Resolution of Odontogenic Keratocysts of the Jaw in Basal Cell Nevus Syndrome With GDC-0449

Leonard H. Goldberg, MD; Jennifer M. Landau, BS; Megan N. Moody, MD, MPH; Natalia Kazakevich, MD; Aton M. Holzer, MD; Adam Myers, MD

Background: Odontogenic keratocysts of the jaw are a central feature of basal cell nevus syndrome (BCNS) and arise from the basal cell layer of the surface epithelium. Although they are benign, they tend to be aggressive, with local invasion of bony structures, extensive growth, and potential for substantial disfigurement and speech dysfunction. Complete surgical resection is the current standard of care; however, the procedures are often technically challenging and are followed by high recurrence rates.

Observations: We report the case of a 55-year-old man with a long-standing history of BCNS. Over a 25-year period, this patient had been treated for many basal cell carcinomas (BCCs). He also had multiple large odontogenic keratocysts in the mandible that had previously been treated using surgical, chemotherapeutic, and radiation treatment techniques. He had also undergone a right inguinal lymph node dissection after BCC metastasis was diagnosed within a lymph node. Owing to the recalcitrant nature of his condition and his history of BCC metastasis, the patient was started on a daily regimen of a new oral drug, GDC-0449, which inhibits the hedgehog signaling pathway, a key genetic contributor in the oncogenesis of BCCs. In addition to complete resolution of all his BCCs at 12-week follow-up, nearly complete resolution of 3 odontogenic keratocysts was documented by serial dental radiographs after 2 years of therapy.

Conclusions: We report the nearly complete regression of multiple BCNS-associated odontogenic keratocysts following nonsurgical treatment with GDC-0449. This novel drug, useful for the treatment of BCC, also appears to be effective for treatment of odontogenic keratocysts.


REPORT OF A CASE

A 55-year-old man with a strong family history of basal cell nevus syndrome (BCNS) had numerous basal cell carcinomas (BCCs) and multiple associated odontogenic keratocysts. The patient was first diagnosed as having BCCs in his early 20s and subsequently underwent treatment for over 750 BCCs. He had other features of BCNS, including odontogenic keratocysts, palmar pits, partial cleft lip, bifid ribs, frontal bossing, and pectus deformity. After numerous surgical procedures for BCCs, including a lymph node dissection after BCC metastasis was diagnosed within a lymph node. Owing to the recalcitrant nature of his condition and his history of BCC metastasis, the patient was started on a daily regimen of a new oral drug, GDC-0449, which inhibits the hedgehog signaling pathway, a key genetic contributor in the oncogenesis of BCCs. In addition to complete resolution of all his BCCs at 12-week follow-up, nearly complete resolution of 3 odontogenic keratocysts was documented by serial dental radiographs after 2 years of therapy.

Most of his existing BCCs resolved after approximately 12 weeks of continuous treatment, and he continued the treatment to prevent development of new BCCs. After 2 years of this regimen, repeated radiographs obtained at a dental visit illustrated nearly complete resolution of existing odontogenic keratocysts without interval development of any new ones. Figures 1, 2, and 3, serial dental radiographs acquired from 2007 to 2010, show progressive involution and regression of 3 odontogenic keratocysts. In this case, it appears that GDC-0449 was effective in the treatment of odontogenic keratocysts associated with BCNS.

COMMENT

The most common complications of BCNS are BCCs and odontogenic keratocysts; these cysts have the potential to be severely disfiguring. Until now, surgery has...
been the only effective treatment option for these cysts. The observed resolution of multiple odontogenic keratocysts in our patient with BCNS during his course of treatment with GDC-0449 was an unexpected benefit. Currently in stage 2 trials, GDC-0449 is not yet widely available to the general public. If and when it is made available, physicians can prescribe this medication for the treatment of odontogenic keratocysts.

Although the exact molecular mechanisms underlying the pathogenesis of BCC have yet to be fully elucidated, it appears that most cases, whether sporadic or hereditary, are related genetically and show aberrations in the hedgehog signaling pathway. The hedgehog signaling pathway involves a dynamic relationship between a series of tumor suppressor genes (patched homologue 1 [PTCH1]) and oncogenes (smoothened homologue [SMO]). This pathway is especially active during embryogenesis, when it functions to regulate cellular proliferation during normal growth and development; it is generally quiescent in adult tissues. As an oncogene, activated SMO leads to cellular division and proliferation. Conversely, PTCH1 is a tumor suppressor gene; when activated, it exerts an inhibitory effect on SMO signaling to keep cell division under control. When the intricate dynamic relationship between these 2 opposing genes is disrupted, oncogenesis is the result; this most commonly occurs as a result of PTCH1 inactivation, or more rarely from SMO activation. The interactions of these particular pathways have been implicated in the growth and development of advanced BCCs. Specifically, a loss-of-function mutation in PTCH1 is the most common molecular aberration found in BCC.

