposing to early BCC development.(34) Loss-of-function mutations in the Ptch 1 gene will result in a subsequent hedgehog signal upregulation and will be particularly important with regard to this analysis as it directly interacts with vismodegib (vismo, GDC-0449 in former times). Vismo attaches and inhibits the activating smoothened homologue –normally impeded by a Ptch1 protein–thus inhibiting smoothened-mediated downstream oncogenic hedgehog signaling in BCC.(35) Physiologically, hedgehog signaling plays a crucial role in cell growth and embryogenesis differentiation, but is typically decreased in adult tissues. Apart from frequent mutations of the Ptch-1 gene, the smoothened or SUFU genes can be affected in decreasing frequencies by additional mutations that lead to the activation of the oncogenic hedgehog pathway and the BCC growth.(33) Therefore, researches have aimed to study the inhibitors of hedgehog pathways in advanced BCC treatment, such as by Vismodegib or Sonidegib.

Several years after initial report of clinical data on Vismodegib, the first Phase I study describing Sonidegib, second FDA (Food and Drug Association) and EMA (European Medicines Agency) approved smoothened inhibitor, was published.(36) At the 2018 American Society of Clinical Oncology Annual Meeting, a 42-month subsequent study of the Sonidegib Phase II BOLT trial in

advanced BCC was presented.(37) In the study, the results of the central analysis showed a total response rate (ORR) of 56.1 percent and 46.1 percent, respectively, for the doses of 200 mg and 800 mg compared in laBCC. The ORR for mBCC was respectively 7.7% and 17.4%. This research found that, irrespective of the two dosing regimes tested (200 vs 800 mg), the disease control rate was around 90 percent.(37) Sonidegib's efficacy and side effects are generally comparable with Vismodegib's large-scale performance in studies.

Pharmacodynamic Properties of Vismodegib

Vismodegib is a member-level Hedgehog pathway inhibitor (HPI) level of its first-of-kind, small-molecule oral(38), approves in the EU of the treatment in adult mBCC patients or laBCC patients considered ineffective for operative therapy or radiation treatments.(39) For adults with mBCC or with the laBCC that has been occurring after an operation or that are not suitable for an operation or radiation, Vismodegib has been approved in the USA.

Vismodegib selectively and strongly inhibits the Hedgehog (Hh) pathway by binding to Smoothened (SMO; a 7-transmembrane protein) thereby down-regulating the activation of Hh target genes in a phase I study.(35,40,41) Skin biopsies showed GLI1 expression was down-modulated >2-fold in 25 (73.5%) out of 34 patients receiving 150-540 mg/day of vismodegib(40), including 10 (76.9%) or 13 patients with LaBCC or mBCC with locally advanced or metastatic solid tumors.(35) However, no correlation between GLI1 expression down-modulation and plasma vismodegib concentrations has been found in the research.(35,40) In Phase 1, patients with local-advanced or metastatic solid tumors(40), including advanced BCC, have witnessed development of anti-tumor activity.(35)

Intrinsic/primary (i.e. no reaction to treatment) or secondary/acquired (i.e. tumor regrowing following initial shrinkage) resistance to targeted anti-cancer therapies such as HPIs is recognized as limitation.(42) The occurrence of primary or secondary Vismodegib resistance remains fairly small (e.g. < 10 percent in 207 patients from France)(43) compared to other targeted treatments.(44) The secondary resistance phenomenon was first observed in a US center and was identified during the first year of treatment in 6 (30 percent) patients with LBCC and none of 8 patients with mBCC.(45) The mean time to regrowth was 13 months.(45) Molecular mechanisms of resistance to Vismodegib include mutations in SMO that damage drug binding and, in a smaller extent, concurrent mutations in downstream effectors of SMO that result in GLI2 amplification.(44,46,47) Teratogenic or embryolethal effects have been exerted by vismodegib in pregnant rats, thus patients must not be treated with it during pregnancy.(39)

Pharmacokinetic Properties of Vismodegib

Vismodegib administered orally exhibited both dose- and time-dependent pharmacokinetics after continuous once-daily dosing in patients with locally-advanced or metastatic solid tumors, predominantly BCC.(40,48,49) This Hh pathway inhibitor (HPI) showed apparent nonlinearity with respect to both dose and time. Dose nonlinearity was observed as increasing the dosage from 150 mg once daily (the approved strength in study) to 270 or 540 mg once daily did not result in higher steady-state plasma concentrations. Temporal non-linearity was observed as the concentration in static plasma was reached faster (usually within 7-14 days) and lower than expected, based on single-dose pharmacokinetic parameters.(40,48,49)

