Vismodegib in advanced basal cell carcinoma

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Vismodegib is an oral small-molecule inhibitor of smoothened homologue protein (SMO), a component of the hedgehog signaling pathway that has been shown to have activity in advanced basal cell carcinoma (BCC). In early 2012, vismodegib was approved by the Food and Drug Administration for treatment of adult patients with metastatic BCC (mBCC) who are not candidates for radiation therapy and adult patients with locally advanced BCC that has recurred following surgery or who are not candidates for surgery or radiation therapy.[1]

Direct targets of hedgehog pathway activity include genes involved in cell proliferation, development, and tissue maintenance. Nearly all BCCs feature genetic alterations in components of the hedgehog pathway that result in overactive hedgehog signaling and uncontrolled proliferation of basal cells. Hedgehog pathway signaling is initiated upon binding of the hedgehog ligand to the patched homologue 1 (PTCH1) receptor, which usually acts to inhibit signaling of SMO. Most BCC tumors have inactivating mutations in PTCH1, leading to aberrant activation of SMO, or, less commonly, activating mutations in SMO.

The approval of vismodegib was based on findings in a single-arm trial in 96 patients with mBCC (33 patients) or locally advanced BCC (63 patients) who had inoperable disease or for whom surgery was not appropriate.[1,2] Patients received vismodegib 150 mg once daily until disease progression, unacceptable toxicity, or discontinuation of the study. The primary endpoint was objective response rate as assessed by independent review. Response was determined according to RECIST criteria in patients with mBCC. In those with locally advanced BCC, response was defined as a decrease of ≥ 30% in the externally visible or radiographic dimension of lesions or complete resolution of ulceration, with external scarring being included in measurement of the externally visible dimension. Progressive disease was defined as an increase of ≥ 20% in the externally visible or radiographic dimension, new ulceration, or new lesion. For patients with multiple target lesions, the sum of the longest diameters was used to determine response.

What's new, what's important

The Food and Drug Administration approved vismodegib for the treatment of adults with metastatic basal cell carcinoma (BCC) or with locally advanced basal cell carcinoma that has recurred after surgery or who are not candidates for surgery or for surgery and radiation. Vismodegib is a novel drug and an inhibitor of hedgehog signaling pathway, which plays an important role in the regulation of cell differentiation and organ formation during normal embryonic development. It becomes inactive in most adult tissues and it is important for tissue maintenance and repair. Its inappropriate reactivation in adult tissues can lead to the development of several human cancers, such as basal cell carcinoma and medulloblastoma.

In a single-arm trial, 104 patients were treated with150 mg of vismodegib daily. The overall response rate was 30.3% in patients with metastatic BCC and 42.9% in patients with locally advanced basal cell carcinoma patients. All of the responses in the metastatic BCC patients were partial. For the evaluable patients with locally advanced BCC, 20.6% had complete responses and 22.2% had partial responses. The side effects of the treatment include muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting, and ageusia. It is an exciting new pathway, new target, and a novel drug. Its role will evolve in the future with further clinical trials.

— Jame Abraham, MD

The median ages for the mBCC and locally advanced BCC groups were 62 and 61 years, respectively, 73% and 56% of patients were men, and all of the patients in both groups were white. In the mBCC group, 97% of patients had received previous therapies, including surgery (97%), radiotherapy (58%), and systemic therapies (30%). In the locally advanced BCC group, 94% of patients had

Report prepared by Matt Stenger, MS.

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How I treat advanced basal cell carcinoma

Basal cell carcinoma (BCC) is an epithelial nonmelanocytic skin cancer that arises from the basal cells located in the lower part of the epidermis. It is the most common cancer worldwide. The head is the most common location for BCC, accounting for 70% of all cases.[1] The trunk is the second-most common site, accounting for 25% of all cases.[2] Although most BCCs are small and curable with surgical resection, some can pose significant morbidity if they are neglected. Effective treatment can be obtained with surgery or radiation therapy; surgery is often the preferred modality based on better outcomes reported in the literature.[3]

For selected low-risk BCC lesions, the curettage and electrodessication approach is often effective. An alternative approach is the surgical excision of the lesion with postoperative pathologic margin assessment. For high-risk disease — defined as a depth of invasion more than 2 mm, a Clark level > IV, perineural invasion, primary site on the ear or nonhair-bearing lip, or being poorly differentiated or undifferentiated — Mohs surgery is recommended. An alternative approach is excision with complete circumferential peripheral and deep margin assessment.[4] Radiation therapy can provide good outcomes in selected cases. It can also be a good option for older patients who are not candidates for surgery. In addition, adjuvant radiation therapy should be considered for BCC with substantial perineural involvement or positive margins after Mohs surgery or excision with CCPDMA.

