approximately 20% to 30% of patients. Characteristically, HFSR presents as painful, hyperkeratotic, erythematous plaques on the palms and soles in areas subject to increased pressure. Other mucocutaneous effects described with anti-VEGF agents include keratoacanthoma, squamous cell carcinoma, splinter subungual hemorrhages, hair depigmentation, and stomatitis.2

Both systemic and cutaneous toxic effects of axitinib are consistent with other agents in the same class, with a significant incidence of HFSR.3,4 Hand-foot skin reaction has been proposed to result from blockade of VEGF receptor and platelet-derived growth factor receptor in areas repeatedly subject to subclinical trauma, disrupting normal vascular repair processes in fibroblasts and endothelial cells.4 While the acral lesions in the present patient were distinct from HFSR, it is possible that a similar process was responsible. Inhibition of VEGF leads to increased vascular tone,1 and so dysregulated vasocnstriction in the skin may disrupt normal tissue repair.4 Indeed, hypertension in patients treated with concurrent sorafenib and bevacizumab, a monoclonal antibody against VEGF, was found to be a risk factor for developing HFSR.5 Vasodilatory agents such as nifedipine may therefore be useful for both hypertension and cutaneous lesions. One patient treated with bevacizumab developed hemorrhagic ulcers and purpuric patches on the lower legs, termed thrombogenic vasculopathy,6 further supporting a direct VEGF-mediated effect. In the midst of continued characterization of toxic effects profiles of newer oncologic agents, our case represents a distinct cutaneous vasculopathy associated with the anti-VEGF agent axitinib.

Veronica J. Shi, BA
Anjela Galan, MD
Ian D. Odell, MD, PhD
Jennifer N. Choi, MD

Author Affiliations: Department of Dermatology, Yale University School of Medicine, New Haven, Connecticut (Shi, Galan, Odell, Choi); Department of Pathology, Yale University School of Medicine, New Haven, Connecticut (Galan).

Corresponding Author: Jennifer N. Choi, MD, Department of Dermatology, Yale University School of Medicine, 333 Cedar St, Laboratory for Medicine and Pediatrics 5040, New Haven, CT 06510 (jennifer.choi@yale.edu).


Conflict of Interest Disclosures: None reported.

Additional Contributions: We are indebted to Edward W. Cowen, MD, MHSc, Dermatology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, for discussion and comments on the manuscript. Dr Cowen received no compensation for his contributions.


Intermittent Vismodegib Therapy in Basal Cell Nevus Syndrome

The use of intermittent vismodegib therapy is a promising and sustainable medical alternative to the current mainstream surgical management of basal cell nevus syndrome (BCNS). We report our clinical experience with intermittent vismodegib therapy in 2 patients with BCNS.

Report of Cases | Patient 1 is a white man in his 40s, and patient 2 is a white woman in her 50s. Vismodegib therapy was started in both cases because the basal cell carcinoma (BCC) lesions in both patients were becoming more aggressive, appearing more frequently, and could not be managed as easily with surgical and other nonsurgical treatments.

The intermittent vismodegib dosing was first administered to patient 1 circumstantially; adverse effects in his case resulted in patient noncompliance with the prescribed noninterrim regimen. However, the dramatic improvement prompted us to suggest intermittent therapy to both patients. The Table contains the dosing regimen, number of BCCs before and after vismodegib therapy, and adverse effects. Both patients agreed to a lifelong intermittent vismodegib regimen but not lifelong continuous daily therapy owing to its adverse effects. The dosing interval was individualized to adverse-effect tolerability and so differs between our patients.

Discussion | An autosomal dominant disorder, BCNS is typically due to mutation of the PTCH1 tumor suppressor gene, resulting in uncontrolled upregulation of the sonic hedgehog pathway and carcinogenesis. Although surgical excisions offer the highest cure rate and lowest rate of recurrence, the on-going repetitive traumatic procedures cause cosmetic disfigurement and lower patients’ quality of life.

Vismodegib is an oral smoothened antagonist approved in 2012 by the US Food and Drug Administration for metastatic, locally advanced, or inoperable BCC. The adverse effects include muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, and constipation. In addition, vismodegib is embryotoxic and teratogenic. Barrier contraception was recommended to our patients during and for 7 months after treatment, and a second method of contraception was advised for our female patient.

Tang et al1 reported a dropout rate of 54% owing to adverse effects in a study of vismodegib treatment for patients with BCNS. The concept of drug holiday is supported by Ally et al,2 who found that 2 of 3 patients who took a 3-month break from vismodegib therapy had similar efficacy of odontogenic cyst shrinkage compared with patients undergoing continuous vismodegib treatment. The intermittent regimen was better tolerated vis-à-vis muscle cramps...
and dysgeusia than the continuous regimen. Similarly, the muscle cramps and dysgeusia in the present patients resolved within 1 month after interrupting the vismodegib regimen.