A selective inhibitor of SMO, GDC-0449 is currently being evaluated in clinical trials for the treatment of BCC and shows extremely promising results. Phase 1 trials have shown clinically significant responses, defined as disappearance of tumors or reduction in tumor size of greater than 50% in patients with advanced and metastatic BCC refractory to conventional therapies. The adverse effects of the drug consist of hair loss, fatigue, muscle spasms, and cardiac conduction abnormalities. To attest to the clinical effectiveness of the drug in treating advanced BCC, our research group has previously reported a case of resolution of all but 1 BCC in the same patient described herein after 12 weeks of oral therapy with this drug.

The present case suggests that GDC-0449 is also effective in treating the odontogenic keratocysts of BCNS. This finding may be further supported by the case report of a patient with BCNS who developed 2 jaw cysts that were genetically analyzed and found to possess distinct PTCH1 loss-of-function mutations similar to those previously implicated in the pathogenesis of BCC. Therefore, it is not surprising that GDC-0449 can cause resolution of these cysts, just as it eliminates BCCs through inhibition of the hedgehog signaling pathway.

The odontogenic keratocysts of BCNS have the potential to cause disfigurement and loss of function. Our patient had undergone multiple procedures to remove his cysts and was left with a noticeable speech impediment. The main treatment options include enucleation, with or without curettage, peripheral ostectomy, chemical curettage (Carnoy solution), and resection. Recurrences are fairly common and may be attributed to incomplete removal of the original cysts, microscopic satellite cysts, and the development of new cysts within the adjacent area. We treated our patient with oral GDC-
0449 for BCCs in BCNS and incidentally noted nearly complete resolution of the odontogenic keratocysts without aggressive treatment.

Accepted for Publication: January 26, 2011.
Published Online: March 21, 2011. doi:10.1001/archdermatol.2011.50
Correspondence: Leonard H. Goldberg, MD, DermSurgery Associates, 7515 Main St, Ste 240, Houston, TX 77030 (goldbl@dermsurgery.org).

Author Contributions: Drs Goldberg, Landau, Moody, Kazakevich, and Holzer had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Goldberg, Landau, Moody, and Kazakevich. Acquisition of data: Landau, Moody, Kazakevich, and Holzer. Analysis and interpretation of data: Goldberg, Landau, Moody, Kazakevich, and Myers. Drafting of the manuscript: Landau, Moody, and Kazakevich. Critical revision of the manuscript for important intellectual content: Goldberg, Moody, Holzer, and Myers. Administrative, technical, and material support: Landau, Moody, Kazakevich, Holzer, and Myers. Study supervision: Goldberg. Financial Disclosure: None reported.

Additional Information: Dr Goldberg is currently a principal investigator for this drug.

REFERENCES


Top Accessed Article: Management of Pigmented Melanocytic Nevi


In this article, Zalaudek and colleagues present a global approach to the examination of benign and malignant pigmented nevi using dermoscopy. They review more than 118 publications and summarize the findings, with attention to dermoscopic criteria and patient-related factors. They provide dermoscopic images of typical benign nevi and illustrate how the appearance of these benign nevi changes with differing Fitzpatrick skin types. They used this method throughout their study, describing dermoscopic patterns and their variations with age, UV exposure, anatomical site, and pregnancy. Similarly, they also review the dermoscopic features of melanoma, with attention to eccentric hyperpigmentation, and compare these images with blue nevi and metastatic melanoma. They continually stress the importance of a thorough skin examination, including assessment of the type and distribution of nevi. With this extensive review, Zalaudek and colleagues offer a more comprehensive approach to dermoscopy whereby the interpretation of these images not only is based on pattern recognition but also is dependent on a wide range of patient-specific factors.

From August 2009 through August 2010, this article was viewed 1842 times on the Archives of Dermatology Web site.

Mary C. Martini, MD

Author Affiliation: Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois.
Contact Dr Martini at the Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL 60611-2997 (mmartini@nmfl.org).
Financial Disclosure: Dr Martini is on the advisory board of Dove Unilever, is an investigator for Melasciences, and owns stock in Pfizer, Merck, and Johnson & Johnson.