Noninvasive monitoring of basal cell carcinomas treated with systemic hedgehog inhibitors: Pseudocysts as a sign of tumor regression

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Background: Oral hedgehog inhibitors (HHIs) have shown significant efficacy in the treatment of basal cell carcinoma (BCC). The evaluation of tumor regression has been performed using clinical photography and radiographic scans. Noninvasive imaging techniques, such as reflectance confocal microscopy (RCM) and high-definition optical coherence tomography (HD-OCT), have been shown to be valuable in detecting BCC in the skin.

Objective: We monitored HHI-treated BCC using RCM and HD-OCT in vivo and correlated morphologic changes seen on imaging to changes in traditional histopathology.

Methods: Six BCCs in 5 patients receiving HHIs (vismodegib or sonidegib) were examined by RCM and HD-OCT before and during treatment. Characteristic features were compared to histopathologic findings, including immunohistochemical analysis.

Results: Characteristic features of BCC in RCM and HD-OCT decreased or disappeared completely during HHI treatment. Half of the clinically complete responding tumors still featured tumor residue. Pseudocystic structures ("empty" tumor nests in imaging) and widespread fibrosis (coarse bright fibers) were new findings and could be confirmed by histopathology.

Limitations: Our study was limited by the number of tumor samples and imaging timepoints.

Conclusion: Using RCM and HD-OCT, HHI-induced regression of BCC can be visualized noninvasively in the skin. The formation of pseudocysts and fibrosis were characteristic signs of BCC response to HHIs. (J Am Acad Dermatol 2014;71:725-30.)

Key words: basal cell carcinoma; hedgehog inhibitor; high-definition optical coherence tomography; noninvasive diagnosis; reflectance confocal microscopy.

Basal cell carcinoma (BCC) is the most common cancer worldwide, with a rising incidence in fair-skinned populations.[1-3] While surgical excision is the treatment of choice in most cases, new strategies using targeted therapy have been recently developed—namely, the inhibition of the hedgehog signaling pathway by small molecules. Under normal conditions, the hedgehog ligand receptor patched (PTCH) suppresses the activation of the smoothened (SMO) protein that otherwise would activate the signaling cascade.[4] In 90% of BCCs, including sporadic BCC, the pathway is reactivated because of molecular alterations in PTCH or SMO.[5] Inactivating mutations of PTCH or activating mutations of SMO results in activation of the downstream targets of the Gli transcription factor

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family, which promote the development of BCC.[6] Hedgehog inhibitors (HHIs) have recently been developed for targeted therapy of BCC. The SMO inhibitor vismodegib is administered orally and has shown objective response rates of 30% to 55% and tumor control rates of 80% to 90% in locally advanced and metastatic BCCs and promising efficacy in patients suffering from basal cell nevus syndrome.[7-10]

Vismodegib was approved by the US Food and Drug Administration in 2012 and in Europe in 2013 for the treatment of metastatic or locally advanced BCC in patients who are not candidates for either surgery or radiotherapy. Another SMO inhibitor, LDE225 (sonidegib), is currently being tested in a clinical phase II trial (National Clinical Trial 01237053) for the treatment of locally advanced and metastatic BCC.

CAPSULE SUMMARY

- Oral hedgehog inhibitors are a newly approved treatment for advanced and metastatic basal cell carcinoma.
- Reflectance confocal microscopy and high-definition optical coherence tomography imaging in vivo reveal pseudocystic structures and extensive fibrosis as signs of hedgehog inhibitor–induced basal cell carcinoma regression.
- Noninvasive imaging devices are a valuable tool to monitor the nonsurgical treatment of basal cell carcinomas.

The treatment responses in previous HHI studies have been evaluated by clinical examination, photographs, magnetic resonance imaging (MRI) or computed tomography (CT) scans, and biopsy specimens obtained from target lesions. However, facing the increasing options of nonsurgical treatment of BCC—including recurrent cicatricial and multiple superficial subtypes—neither repeated biopsy specimens nor clinical evaluation only seem reasonable for evaluation of the therapeutic efficacy, while MRI and CT imaging are only applicable in large lesions. In this context, high-resolution skin imaging techniques, such as reflectance confocal microscopy (RCM) and high-definition optical coherence tomography (HD-OCT), are becoming interesting options for treatment monitoring and evaluation. It has already been shown that both methods are successful in the diagnosis of nonmelanoma skin cancer and are valuable in the recognition of specific features of BCC in vivo.[11-14]

The purpose of our study was to correlate histopathologic changes during HHI treatment to those detected on RCM and HD-OCT imaging.

METHODS

Participants and treatment protocol

We investigated 6 biopsy-proven BCC lesions (3 superficial, 2 nodular, and 1 cicatricial BCC subtype) of 5 patients, 3 of whom had nevoid BCC syndrome, who were receiving either vismodegib (3 patients) or sonidegib (2 patients) at the Department of Dermatology, University Hospital, University of Munich. Informed written consent was obtained from each patient. The lesions were examined by RCM and HD-OCT before treatment with HHIs and a timepoint between 9 and 24 weeks of HHI therapy. A biopsy specimen of the lesion was obtained between 1 to 7 days after imaging. The study had been approved by the local ethics committee of the Medical Faculty of the University of Munich, Germany.

RCM and HD-OCT

RCM and HD-OCT imaging was performed using commercially available devices (Vivascope 1500 [Mavig GmbH, Munich, Germany] and Skintell [AgfaHealthCare, Mortsel, Belgium]), which have been described elsewhere in detail.[12,15] RCM and HD-OCT offer lateral and axial resolution of 1.25 to 2.5 μm and 3 μm, respectively, and a penetration depth of about 250 μm and 570 μm, respectively. Each BCC lesion was systematically analyzed using RCM and HD-OCT. According to the literature, we defined the following criteria characteristic for BCC in RCM imaging: bright or dark tumor islands, streaming, spoke-wheel sign in tumor nests, and cleft-like spaces.[15] According to our previous publication, we defined the following criteria characteristics for BCC in HD-OCT imaging: grey/dark tumor nests, spoke-wheel sign, cleft-like spaces, and bright peritumoral stroma.[12]

Histologic evaluation

Biopsy specimens of the lesions were obtained both before and during HHI treatment and prepared for conventional histology using hematoxylin–eosin stain. Additional immunohistochemical analysis was performed in 3 lesions for the detection of BerEp4 (epithelium-specific membrane antigen; Dako, Glostrup, Denmark), Bcl2 (antiapoptotic protein; Cell Marque, Rocklin, CA),[16] and Verhoeff–van Gieson elastin stain (Carl Roth GmbH, Karlsruhe, Germany) for the differentiation of scar tissue from solar elastosis.