Vismodegib for the treatment of basal cell skin cancer

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Skin cancer, both melanoma and nonmelanoma, is the most prevalent cancer in the United States, with basal cell skin cancers being the most common. The American Cancer Society has estimated that more than 3.5 million basal and squamous cell skin cancers (nonmelanoma skin cancers [NMSCs]) are diagnosed annually, and the incidence of NMSC is rising. Basal cell skin cancer is a treatable cancer and likely curable; in fact, the associated mortality rate is declining. In the United States, approximately 3000 people die each year from NMSCs, and the majority of these patients are immunocompromised or elderly.

Although basal cell carcinomas (BCCs) are rarely deadly, they can be disfiguring and cause large areas of destruction, involving the soft tissue and extending to bone. These carcinomas can also be expensive to treat. The annual estimated cost of treating NMSCs in Medicare recipients is over $400 million, making them the fifth most costly type of malignant cancer to treat (behind lung, prostate, colon, and breast cancers) and accounting for 4.5% of costs associated with the management of all types of cancer.

The treatment intent for BCC is curative, with a focus on retaining function and cosmetic appearance. Low-risk BCCs are small, well defined, and not in the site of prior radiation therapy and occur in patients who are not immunocompromised. Surgical excision is the preferred therapy for these patients, though radiation therapy may be used for patients who are not surgical candidates.

If neither surgery nor radiation therapy is feasible or if both are contraindicated, topical therapies are available, but these treatments are less likely to be curative. Topical treatments include imiquimod, fluorouracil, photodynamic therapy (with porfimer sodium, methyl ami-
Vismodegib (2-chloro-N-[4-chloro-3-(pyridin-2-yl)phenyl]-4-[methylsulfonyl]benzamide) is a small molecule that potently inhibits signal transduction in the hedgehog signaling pathway by binding and inhibiting smoothened homolog (SMO), a 7-transmembrane protein in the pathway. During embryogenesis, the hedgehog signaling pathway is an important regulator of epithelial and mesenchymal interactions involved in cell growth and differentiation. The pathway is normally not active in adults, but mutations in this pathway can cause constitutive signaling that leads to the proliferation of basal skin cells, which then causes the carcinoma. The most common mutation in basal cell carcinomas is inactivation of patched homolog 1 (PTCH1), a 12-transmembrane receptor, thereby inhibiting SMO. This loss-of-function mutation causes uncontrolled proliferation due to a lack of inhibition of the pathway. There is also a less-common gain-of-function mutation that constitutively activates SMO. Vismodegib treats BCCs by inhibiting pathway activation through SMO signal transduction. This prevents nuclear localization of GLI1 transcription factors and target gene induction that cause the proliferation and continued survival of the carcinoma through angiogenesis.

To evaluate disruptions in the hedgehog signaling pathway, the potential targets of vismodegib, mutations in PTCH1 and SMO were evaluated and expression changes in GLI1 were evaluated in a subset of patients enrolled in the first published clinical trial of vismodegib. Mutations in the PTCH gene were identified in 9 of 10 patients with available samples, and 1 of 10 patients had a mutation in SMO. The patient with an SMO mutation had stable disease when treated with vismodegib, but the overall number of mutations was too low to determine if these mutations determined which patients were likely to respond to vismodegib. Likewise, GLI1 was overexpressed in tumor tissue versus normal tissue; however, the number of mutations was too low to correlate with response. However, these results showed that the hedgehog signaling pathway is involved in the production and continued growth of BCCs.

Pharmacokinetics

An atypical pharmacokinetic profile was noted for vismodegib in an early Phase I trial, showing that there was little decline in plasma vismodegib concentration during a 7-day observation period after administration of a single oral dose. After continuous daily use, steady-state plasma concentrations were achieved earlier than expected (within 7–14 days); plasma drug concentrations did not increase with increasing dose levels, suggesting nonlinear pharmacokinetics with regard to dose and time.

