The Use of Vismodegib to Shrink Keratocystic Odontogenic Tumors in Patients With Basal Cell Nevus Syndrome

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IMPORTANCE Keratocystic odontogenic tumors (KCOTs) of the jaw affect more than 65% of patients with basal cell nevus syndrome (BCNS). Surgery frequently causes facial disfigurement and is not always curative. Most BCNS-related and some sporadic KCOTs have malignant activation of the Hedgehog signaling pathway.

OBSERVATIONS We examined the effect of vismodegib (an oral Hedgehog pathway inhibitor) on KCOT size in patients with BCNS enrolled in a clinical trial testing vismodegib for basal cell carcinoma prevention (NCT00957229), using pretreatment and posttreatment magnetic resonance imaging. Four men and 2 women had pretreatment KCOTs (mean longest diameter, 2.0 cm; range, 0.7-3.3 cm), occurring primarily in the mandible. Patients were treated with vismodegib, 150 mg/d, for a mean (SD) of 18.0 (4.8) months (range, 11-24 months). Four patients experienced a size reduction and 2 had no change. Vismodegib reduced the mean longest diameter of KCOTs in all patients by 1.0 cm (95% CI, 0.03-1.94; P = .02) or 50% from baseline. We observed no enlargement of existing KCOTs or new KCOT development.

CONCLUSIONS AND RELEVANCE Vismodegib shrinks some KCOTs in patients with BCNS and may offer an alternative to surgical therapy. These effects were maintained for at least 9 months after drug cessation in 1 patient. Further studies assessing long-term efficacy and optimal maintenance regimens should be performed.

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Basal cell nevus (Gorlin) syndrome (BCNS) (OMIM 109400) is a rare autosomal dominant disease in which affected individuals can develop a panoply of phenotypic abnormalities, the most prominent of which are basal cell carcinomas (BCCs) of the skin and keratocystic odontogenic tumors (KCOTs) of the jaw. The incidence of KCOTs varies from 4% to 16.5% of oral pathology specimens; however, they affect 65% to 100% of patients with BCNS. Multiple KCOTs, which typically grow rapidly, are often the earliest presenting feature of BCNS. Surgery is the standard of care, but it frequently causes facial disfigurement and is not always curative. To our knowledge, there is no effective nonsurgical therapy for KCOTs.

Patients with BCNS inherit 1 defective copy of the tumor suppressor gene PATCHED 1 (PTCH1) (OMIM 601309), which encodes a primary inhibitor of the Hedgehog (HH) signaling pathway. Functional loss of the second allele leads to activation of the HH pathway signaling. Keratocystic odontogenic tumors in patients with BCNS and in 30% of sporadic lesions harbor somatically acquired PTCH1 mutations and increased HH target gene expression (GLI1). They also have been seen in heterozygous Ptch1 knockout mice and in K5-Gli2 transgenic mice. This discovery highlights the possibility that the newly approved targeted HH pathway inhibitor, vismodegib (Erivedge), might be effective for KCOT treatment. We conducted a substudy in patients enrolled in a recent clinical trial testing vismodegib for BCC prevention to determine its effect on KCOT size in patients with BCNS.

This study received institutional review board approval by Children’s Hospital Oakland Research Institute, and all participants provided written consent.

Report of Cases

Of 41 patients with BCNS enrolled in a clinical trial (NCT00957229) testing vismodegib (150 mg/d) for BCC prevention, 18 participated in the KCOT substudy and had pretreatment (baseline) magnetic resonance imaging (MRI). We performed posttreatment MRI in 8 patients with KCOTs at baseline who had received at least 11 months of vismodegib after the pretreatment MRI (Figure 1).
We recorded reasons for not having an MRI, time interval between MRIs, treatment duration, and KCOT characteristics. We calculated the percentage reduction in KCOT size (longest diameter in centimeters) from baseline and used the Wilcoxon signed rank test to compare the change in KCOT diameters before and after vismodegib treatment.

We excluded patients without paired MRIs from the analysis. We examined face and neck MRI (1.5 or 3.0 T) with coronal, sagittal, and axial T1 fast spin-echo and multipanlar T2 to demonstrate the intrinsic high T2 signal of KCOTs. A single study radiologist (T.J.) compared all paired MRIs and/or reports.

