The Hedgehog Pathway: Updates in Safety and Efficacy in Basal Cell Carcinoma Treatment

Recent findings may improve how physicians understand BCCs and, more specifically, how hedgehog inhibitors can be harnessed to treat them.

BY JONATHAN WOLFE, MD

The Hedgehog pathway inhibitor vismodegib (Erivedge, Genentech) was approved two years ago for the treatment of advanced basal cell carcinomas (BCC). It was approved based on a single, non-randomized Phase II trial showing it to be both safe and effective. Since its approval, researchers have continued to delve deeper into the safety, efficacy, and other factors related to the treatment with vismodegib. Recent findings, in particular, may improve how physicians understand BCCs and, more specifically, how vismodegib can be harnessed to treat them.

NOTABLE RECENT FINDINGS

A recent article published in the Journal of the American Academy of Dermatology examined the safety and efficacy of vismodegib in an expanded access study.¹ Researchers examined 119 patients who received 150mg vismodegib daily until disease progression or intolerable toxicity, for a median of 5.5 months. They found that objective responses occurred in 46.4 percent of cases of locally advanced BCC and 30.8 percent of cases of metastatic BCC. Moreover, response was negatively associated with prior systemic therapy in patients with locally advanced BCC. Mean follow-up for safety was 6.5 months, with muscle spasms (70.6 percent), dysgeusia (70.6 percent), alopecia (58.0 percent), and diarrhea (25.2 percent) as the most common adverse events. This study supports previously published findings and provides important clinical data in support of the efficacy and safety of vismodegib for the treatment of advanced BCC.

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Although continued clinical findings represent the best means of understanding the therapeutic benefit of vismodegib, one review examining the economic and psychological aspects of BCC shows the utility of vismodegib in a different but no less relevant context.² Noting the paucity of effective therapies for advanced stage disease, the authors noted that the approval of vismodegib carries with it a renewed sense of optimism.

For individuals with advanced disease where surgical options are not an option, vismodegib offers patients an option to avoid large procedures leading to disfigurement and long term complications. This is particularly true in older patients, or those with multiple medical issues who may not be able to tolerate such maneuvers. Further, vismodegib could be utilized as a tumor debulk- ing agent, similar to radiation, prior to surgery.
this approach has not been rigorously studied to date, it certainly appears as if this oral agent could be utilized in such a way.

Of course, vismodegib carries with it a large expense, and there are controversial reports of rebound growth after discontinuation of therapy. Further resistance to vismodegib has been reported, and long-term follow-measured in years has yet to be formally documented in the literature.

**CONTROVERSIAL CASE REPORT**

In terms of safety, one report published in 2012 caused some concern regarding BCC recurrence after cessation of vismodegib. The publication in question reported a rebound of BCC after discontinuation of treatment in a patient with nevoid basal cell carcinoma syndrome. The patient was receiving vismodegib 150mg as part of an unreferenced clinical trial and discontinued treatment after seven months because of intolerable side effects. The authors suggest a rebound of BCC, as well as increase in subclinical extensions after discontinuation of therapy. However, a recent editorial published in *Dermatologic Surgery*, the same journal that published the initial report, disputes these findings. The authors of the editorial maintain that there is no basis for the 2012 publication’s assertion.

Based on a review of the case report, the authors of the recent editorial argue that the patient in question may indeed have experienced recurrence of some tumors, which they point out is a well-known phenomenon. But they dispute the claim of a “rapid resurgence” or “rebound,” citing a lack of evidence for such an effect. They conclude that such characterizations are misleading and inaccurate. Nevertheless, the reported case highlights the need for further understanding of histologic and clinical changes after vismodegib, the authors note.

**CONCLUSION**

While sufficient evidence was lacking in the original 2012 case report, the disputed findings nevertheless raise important questions about the broader application of newer therapies. Vismodegib has no doubt proven to be an essential agent in the treatment of inoperable BCCs, but we still have much to learn about its long-term application. Moreover, the availability of effective agents such as vismodegib should compel all physicians who treat patients with BCCs to consider the larger impact of BCC on patients’ lives (see sidebar), and to qualify not only the risk benefit ratio for each patient, but also think about the broader implications of treatment.

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