To evaluate the atypical pharmacokinetics of vismodegib, alpha-1 acid glycoprotein (AAG) levels were evaluated and demonstrated a strong correlation between AAG and vismodegib plasma concentrations. Given vismodegib’s poor solubility and slow elimination, the authors hypothesized that (1) the intestine acts as a continuous source of drug to the systemic circulation while AAG in the systemic circulation acts as a sink and (2) changes in AAG levels are the primary determinant of plasma vismodegib concentrations.

This hypothesis was further tested in a Phase I, open-label, single-center study conducted with 12 fasting, white, postmenopausal, healthy women. Subjects received a 10-μg 14C-labeled i.v. bolus dose of vismodegib administered two hours after administration of a single 150-mg oral dose of vismodegib (6 patients) or after seven days of using vismodegib 150 mg daily orally (6 patients).

For the single-dose group, the terminal elimination half-life (t1/2) was comparable after the oral dose of vismodegib (11.3 days) and the i.v. dose (13 days). After a single dose, vismodegib had a moderate volume of distribution (V) of 16.4 L and an absolute bioavailability of 31.8%.

For the multiple-dose (steady-state) group, the terminal t1/2 after the i.v. dose was 10.3 days, similar to that of the single-dose group. However, there was a 77% decrease in bioavailability (7.36% versus 31.8%), a 63% increase in V (26.8 L versus 16.4 L), and an 81% increase in clearance (CL (78.5 mL/hr versus 43.4 mL/hr) in the multiple-dose group compared with the single-dose group. The increases in V and CL were results of the vismodegib unbound fraction increasing 2.4-fold (because of an increase in AAG saturation) after 7 days of oral vismodegib use compared with a single oral dose. Vismodegib binds to AAG with a higher affinity than to human serum albumin, so vismodegib’s unbound fraction is dependent on AAG saturation.

Thus, vismodegib’s nonlinear pharmacokinetics are the result of low solubility at a physiological pH and the increase in the unbound fraction of the drug due to AAG saturation. This nonlinearity means there will not be accumulation of vismodegib after continual daily administration despite the long t1/2.
Vismodegib

Vismodegib is very slowly eliminated (t½ = 10–13 days) and that its two primary metabolites are formed through hepatic oxidation by cytochrome P-450 (CYP) isoenzymes 3A4/5 and 2C9. Other metabolites are formed by glucuronidation or sulfation and by pyridine ring opening. However, these investigators found that unchanged vismodegib represented greater than 98% of the total circulating drug or drug components, with 82.2% recovered in the feces and only 4.4% in the urine.

Patients treated simultaneously with vismodegib and with CYP3A4 inducers or CYP3A4 inhibitors had comparable steady-state plasma concentrations, so CYP inhibition is not expected to affect systemic exposure of vismodegib. In vitro studies found that vismodegib is a substrate of P-glycoprotein. Clinically significant, metabolism-based drug interactions involving vismodegib have not been reported.

Proton-pump inhibitors, histamine H2-receptor antagonists, antacids, and other agents that increase gastrointestinal pH may reduce the solubility and bioavailability of vismodegib. Concurrent administration of these agents and vismodegib should be avoided.

Clinical efficacy

A multicenter, two-stage, Phase I/II trial was conducted in 68 adult patients. For the Phase I portion of the trial, patients with any solid tumor that was refractory to conventional treatments were enrolled, and vismodegib doses were increased from 150 to 540 mg orally daily. No dosage-limiting toxicities were observed at any dose. The authors selected 150 mg daily as the dosage for the Phase II portion of the trial, because higher dosages of vismodegib did not achieve higher plasma concentrations. In the Phase I portion, 3 patients with advanced or metastatic BCC were enrolled, with 2 responding to therapy. In the Phase II portion, 48 patients were enrolled, 30 of whom had locally advanced or metastatic BCC. Patients were given vismodegib 150 mg daily by mouth until the disease progressed or intolerable drug toxicities developed; some patients received 270 mg daily because of difficulty obtaining the 150-mg dosage form. A new formulation of the 150-mg dose was evaluated in 16 of the 48 patients enrolled in the Phase II portion.