Owing to its solubility-limited, saturable absorption and high-affinity as well as saturable plasma protein binding, it is expected to be nonlinear multiple-dose pharmacokinetics.(50) Vismodegib possesses low aqueous solubility(39) and showed a moderate mean absolute bioavailability following a single dose (31.8%) and decreased considerably after continuous once-daily dosing (to 7.4%).(49) More than 99% of circulating Vismodegib is bound to plasma proteins; the drug binds to both serum albumin and α_1-acid glycoprotein (AAG). The binding of Vismodegib to AAG at clinically important concentrations has been saturated, and a study in 2011 found a strong association between plasma concentrations at the overall levels of Vismodegib and AAG.(48) Vismodegib can be taken regardless of meals, as food primarily does not affect its steady-state pharmakokinetics.(51) The distribution is small between 16.4 and 26.6 L.(39)

The pharmacokinetic profile of Vismodegib is also characterized by a slow rate of systemic elimination, mainly as the outcome of hepatic metabolism and unchanged drug biliary/intestinal excretion; mean recovery of administered Vismodegib dose in faeces and urine was 84 and 4.4%, respectively.(39,48,52,53) Vismodegib parent drug (which accounts for more than 98% of total circulating Vismodegib-related components) undergoes oxidation, glucuronidation, and a rare pyridine ring cleavage; the cytochrome P450 2C9 isoenzyme seems to be partly accountable for the metabolism of Vismodegib in vivo. Approximately 12 days after the single dose and 4 days after the continuous regular day dosing(39), Vismodegib's approximate half-life of terminal removal represents improved clearance seen with repeated dosing.(52)

Vismodegib's pharmacokinetics, based on population pharmacokinetical study, do not seem to be influenced by age, gender and mild or moderate renal impairment, but the data for patients with severe renal impairment are very restricted and poor.(39) Although its elimination is mostly done through liver, the pharmacokinetics of the Vismodegib in patients with advanced solid malignancies and mild, moderate, or severe hepatic impairment [classification based on National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria] were similar to those in patients with normal hepatic function.(39,54)

Women who have childbearing potential should not become pregnant or pregnant while on medication (and after 2 years).(39) Sexually-active men using Vismodegib will also use methods for contraception as the manufacturer suggests, since Vismodegib is found in semen. The degree to which the medication is excreted in breast milk is unknown; women must not feed while taking the medication (and two years later).(39) EU SPC states than, due to safety concerns,

Vismodegib should not be used in children and adolescents aged <18 years; there have been reported cases of premature epiphyseal closure and precocious puberty in paediatric patients exposed to the drug.(39) No contraindications have been identified in US prescription records, but the FDA has a black box warning that Vismodegib may lead to embryo-foetal death or serious birth defects.

Phase II Studies of Vismodegib

ERIVANCE BCC

The ERIVANCE BCC was a one-arm, two-cohort, non-randomized, open-label experiment, with a total of 104 patients studied at 31 sites across Europe, Australia and the United States.(55) Eligible patients were 18 years old or older, had a histologically-confirmed diagnosis of laBCC or mBCC, an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2 and adequate organ function. Individuals with BCCNS were permitted to enroll if they met all other inclusion criteria.(55–57) Patients with laBCC needed to provide ≥ 1 target lesion measuring ≥ 10 mm for which procedure was against-indicated or considered insufficient due to inoperability, repeated recurrence of treatment or expectation of substances or malformations. This had to do so because it has been found ineffective for radiation and radiation therapy. The Response Evaluation Criteria for Solid Tumor (RECIST) version 1.0 guidelines allowed patients with mBCC to have measurable disease. Contrary to the requirements of eligibility or the improper essence of surgery or radiotherapy was not included for patients with mBCC.(55–57)

LaBCC consisted of 63 patients (including 21 BCCNS54 patients), while the mBCC cohort contained 33 efficacevaluable patients (none had BCCNS).(55) The median age of all patients was 62 years; 61.5% were males. Among patients with laBCC, 79% had not received radiotherapy to a target lesion; 38% had an inoperable tumor, while 62% were deemed inappropriate for surgery.(55)

In patients with advanced BCC, Vismodegib displayed high activity and produced long term responses.(55–57) The median period of Vismodegib therapy was approximately 10 months for primary research, carried out after all the patients had a capacity to be followed for 9 months or more.(55) For the laBCC cohort, the primary outcome of the independently-assessed overall response rate (ORR) was 42.9% [complete response (CR) 20.6%, partial response (PR) 22.2%]; this was significantly ($p < 0.001$) greater than the null hypothesis of 20%.(55) Similarly, the primary outcome of the self-assessed ORR for the mBCC cohort was likewise 30.3% (all PRs). It was significantly (p= 0.001) greater than the 10% null hypothesis.(55)