Surgical resection should be considered a definitive therapy in most cases of BCC. However, for patients with low-risk superficial BCC, topical treatments with imiquimod 5%[5] or fluorouracil 5%[6] are reasonable options as first-line therapy. For patients who have multiple recurrences, locally advanced or metastatic disease, my recommendation for standard of care treatment is vismodegib, a targeted drug that inhibits the hedgehog signaling pathway, which is activated in most BCCs. Almost all of the patients in the study that was the basis for the approval of vismodegib had undergone previous treatments including surgery, radiation therapy, and topical and/or systemic therapy. The response rate was 30% in the metastatic BCC group, with 64% of patients achieving stable disease. For patients in the locally advanced BCC group, the response rate was 43%, with 38% of patients achieving stable disease. The median duration of response was 7.6 months in both groups.[7] Systemic chemotherapy using a carboplatin or cisplatin-based regimen is also a reasonable option in selected patients.

References

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— Hung T. Khong, MD

received previous therapies, including surgery (89%), radiotherapy (27%), and systemic or topical therapies (11%). Among the mBCC patients, 61% had ≥ 3 target lesions, with the most frequent sites being lung (67%) and lymph nodes (21).

In the mBCC group, the median duration of treatment was 10.0 months (range, 0.7-16.4 months), and 58% of patients were still receiving vismodegib at the time of analysis. On independent review, the objective response rate was 30% (95% CI, 16%-48%); the rate was significantly higher than the null hypothesis of 10% ($P = .001$). All of the responses were partial; 64% of patients had stable disease (including 3 patients with unconfirmed response who had tumor shrinkage > 30%) and 3% had progressive disease. Most patients had tumor shrinkage. On independent review, median duration of response was 7.6 months (range, 2.1-11.1 months) and median progression-free survival (PFS) was 9.5 months (95% CI, 7.4 months to not estimable). Data on overall survival (OS) were not mature at the time of analysis.

In the locally advanced BCC group, the median duration of treatment was 9.7 months (range, 1.1-18.7 months), and 45% of patients were still receiving vismodegib at the time of analysis. The objective response rate was 43% (95% CI, 30%-56%), which was significantly higher than the null hypothesis of 20% ($P < .001$). The

complete response rate was 21%; 38% of patients had stable disease and 13% had progressive disease. Most of the patients had tumor shrinkage. The median duration of response was 7.6 months (range, 1.0-12.9 months) and median PFS was 9.5 months (95% CI, 7.4-11.9 months). Data for OS are not yet mature.

All of the patients had 1 or more adverse events during the study, with 57% having adverse events no higher than grade 2. The most common adverse events of any grade were muscle spasm (68%), alopecia (63%), dysgeusia (51%), weight decrease (46%), fatigue (36%), nausea (29%), decreased appetite (23%), and diarrhea (22%). The most common grade 3 or 4 adverse events (≥ 2%) were weight decrease (5%), muscle spasm (4%), fatigue (4%), and decreased appetite (3%). Adverse events led to the discontinuation of study treatment in 13 patients (12%), with the most common such adverse event being muscle spasm (2 patients).

Serious adverse events occurred in 25% of patients. Fatal adverse events were reported in 7 patients (6 in the locally advanced BCC group). The causes of death were unknown for 3 patients and hypovolemic shock, myocardial infarction, meningeal disease, and ischemic stroke in 1 patient each. All 7 patients had clinically significant risk factors or coexisting conditions at baseline. The potential relationship of these events with vismodegib treatment is unknown.

Safety data in the product labeling are based on a total of 138 patients with advanced BCC receiving vismodegib at ≥ 150 mg daily in clinical trials.[1] In this data set, 3 of 10 premenopausal women had amenorrhea during treatment. Grade 3 laboratory abnormalities observed in the total population were hyponatremia (4%), azotemia (2%), and hypokalemia (1%).

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