Overall response rate (ORR) was the major efficacy outcome of this study. Responses of tumors that could be radiologically measured were categorized using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria; otherwise, tumor response was assessed using clinical criteria, including physical examination documented by digital photography was used for evaluation by central review.

Of the 96 evaluable patients, 33 had metastatic BCC and 63 had locally advanced BCC. All patients were white, 61% were women (73% had metastatic BCC, 56% had locally advanced BCC) and 39% were women (27% in the metastatic group, 44% in the locally advanced group), and the median age was 62 years. Patients were enrolled in the trial from January 2007 to December 2008, and data were collected until the end of February 2009. The median duration of therapy was 9.8 months, with an 8.8-month median response time at the time the data were reported. All 33 patients had progressive tumors that were not responsive to prior treatments, including surgery, radiotherapy, and systemic therapy.

Of the 18 patients with metastatic BCC, 9 had a partial response, 7 had stable disease, and 2 patients had progressive disease. Of the 15 patients with locally advanced BCC, 2 had a complete response, 7 had a partial response, 4 had stable disease, and 2 had progressive disease. The ORRs in patients with metastatic disease and locally advanced tumors were 50% (95% confidence interval [CI], 29–71%) and 60% (95% CI, 33–83%), respectively.

A multicenter, two-cohort, Phase II trial of vismodegib 150 mg daily was conducted in 104 adult patients with BCC (33 patients with metastatic BCC and 71 with advanced BCC). The ORR was the major efficacy outcome (including response, progressive disease, and stable disease) and was used to determine whether patients with metastatic BCC had a response rate of >10% and whether patients with locally advanced BCC had a response rate of >20%. A decrease of ≥30% of the visible or radiographic dimension or resolution of ulceration defined a response. An increase of ≥20% of the visible or radiographic dimension, a new tumor, or new ulceration defined progressive disease. Tumors that could be radiologically measured had responses categorized using RECIST criteria; otherwise, physical examination documented by digital photography was used for evaluation by central review.

Of the 96 evaluable patients, 33 had metastatic BCC and 63 had locally advanced BCC. All patients were white, 61% were men (73% had metastatic BCC, 56% had locally advanced BCC) and 39% were women (27% in the metastatic group, 44% in the locally advanced group), and the median age was 62 years. Patients were enrolled in the trial from February 2009 to November 2010, and data were collected for 9 months after the final patient was enrolled. The median duration of response was 7.6 months for both groups. The majority of patients with metastatic BCC (97%) enrolled in the study had prior surgery, 58% had prior radiation therapy, and 30% had systemic therapy.
therapy in the past. The majority of patients with locally advanced BCC (89%) had previously had surgery, radiation therapy (27%), and systemic or topical therapy (11%).

In both groups, the primary objective was met.13 The 33 patients with metastatic BCCs had a response rate of 30% (95% CI, 16–48%; p = 0.001 compared with the null-hypothesis rate of 10%), and the 63 patients with locally advanced BCC had a response rate of 43% (95% CI, 30–56%; p < 0.001 for comparison with the null-hypothesis rate of 20%).

Basal-cell nevus syndrome (BCNS), also called Gorlin syndrome, is a rare, autosomal-dominant, heritable disorder, occurring in approximately 1 of every 19,000 live births.15 BCNS may cause hundreds to thousands of BCCs in a single patient. BCNS is caused by inheriting one defective copy of PTCH1, with subsequent loss of the other allele occurring sporadically. Like sporadic BCC, BCNS is typically managed by surgery; however, patients with BCNS may need hundreds to thousands of surgeries over their lifetime.15 A recent study enrolled 42 patients with BCNS who were randomly assigned, in a 2:1 ratio, to receive oral vismodegib 150 mg daily or placebo.16 Patients received vismodegib for a maximum of 18 months or until the occurrence of intolerable toxic effects or clinical worsening of disease (defined as more than 60 new surgically eligible BCCs). The primary endpoint was the rate of appearance of new BCCs that were eligible for surgical resection (i.e., having a diameter of >3 mm on the nose or periorbital skin, >5 mm elsewhere on the face, or >9 mm on the trunk or limbs).