The findings of the primary analysis are confirmed by update 56 analysis, which was conducted for 12 months and 30 months (final) despite the opportunity for all of the patients to be followed up for a period of 21 and 29 months.; at the time of both these analyzes the median period of Vismodegib exposure was about 13 months.(56,57) In general, 56 investigator-assessed ORRs across patient subgroups, including violent historical subtypes (e.g. infiltrative BCC), were identical for the 30-month update. In the laBCC and mBCC cohorts respectively, the median time to response (TTR) was 4.6 and 1.9 months.(57)

It is noteworthy that the median duration of response (DOR), based on independent and/or investigator evaluations, in the laBCC cohort has been increased. (56,57) For instance, median DOR evaluated by the investigator was more than threefold between 7.6 months during the primary analysis and 26.2 months at the 30-month update. In mBCC cohort the median investigator-assessed DOR increased from 12.9 months, but less significantly, in the primary study, to 14.7 and 14.8 months, respectively at 12 and 30 months; however, independently tested median DOR was unchanged with additional follow-up in this cohort.(56,57)

A separate review carried out at the time of the 12-month update examined the clinical advantage of laBCC patients resulting from Vismodegib treatment by an independent review panel.(58) The consensus of the three clinical experts who judged pre-treatment and post-treatment photographs was that 76.2% of the patients achieved significant or some clinical benefit from treatment. In relation to disease burden at baseline, 91.7% of patients with mild or moderate disease derived clinical benefit, while 73.5% of patients with severe, moderately severe or very severe disease derived clinical benefit. Clinical benefit scores showed good concordance with independently- and investigator- assessed ORRs.(58)

The median progression-free survival (PFS) measured by the investigators of the laBCC cohort was increased from the primary study by 1.6 months to the 30-month updates, while the PFS remained significantly unchanged in the mBCC cohort. Median OS for the laBCC cohort was not determined; it was 33.4 months for the mBCC cohort.(57)

STEVIE

STEVIE was an open-lab study with a single-arm, two-cohort, non-randomized, planned specifically for safety evaluation.; efficacy and quality of life (QOL) outcomes were assessed as secondary endpoints.(59,60) Eligibility criteria were similar to that of ERIVANCE BCC. Another argument was that, according to RECIST version 1.1, STEVIE has enrolled individuals with measurableand/or non-measurable disease.(59) Like those entering ERIVANCE BCC, patients with laBCC entering STEVIE were required to have received radiotherapy (unless contraindicated or inappropriate) and to have a lesion that was ineligible (i.e. inoperable or inappropriate) for surgery.(59,60)

In advanced BCC, STEVIE is currently the biggest study in which a total of 1215 evaluable patients have been recruited at 167 locations across 36 countries.(60) The laBCC cohort (n = 1119) included 1077 patients with histologically-confirmed, measurable baseline disease (of whom 208 had BCCNS), while the mBCC cohort (n = 96) included 84 patients who like-wise had histologically-confirmed, measurable baseline disease (of whom five had BCCNS). Most significantly, registered patients are representative of patients encountered in clinical practice in the real world. The average age of all study population was 72 years, with 57.1% of males.(60) Almost 34% (72%) of laBCC patients had no prior radiation treatment; 39% were inoperable to a tumour; 61% had surgical contraindications.(60) The pre-planned interim and primary analyses were scheduled to be performed after 500 and ≈ 1200 patients, respectively, had the potential to be followed up for ≥ 12 months; the median duration of exposure to vismodegib at the time of these analyses was ≈ 8.5 months.

Vismodegib has been associated with high levels of tumor control in STEVIE, consistent with previously reported ERIVANCE BCC results.(59,60) At the data cutoff for the primary analysis, 68.5% of the patients with laBCC achieved an investigator-assessed objective response, including 33.4% who achieved a CR. The median DOR was 23.0 months; the median TTR was 3.7 months. In comparison, the proportion of mBCC patients was 36.9%, mostly [27 of 31 (87%)] PRs. The median DOR was 13.9 months, but the median TTR was not-estimable.(59,60)