Results

Of the 41 patients enrolled in the original clinical trial, 8 we obtained baseline MRIs in 18, of whom 9 (50%) had KCOTs. Twenty-three patients refused to participate in the MRI–KCOT study because they had no history of tumors or had recent negative dental imaging, were unable to fit into the MRI scanner, or perceived having an MRI scan as an inconvenience (Figure 1).

We excluded from our analysis 3 of the 9 patients with KCOTs diagnosed on baseline MRI because 2 had tumors removed and 1 had a movement artifact on posttreatment MRI, precluding exact measurement. We performed posttreatment MRIs in 2 patients with no KCOTs at baseline due to new jaw pain to assess for recent growth of KCOTs while receiving vismodegib. Thus, a total of 6 patients with paired KCOT MRIs are included in the final analysis (Table and Figure 1).

Study participants included 4 men and 2 women, with a mean (SD) age of 51 (8) years (range, 37-59 years) (Table). All patients had previous removal of KCOTs, with most having had at least 2 procedures.

In 6 patients with a total of 9 documented KCOTs, we obtained posttreatment MRIs within a mean (SD) of 19.5 (4.0) months (range, 13-23 months) after baseline imaging. During this interval, we treated these patients with vismodegib for a mean (SD) of 18.0 (4.8) months (range, 11-24 months); 3 patients took drug breaks (ie, a brief period off vismodegib treatment) (Table). The baseline MRI of 1 of the 6 patients was performed 5 months after starting vismodegib, with 2 KCOTs seen. The mean longest diameter of baseline KCOTs was 2.0 cm (range, 0.7-3.3 cm). In 6 of 9 patients, KCOTs occurred primarily in the mandible. Of the 6 patients with tumors, 4 experi-

Table. Percentage Change in Cyst Size From Baseline to Posttreatment Magnetic Resonance Imaging

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>KCOT Location</th>
<th>Total Months Taking Drug by Posttreatment MRI*</th>
<th>Months Between MRIs</th>
<th>Baseline KCOT Size, Longest Diameter, cm</th>
<th>Posttreatment KCOT Size, Longest Diameter, cm</th>
<th>Change in Cyst Size, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/55</td>
<td>R maxilla L mandible</td>
<td>18</td>
<td>13</td>
<td>3.1</td>
<td>0</td>
<td>-100</td>
</tr>
<tr>
<td>2/M/59</td>
<td>Midline mandible</td>
<td>24</td>
<td>23</td>
<td>0.7</td>
<td>0.7</td>
<td>0</td>
</tr>
<tr>
<td>3/M/51</td>
<td>R mandibular ramus</td>
<td>20a</td>
<td>23</td>
<td>2.3</td>
<td>2.3</td>
<td>0</td>
</tr>
<tr>
<td>4/M/48b</td>
<td>L maxilla L mandible</td>
<td>11b</td>
<td>22</td>
<td>3.2</td>
<td>0.9</td>
<td>-100</td>
</tr>
<tr>
<td>5/M/37</td>
<td>L maxilla R mandible</td>
<td>21</td>
<td>19</td>
<td>3.3</td>
<td>2.0</td>
<td>-25</td>
</tr>
<tr>
<td>6/I/57</td>
<td>Right mandible</td>
<td>14a</td>
<td>17</td>
<td>1.3</td>
<td>1.2</td>
<td>-8</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td>18.0 (4.8)</td>
<td>19.5 (4.0)</td>
<td>2.0 (1.0)</td>
<td>1.0 (0.9)</td>
<td>-50 (45)</td>
</tr>
</tbody>
</table>

Abbreviations: KCOT, keratocystic odontogenic tumor; L, left; MRI, magnetic resonance imaging; R, right.

* Accounting for drug breaks (ie, a brief period off vismodegib treatment).

b Patients 3, 4, and 6 took 3 months of drug breaks between MRIs.

b Second posttreatment MRI 9 months after discontinuation of vismodegib: L maxilla KCOT, 0 cm; L mandible KCOT, 0.7 cm.
enced a reduction in KCOT size and 2 had no change. Vismodegib reduced the longest diameter of all monitored KCOTs by a mean of 1.0 cm (95% CI, 0.03-1.94; \(P = .02\)), that is, by 50% from baseline. No enlargement or new KCOTs occurred in any case, including the 2 patients without KCOTs at baseline. In one patient with 100% resolution of 1 KCOT with vismodegib, there was no recurrence 9 months after drug cessation (Figure 2). All patients experienced mild adverse effects (grade 1) of taste loss, muscle cramps, and hair loss, as previously reported. Three experienced grade 2 muscle cramps and gastrointestinal disturbance, necessitating brief drug breaks.