More than 2000 existing and 694 new, surgically eligible BCCs were followed as part of the study.16 One patient did not receive vismodegib or placebo and was excluded from the efficacy analysis. The 41 remaining patients were followed for a mean of 8 months (range, 1–15 months) after enrollment. The per-patient rate of new, surgically eligible BCCs was significantly lower with vismodegib than with placebo (2 versus 29 cases per group per year, p < 0.001). While not the primary endpoint, existing surgically eligible BCCs, expressed as the percent change from baseline in the sum of the largest diameters (mean, −65%, versus −11% with placebo; median, −71%, versus −21% with placebo; p = 0.003) also significantly decreased in patients treated with vismodegib.

Adverse effects

In the trial conducted by Von Hoff et al.,3 patients were followed for up to 30 days after the conclusion of treatment to assess adverse reactions. The investigators found vismodegib to be well tolerated, with most adverse effects categorized as mild to moderate. No grade 5 toxicities were reported. Grade 4 toxicity (asymptomatic hypotension) occurred in 1 (3%) of 33 patients, indicating serum sodium monitoring may be necessary. The most common grade 2 event was muscle spasm, occurring in 3 (9%) of 33 patients; other grade 2 events included dysgeusia, anorexia, and weight loss in 2 patients each (6%) and dyspepsia and hypocalcemia in 1 patient each (3%). The most common grade 3 event was fatigue, occurring in 4 patients (12%); other grade 3 events included weight loss and dyspea in 2 patients each (6%) and muscle spasm, atrial fibrillation, aspiration, back pain, corneal abrasion, dehydration, keratitis, lymphopenia, pneumonia, urinary tract infection, a prolonged Q–T interval, increased serum alkaline phosphatase levels, and increased serum potassium levels in 1 patient each (3%).

In the trial by Sekulic et al.,14 the adverse events reported were similar to those observed by Von Hoff et al.8 and were mostly mild to moderate in severity. Adverse effects of any grade included muscle spasms (68%), alopecia (63%), dysgeusia (51%), decreased weight (46%), fatigue (36%), nausea (29%), decreased appetite (23%), and diarrhea (22%).

In the BCNS trial by Tang et al.,16 in which vismodegib was compared with placebo, grade 1–2 adverse effects that were significantly more common in the vismodegib-treated group were hair loss (occurring in 62% of the vismodegib group, p = 0.004), muscle cramps (81%, p < 0.001), taste disturbance (85%, p < 0.001), and weight loss of >5% (42%, p = 0.003). There was no significant difference in grade 3–4 adverse events between the groups, and no grade 5 toxicities were reported. After a mean observation period of 7 months, 27% of patients receiving vismodegib had stopped taking the drug because of adverse effects; approximately 11 months later, at the cutoff time for data collection, 54% of patients receiving vismodegib had discontinued the medication due to adverse effects.

The package insert for vismodegib includes a black-box warning.12 In animals, the drug has been shown to cause toxicity in embryos (death before birth) and to have teratogenic effects (malformations, severe midline defects, and missing digits). Therefore, pregnant women should not use vismodegib, and a patient’s pregnancy status needs to be confirmed before initiating vismodegib to avoid embryo–fetal death and severe birth defects. Women of childbearing age taking vismodegib should be advised to use effective contraception for at least 7 months after taking the last dose. Men should also be advised that vismodegib can be passed through the semen, and condoms with spermicide should be used for at least 2 months after taking the last dose when having sexual intercourse with women. In addition, patients taking vismodegib should not donate blood for at least 7 months after vismodegib discontinuation.
Dosage and administration

Vismodegib is available as a 150-mg capsule, and the approved dosage is 150 mg orally once daily. This dosage should be taken until the disease progresses or intolerable drug toxicities develop. Vismodegib may be taken with or without food, but the capsules must be swallowed whole and not opened or crushed. Whether the capsules can be administered via a gastrostomy tube has not been studied. No i.v. formulation is currently available. To date, no formal studies have been completed to establish dosage adjustments for patients with renal or hepatic impairment. Therefore, caution and close monitoring are suggested in these populations.