A subgroup analysis showed that BCCNS patients were better than those without BCCNS when reacting to Vismodegib therapy. This could be a reflection of the former, on average, being younger and having smaller tumours and a better ECOG PS, than the latter. The non-BCCNS patients, however, represented both the laBCC cohort and the MBCC cohor t the predominant subgroup; the ORRs for these subgroups were identical to those of the general cohorts. The ORRs for these cohorts were identical. The ORR was similarly comparable for all non-BCCNS patients within the laBCC and mBCC cohorts, suggesting that the addition of patients with BCCNS did not have an impact [66.2% (CR 31,4%, PR 34,9%), vs. 63% (CR 28,2%, PR 34,7%)]. The median PFS for the laBCC and mBCC cohorts was 23.2 and 13.1 months, but due to data immaturity the median OS was not estimable.(60)

Vismodegib's effect on QOL was evaluated with the Skindex-16 validation instrument.(59,61) Patients with laBCC had more trouble at the baseline than symptoms or impact on their work due to the impact of their disease on their emotions.; during the after-baseline tests, they recorded clinically significant changes to emotional scores of Skindex 16 with stable symptoms and functional scores.. Improved emotional qualities were compatible with clinical answers at the end of the test. So far, QOL data have not been reported for the mBCC cohort.(59,61)

Currently only interim analysis offers interesting information on the effect of treatment breaks (i.e. dosage interruptions) on patient outcomes.(62) The efficacy of Vismodegib did not appear to be compromised in the subsets of patients who had 0, 1, 2 and ≥ 3 treatment breaks, with the ORRs being 61% (CR 30%, PR 31%), 65% (CR 33%, PR 32%), 95% (CR 51%, PR 44%) and 85% (CR 39%, PR 46%), respectively (*n* = 368, 76, 41 and 14). Median PFS was 19.8 and 19.0 months in the subsets of patients who had 0 and 1 treatment break; for the subsets of patients that had two or three treatment breaks, however, it was not calculated. No findings were published separately for the laBCC and mBCC cohorts.(62)

Studies on Vismodegib for Periocular BCC

In 7 institutions in the United Kingdom, Australia and New Zealand, an international case series multi-center analysis was carried out, which yielded results for 13 patients.(63) Of the study participants, seven were male (54 percent). All BCCs were ill-defined, with orbital participation at presentation of seven (58 percent). Time for median treatment (from 2 to 36 months) was 7 months. In 11 out of 13 patients, the most common was exhaustion in 6 patients (46%). The follow-up median has been 24 months (interval 12-48 months). Complete response was observed in 5 of 13 patients (38%) and a partial response in 8 of 13 patients (62%). After Vismodegib, six patients had additional surgery, three marked as globe-sparing operations. Three patients (23 percent) developed recurrence and eventually experienced exenteration.(63)

The previous multicenter study concluded that the use of Vismodegib could avoid patients being subjected to a surgical and psychological morbidity or to a disfiguration procedure.(64,65) In this study, Vismodegib participants established a adequate tumor reduction in 3 out of 13 cases enabling excision operation to be performed globe-sparing excision instead of the anticipated exenteration.(63)

In Israel there was a retrospective case series to test Vismodegib's efficacy with the treatment of orbital and advanced periocular basal cell carcinoma. The cohort recruited 21 patients (median age 76 years old) whose background, treatment, and outcome data were retrospectively collected from the medical records of all patients with locally advanced and metastatic orbital or periocular BCC treated with the drug in 2012 until 2017 at 2 tertiary medical centers.(66) The mean treatment period was 9 months, followed by 26 (9-60 months) months in total and 17 months following cessation of treatment. Complete clinical response was found in 10 patients, partial in 10 patients, and stable in 1 patients. 5 of the full respondents had a complete response at 16 months, and 3 had a recurrence 8 months later, who stopped seeking medication. Nearly all adverse reactions related to treatment were grade 1 or 2 (low grade).(66) Muscle spasm (76%), followed by dysgeusia (57%), alopecia (47%) and weight loss (47%) and decreased appetite (19%) have been the most common complications observed in that study. Hepatotoxicity (10%) was the only adverse condition of grade 3 or 4. Eight patients quit treatment due to side effects. The majority of 5 people died of Vismodegib, but one was died from potential treatment-related sepsis (grade 5 adverse event) for reasons unrelated to treatment with Vismodegib.(66)

