Treatment of Margin Positive Basal Cell Carcinoma With Vismodegib: Case Report and Consideration of Treatment Options and Their Implications

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ABSTRACT

Historically, basal cell carcinomas (BCCs) that are neither surgically resectable nor candidates for radiation therapy have had few treatment options. The hedgehog pathway inhibitor, vismodegib, represents a new opportunity for the treatment of such patients. Vismodegib has approval from the United States Food and Drug Administration for treatment of metastatic BCC, locally advanced BCC recurring after surgery, and BCC that is not treatable via surgery or radiation. We present the case of a patient with a BCC infiltrating the spinal column that was neither possible to fully remove surgically nor a candidate for primary treatment with radiation. Treatment with vismodegib followed by adjuvant radiation therapy resulted in complete disease clearance. Vismodegib represents a promising treatment option for patients with surgically non-resectable BCCs that are not candidates for radiation therapy. Mechanism of action, benefits, and adverse events of vismodegib are reviewed, along with a brief discussion on newer options in the hedgehog inhibitor class.

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INTRODUCTION

Basal cell carcinoma (BCC) is frequently associated with mutations in the s (PTCH) gene leading to dysregulation of the hedgehog (Hh) pathway.[1-3] This mutation is seen in more than 90% of BCCs and causes uninhibited tumor growth. Fortunately, the majority of BCCs are easily treated with a variety of modalities including surgery (electrodesiccation and curettage, Mohs), radiation, topical immunomodulation, and cryosurgery. However, for some patients, the removal of a BCC, either using Mohs micrographic surgery or intraoperative frozen sections, may not result in clear pathologic margins. For these patients, subsequent treatment is not standardized, but options usually include additional Mohs, radiation, or, for those unable to undergo further surgery or radiation, topical 5-fluorouracil, topical imiquimod, photodynamic therapy, or cryotherapy.[4-7] Lesions that are surgically non-resectable due to their proximity to vital structures or the risk of cosmetic deformation may also not be subject to radiation therapy. Moreover, when surgical extirpation of BCCs is aborted because of their proximity to adjacent sensitive structures, such as peripheral motor nerves or the central nervous system, the possibility of adjunctive radiation therapy is often ruled out too. Until recently, traditional chemotherapy has been ineffective for the treatment of BCCs, and patients with non-resectable BCC have had few treatment options. However, the advent of vismodegib (Erivedge®; Genentech) presents an opportunity to treat patients with partially resected disease.

This population of patients represents an unmet need with historically few treatment options. In this report, we discuss one patient treated with vismodegib following positive surgical margins. In addition to a discussion of vismodegib, therapeutic choices available to control BCC postoperatively when positive margins are obtained will also be discussed.

Case Report

A 69 year-old man presented to his primary care physician with a large lesion on his back (Figure 1). According to the patient, the lesion had been there for more than 10 years and was not causing him any discomfort. He had been caring for the lesion at home with simple dry dressing changes. However, when it began to bleed on a consistent basis, he sought care from his primary care physician. The patient was ultimately admitted to the hospital for evaluation and management of the lesion.

Examination at presentation revealed a 24 cm x 30 cm lesion on his middle back. There was adhesion to the underlying structures with a friable, hypergranulated surface. Computed tomography (CT) scans revealed a large lesion extending from T5 to T11 that measured approximately 17 cm (Figure 2). A surgical biopsy demonstrated an infiltrative BCC (Figure 3). Based on the physical examination, it was decided that resection of the lesion would be the optimal treatment approach.

FIGURE 1. Preoperative presentation of the basal cell, which spans the entire width of the patient's back. The surface is friable and bleeding.

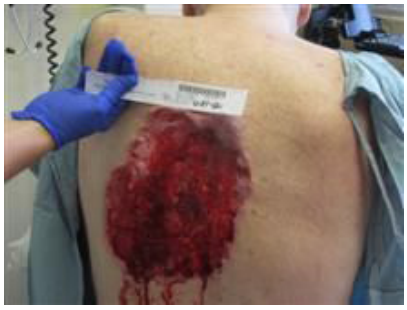


FIGURE 2. Computed tomography scan obtained prior to surgery demonstrates the depth and span of the lesion. The size of the lesion fulfills criteria for use of oral treatment with vismodegib.

