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Surgical Excision After Neoadjuvant Therapy With Vismodegib for a Locally Advanced Basal Cell Carcinoma and Resistant Basal Carcinomas in Gorlin Syndrome

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Vismodegib is useful to treat locally advanced or metastatic basal cell carcinomas (BCCs),¹ but to our knowledge, its use as a neoadjuvant to shrink BCCs before surgery has not been reported. This case illustrates the role of vismodegib as a neoadjuvant agent. In addition, this case highlights the fact that a patient with Gorlin syndrome can develop resistant BCCs while taking vismodegib, a phenomenon not widely recognized although recently reported.²

Report of a Case

A 55-year-old white man with Gorlin syndrome, including a history of multiple basal cell carcinomas (BCCs), jaw cysts, and palmar pits, presented with a 10-year history of a previously untreated 13 × 17-cm ulcer on the right scalp (Figure 1A). Biopsy showed a BCC with osteoid formation, and a computed tomography (CT) scan of the head revealed large regions of erosion through the calvarium, some of which extended to the dural surface (Figure 1D). Nointracranial extension was identified.

Owing to the advanced nature of his BCC, he began treatment with vismodegib,¹ 150 mg/d, and was treated for 51 weeks with dramatic regression of the ulcer (Figure 1B), including decreased size of the skull defect (Figure 1E). However, while undergoing continuous vismodegib therapy, he developed a new nodule in the posterior scalp and biopsy-confirmed nodular BCC, representing secondary (acquired) resistance (Figure 1B, white arrow). In addition, a new rapidly growing tragus lesion extending into the external auditory canal (EAC) was noted and found to be nodular BCC on biopsy (Figure 1B, yellow arrow).

Given the persistence of the original ulcer and development of new BCCs demonstrating acquired resistance, the patient had the lesions surgically excised by the otolaryngology team. Frozen sections of the ulcer showed no BCC, although final pathologic findings were positive for BCC in the region near the forehead, with negative surgical margins. The BCCs with acquired resistance were excised with negative margins. Inspection of the calvarial bone by the neurosurgery team revealed no BCC involvement, although there was a small

cerebrospinal fluid leak from where the rough bone edge met dura, which was closed with synthetic absorbable sealant.

Full-thickness skin grafts from his left anterior thigh and right neck were used to cover the scalp and tragus/EAC defects. The patient recovered well and was discharged after 6 days in the hospital. Figure 1C shows the patient 2 months after surgery. Because the pik3c (phosphatidylinositol 3-kinase catalytic) enzymes and Gli transcription factors have been associated with vismodegib resistance in medulloblastomas,³ we interrogated the levels of these transcripts in the 2 resistant tumors, R1 and R2 (Figure 2). While definitive studies on resistance mechanisms are under way, both tumors showed elevations of pik3c (isoform 2a), and R2 showed elevation of Gli1, ptch1 protein, and all isoforms of pik3c. Studies are ongoing to further identify resistance mechanisms in drug-treated BCCs.

Discussion

This case illustrates 2 points. First, vismodegib can be used as a neoadjuvant to shrink a large locally advanced BCC prior to surgery, leading to a smaller and less morbid procedure. Vismodegib is currently approved by the US Food and Drug Administration for locally advanced or metastatic BCCs, but its use as a neoadjuvant prior to surgery could be useful. Second, acquired (secondary) resistance to vismodegib can occur while a patient is undergoing continuous drug therapy, even in patients with Gorlin syndrome. These patients can be effectively treated with surgical excision. Future studies may confirm the utility of vismodegib as a neoadjuvant therapy in locally advanced or even operable BCCs to shrink the lesions prior to surgical excision, leading to less scarring and morbidity.

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Figure 1.

Clinical and computed tomographic (CT) images of a 55-year old man with Gorlin syndrome. The patient's locally advanced basal cell carcinoma (BCC) regressed under treatment with neoadjuvant vismodegib but demonstrated areas of drug resistance.

Residual BCC and resistant areas were excised. A, Locally advanced BCC on the right scalp prior to treatment. B, Tumor shrinkage after 51 weeks of vismodegib therapy showing development of 2 areas of resistant BCC (arrowheads). C, After surgical excision, the patient received full-thickness skin grafts to cover the right scalp and the right tragus/external auditory canal, shown here at 2 months after surgery. D, Pretreatment axial CT image shows bony defects of the calvarium under the BCC. E, Posttreatment CT scan shows shrinkage of the calvarial defect after vismodegib therapy.

Figure 2.

Vismodegib-resistant basal cell carcinoma (BCC) tumors (hBCCSmos) show increased levels of Gli transcription factors and pik3c (phosphatidylinositol 3-kinase catalytic) enzymes. Tumor hBCCSmo^{R1} was on the tragus and hBCCSmo^{R2} was on the posterior scalp. A, Compared with normal skin from the same patient, both resistant tumors showed elevation of pik3c (isoform 2a) level. Tumor hBCCSmo^{R2} showed elevations of Gli1, ptch1 protein, and all isoforms of pik3c levels. Analysis was undertaken by quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR) performed in triplicate (RNeasy Mini Kit; Qiagen). Transcripts were quantified in triplicate using Brilliant II SYBR Green qRT-PCR Master Mix Kit (Agilent Technologies) with primers to human *GLI1*,⁴ *PTCH1*,⁴ and *PIK3C* isoforms.⁵ B, Immunofluorescence analysis performed on

formalin-fixed, paraffin-embedded tissue shows that Gli1 protein levels are elevated in tumor hBCCSmo^{R2} but not in hBCCSmo^{R1} compared with normal skin from the same patient. The top row of images depicts tissues viewed without fluorescence; the bottom row of images depicts tissues viewed with fluorescence. Immunofluorescence studies were performed with anti-Gli1 (1:500; Cell Signaling) and Hoechst 33342 (1:10 000; Invitrogen). Confocal images were acquired on a Leica SP2 AOBS Laser Scanning Microscope with an HCX PL APO 63× oil-immersion objective.