Discussion

We found that vismodegib can shrink some KCOTs in patients with BCNS, with a mean size reduction of 50% in our study. Two patients had complete resolution of 1 or more KCOTs, with no enlargement of existing tumors or development of new lesions in any case. We found no KCOT relapse after a 9-month drug discontinuation in 1 patient, who also had minimal BCC recurrence at that time.

Vismodegib is an oral HH pathway inhibitor approved for the indefinite treatment of locally advanced or metastatic BCCs. In one case report, Goldberg et al\(^3\) incidentally noted resolution of KCOTs in 1 patient with BCNS treated with vismodegib (270 mg/d) for 2 years. This dose was used in phase I studies before the data demonstrated the 150-mg/d dosage to be the most efficacious. In 1 patient, there was no KCOT recurrence 9 months after drug cessation. In fact, there was further size reduction, albeit minimal, of the mandibular tumor. Interestingly, this patient had recurrence of only 1 BCC in the same period, a much lower recurrence rate than previously reported.\(^8\) The incidence of KCOT recurrence in reported series varies from 0% to 62%, with a higher recurrence rate in BCNS-related tumors (>80%) compared with sporadic tumors.\(^11\) This variability could relate to the diverse nature of the cases reported, the different treatment protocols used, and variations in posttreatment monitoring. The management of KCOTs remains controversial. Conservative therapy, such as simple enucleation or marsupialization, has a recurrence rate of 50% compared with a lower rate following aggressive complete resection.\(^12\) Recurrence, which typically develops within 5 years of treatment, is thought to occur due to incomplete removal of the original cysts, the presence of microscopic satellite cysts, or new cyst development in adjacent areas.\(^13\) Relapse has been reported even after 41 years,\(^14\) necessitating long-term follow-up, particularly since these tumors have locally aggressive behavior and, rarely, malignant potential (primary intraosseous squamous cell carcinoma).\(^4\)

Limitations of this study include possible selection bias since only a subset of patients elected to undergo imaging, selecting for patients with recent or symptomatic KCOTs. Most of the 41 clinical trial patients reported previous surgical treatment for KCOTs. We studied only patients with BCNS, thus limiting the generalizability of the results to syndrome-related KCOTs. However, since 30% of sporadic KCOTs harbor a \(PTCH1\) mutation,\(^4\) vismodegib could be effective for a significant percentage of sporadic tumors. In addition, analysis of KCOT tissue to assess for \(PTCH1\) mutations could explain some vari-

Figure 2. Magnetic Resonance Images of Patient 4

Serial sagittal T2-weighted magnetic resonance images demonstrating the size change in the left maxillary keratocystic odontogenic tumor (arrows) (A) from baseline, (B) after 11 months of vismodegib, and (C) 9 months after drug discontinuation.
ability in response. Strengths include the availability of pretreatment and posttreatment MRIs for KCOT size analysis, as well as, to our knowledge, the largest number to date of patients with KCOTs treated with vismodegib. We chose to image with MRI instead of dental radiographs to improve KCOT measurement and avoid exposure to ionizing radiation, which can induce BCCs in patients with BCNS.15

Conclusions

Our findings confirm functional involvement of the HH pathway in KCOTs and illustrate the usefulness of treatment with molecularly targeted drugs such as vismodegib. This is particularly important for patients with multiple KCOTs, who can be left with facial disfigurement and a speech impediment following multiple surgical procedures. Vismodegib offers a non-surgical treatment option, potentially revolutionizing the management of KCOTs in BCNS. It is difficult to predict which patients develop KCOTs due to variable expression in BCNS; however, MRI may be used for screening during the initial diagnostic workup and for those with jaw symptoms. Further studies into optimal maintenance regimens of vismodegib for KCOT treatment are required. An ongoing clinical trial (NCT01556009) assessing its use as maintenance therapy for BCCs may yield more information.