Although pharmacokinetic studies have shown suboptimal efficacy and similar incidence and severity of adverse effects when vismodegib, 150 mg, was used once weekly or 3 times weekly, no studies to our knowledge have investigated the efficacy of continuous daily doses with drug breaks in between.2 We found a mean of 1.4 new surgically eligible BCCs per year per patient undergoing intermittent therapy, which is comparable to the 2.0 new surgically eligible BCCs per year per patient found by Tang et al1 in patients undergoing a standard continuous daily regimen.

Vismodegib resistance occurs in patients who undergo continuous vismodegib dosing.4 The frequency of resistance in patients who undergo an intermittent form of treatment is largely unknown. Combination therapy with hedgehog pathway inhibitors downstream of smoothened, such as itraconazole and arsenic trioxide, provide opportunities to increase efficacy and possibly reduce the incidence of resistance.5,6

Conclusions | Overall, our clinical experience suggests that intermittent therapy is an effective way to overcome problems with adverse effects and compliance with vismodegib treatment of BCNS. Photographic and histologic documentation of tumors and randomized clinical trials are warranted to quantify the ideal duration of the intermittent regimen and compare the addition of combination therapies to overcome potential drug resistance.

Xinyi Yang
Scott M. Dinehart, MD

Author Affiliations: Faculty of Medicine, University of New South Wales, Sydney, New South Wales, Australia (Yang); Arkansas Skin Cancer Center, Little Rock (Dinehart).

Corresponding Author: Xinyi Yang, 101 Excelsior Parade, Carey Bay, NSW, Australia 2283 (cynthiayang9@gmail.com).


Conflict of Interest Disclosures: Dr Dinehart serves as a consultant and speaker for Genentech. No other conflicts are reported.

Additional Contributions: We are indebted to Mark Lebwohl, MD, Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, for revision of the manuscript. Dr Lebwohl received no compensation for his contributions.


Bullous Pemphigoid Associated With Linagliptin Treatment

Drug-induced bullous pemphigoid (BP) has been recently reported in association with sitagliptin and vildagliptin, 2 dipeptidyl peptidase-4 (DPP-4) inhibitors used in the treatment of type 2 diabetes mellitus (T2DM). Herein, we report the development of BP in 2 patients with T2DM treated with linagliptin, another DPP-4 inhibitor.

Report of Cases | Case 1. A man in his 60s with psoriasis and T2DM presented with pruritus and erythematous tense bullae on the limbs (Figure 1). The clinical diagnosis of BP was confirmed by histologic findings showing a subepidermal blister containing eosinophils (Figure 2) and direct immunofluorescence analysis showing a linear deposit of IgG and C3 at the basement membrane zone. Enzyme-linked immunosorbent assay was performed and demonstrated reactivity with the recombinant proteins of NC16a and C-terminal domains of BP180. Treatment with topical clobetasol propionate, 0.05% (50 g/d), improved the lesions, but the patient presented with another flare of BP 2 weeks later. Linagliptin treatment, which had begun 4 months previously, was stopped. One week later, under treatment with the same topical corticosteroid applications, the lesions healed completely; there was no clinical recurrence of BP during 3 months of follow-up.

Case 2. A woman in her 70s with T2DM presented with a 2-month history of pruritus and tense bullae on the trunk. The diagnosis

Table. Treatment Regimens, Other Treatments, and BCC Numbers Before and After IVT

<table>
<thead>
<tr>
<th>IVT Regimen</th>
<th>Dermatologic Follow-up</th>
<th>Treatments Before IVT</th>
<th>Biopsy-Detected BCCs, No./y</th>
<th>Years Before IVT</th>
<th>Years After IVT</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>1 Month on, 2 months off</td>
<td>Every 6 weeks</td>
<td>Curettage and electrodessication, Mohs surgery</td>
<td>12 11 15 9 2 1</td>
<td>2 1</td>
<td>Muscle cramp, dysgeusia</td>
</tr>
<tr>
<td>Patient 2</td>
<td>2 Months on, 2 months off</td>
<td>Every 3 months</td>
<td>Imiquimod, surgical excision, Mohs surgery</td>
<td>4 1 4 5 1 NA</td>
<td>Dysgeusia, muscle cramp, diffuse alopecia</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BCC, surgically eligible basal cell carcinoma; IVT, intermittent vismodegib therapy; NA, not applicable; VT, vismodegib therapy.