Cost of therapy

For 1 month of treatment with vismodegib, the estimated cost is $7,500, so 10 months of treatment would cost $75,000, which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment vismodegib, the estimated cost is $75,000, 17 which was $7,500, so 10 months of treatment

Place in therapy

Vismodegib is an oral SMO inhibitor recently approved for the treatment of BCC. It is effective in both locally advanced and metastatic BCCs, with response rates ranging from 30% to 60% in two clinical trials. Patients enrolled in these trials had BCCs that were refractory to standard treatments, and vismodegib was not compared to alternative therapies or placebo. While these are impressive results in this treatment-refractory population, it is important to note that vismodegib has not been evaluated as first-line therapy or compared with standard therapy and should generally not be recommended as first-line therapy for BCC.

Patients who are not candidates for surgery or radiation—typically those whose tumor is large or in an inaccessible location—may be treated with vismodegib in the first-line setting. Since most patients have a partial response with vismodegib, the use of vismodegib in the neoadjuvant setting, where the desired endpoint is that vismodegib treatment shrinks the tumor to a surgically amenable size, may be an important future indication.

Another population for whom first-line vismodegib may be considered is patients with metastatic BCC. As of 2004, fewer than 300 cases of metastatic BCC had been reported, with the frequency in large series ranging from 0.0028% to 0.1% of all BCCs. The majority of these patients were treated with cisplatin-based chemotherapy, with ORRs up to 77%, including complete response rates up to 45%. Given the small number of patients with metastatic BCC and the lack of an agreed-upon standard, it is unlikely a comparison of vismodegib and cytotoxic chemotherapy will be performed.

Some discussion of differences between the therapeutic approaches for BCC is appropriate. The expected complete response rate with cisplatin is 45%, while complete responses with vismodegib are rare, suggesting that if compared head-to-head, cisplatin-based chemotherapy would likely be more efficacious. Alternatively, cytotoxic cisplatin-based chemotherapy is likely to have significant toxicities, including neutropenia and renal failure, and vismodegib is well tolerated. Considering efficacy and toxicity, cisplatin-based chemotherapy may be more appropriate in healthier patients, while vismodegib may be preferred in populations where a treatment option with less toxicity is desired.

Vismodegib has also recently been evaluated in patients with BCNS, showing that vismodegib may have chemopreventive properties in this population. Vismodegib was able to decrease the number of new BCCs as well as decrease the size of existing BCCs and represents a promising advance for this patient population.

There are two major limitations to vismodegib use: toxicity and cost. While the toxicities are mild to moderate (grade 1–2) and would be considered a nuisance (hair loss, muscle cramps, taste disturbances) in a typical population with a life-threatening illness, BCCs are rarely life threatening, and fewer than half of patients with BCNS were willing to tolerate 18 months of vismodegib therapy, seemingly preferring fairly frequent surgical procedures over daily oral therapy. Further, the monthly cost of vismodegib is $7500, compared with less than $2000 per surgery, suggesting that surgery may be a more cost-effective approach.

Future directions

While the importance of the hedgehog signaling pathway was first noted in BCNS and BCC, aberrant hedgehog pathway activity also occurs in many other human cancers, and SMO antagonists have shown promising results in medulloblastoma and hematologic malignancies.

Conclusion

Vismodegib was recently approved for the treatment of locally advanced or metastatic BCC that is refractory to standard treatments or if patients are not candidates for surgery or radiation. Vismodegib may have little effect on the treatment of BCC, given its high cost, the high cure rates achieved with standard therapies, and its unacceptable toxicity profile in patients with a non-life-threatening disease. However, vismodegib’s novel mechanism of
action, oral dosage form, preliminary efficacy, and tolerability compared with cytotoxic chemotherapy may make it an attractive candidate for the treatment of other cancers.

References