Other studies recruited from the two hospitals from May 2012 to 2014 all patients who met Vismodegib requirements with periocular or orbital BCCs. All patients were then followed up monthly. Demographics, tumor size, treatment period including dosing regimen, adverse effects, response rate, length of response, progression-free survival, and metastatic disease at presentation were all collected.(67) All 15 patients in the study were diagnosed with biopsy-proven BCCs without metastatic disease. The mean lesion longest dimension was 51 mm and 7 cases (47 percent) reflected recurrence following previous surery and/or radiotherapy. The mean treatment duration as 13 months and mean follow-up duration 36 months. Ten patients (67%) had a complete response, 3 (20%) showed a partial response, and 2 had preogressive disease following an initial partial response (13%). In one patient, 55% partial response resulted in clear margins for subsequent surgical resection. The study also showed that Vismodegib played a neoadjuvant role, but additional study was required.(67)

Research supporting the use of Vismodegib is increasing in periodic and intraorbital BCCs, partially because of the clinical evaluation on what is to be covered by the concept

on LaBCC.(68) After only 15 days of Vismodegib, Jacobsen reported complete eyelid BCC resolution. Other reports(69) presented a small case series of 6 patients with intraorbital BCC treated with Vismodegib as adjuvant or sole therapy and noted 80% to 95% tumor mass reduction in the 4 cases of intraorbital BCC treated with Vismodegib alone, compared with complete clearance when paired with surgery. Another series of intraorbitally recurrent BCCs treated with Vismodegib showed improvement in 1 patient, 15% response in 1, and 80% and 90% responses in 2 patients after combined 16 weeks and 8 months of follow-up.(70) The other studies included 1 case of intraorbital BCC exenteration after treatment with Vismodegib and 2 cases of intraorbital BCC with partial response or stable disease.(71) The few examples applied to the reported BCC intraorbital cases only, though the number also includes advanced periodic BCC reports that would require exemption if no use had been made of vismodegib. Unfortunately, initial Vismodegib reactions and subsequent resistance requiring exenteration are also reported.(72)

DISCUSSION AND CONCLUSION

Vismodegib has been a well-established treatment choice for patients with locally advanced or metastatic BCC in clinical practice since it was officially approved more than 5 years ago. Given its advantages, Vismodegib's side effects are inevitable and contribute to a substantial rate of discontinuation of treatment, restricting full access to the medication as mentioned in previous studies. For some patients, therefore, long-term treatment with Vismodegib can not be feasible. Clinical end points that can provide evidence for optimum treatment duration (lifelong/continuous treatment vs treatment until best response) are still studied by researchers.

In advanced BCC, neoadjuvant Vismodegib therapy could be increasingly incorporated into the multimodality therapeutic strategy that is specifically customized for every patient. This imposes a lasting and careful response after neoadjuvant therapy to the VISMONEO route, as the production of skip lesions with Vismodegib is possible and must be excluded.Attempts are also being made to gather more detailed clinical information on the use of Vismodegib in long-term studies. Vismodegib can be a significant contributor to the management of Basal Cell Carcinoma in the future as any other Hh pathway inhibitor.

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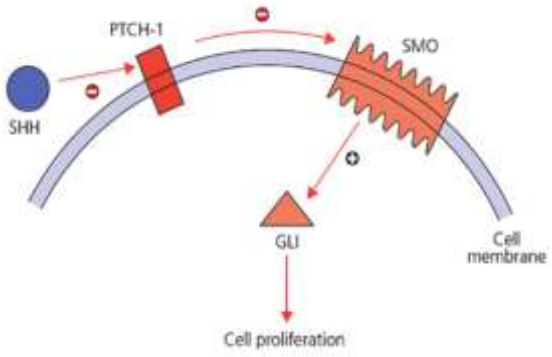

Figure 1. Interactions between Shhh, Ptch-1, and Gli-1. (13)

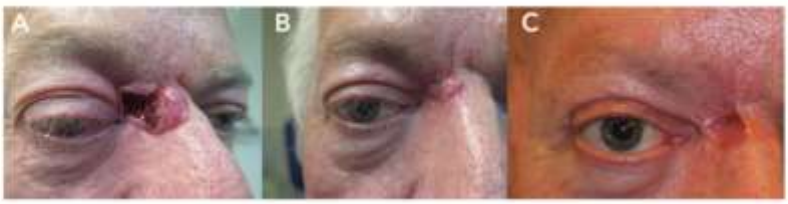

Figure 2: Example of tumor regression course of Vismodegib and subsequent resection and reconstruction with full thickness skin graft. Male patient with medical canthal / bridge of nose BCC at presentation (A), treated with Vismodegib showing partial response (B), Subsequent resection and reconstruction with no recurrence at 2 years (C). [Reproduced from: Vismodegib for periocular basal cell carcinoma: an international multicenter case series