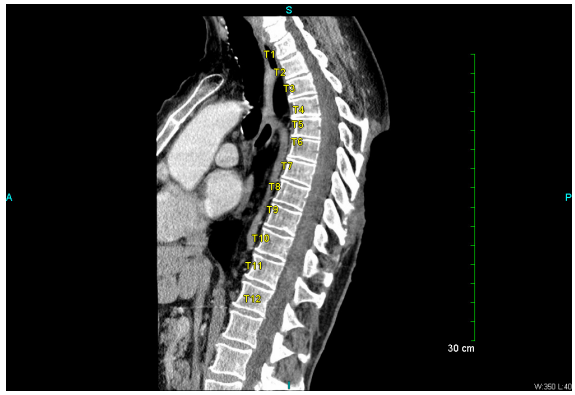


FIGURE 3. Pathologic evaluation of a biopsy revealed an infiltrative basal cell carcinoma.

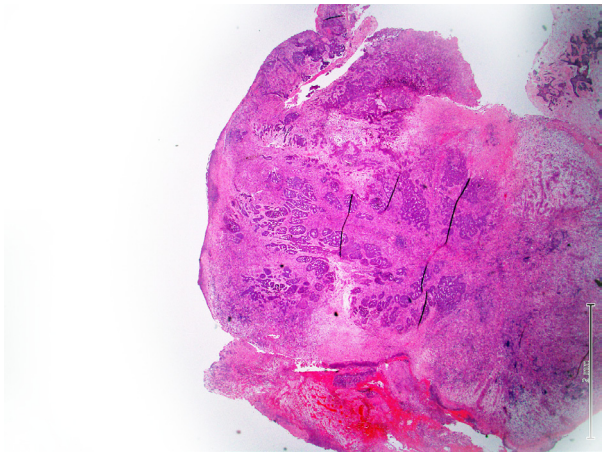
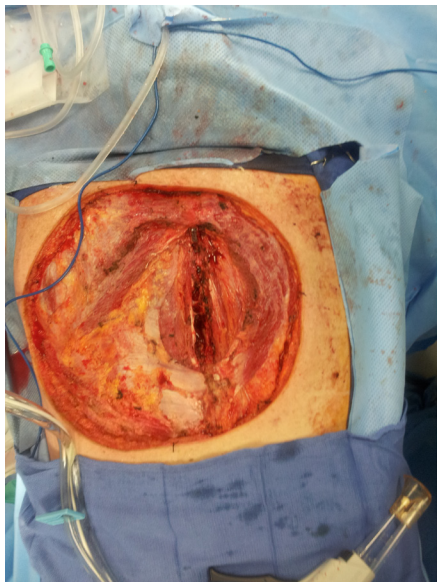


FIGURE 4. Intraoperative examination of the depth and breadth of the lesion. Clear surgical margins were not achievable.



Alternatives to surgery, including radiation and topical imiquimod, were considered. Given the extensive size of the tumor and the dose of radiation required with proximity to the spinal cord, radiation would pose significant risk to the central nervous system. Topical imiquimod was considered inappropriate because it would likely be ineffective for such a deep tumor.

During surgery, it became apparent that the size and depth of the tumor were substantially greater than initially appreciated via CT scan and that the tumor had infiltrated into the spinous processes of multiple vertebrae (Figure 4). Alternatives for treatment included complete resection of the affected spinous processes or termination of the surgical procedure. Because of the length of the procedure and the involvement of multiple vertebral levels, it was elected to terminate the resection and reconstruct the defect using left and right paraspinous muscle flaps as well as right and left latissimus dorsi flaps. A second stage operation was performed for skin graft closure over the muscles.

The patient had an uneventful recovery and his surgical site healed without any complications. Treatment options for the patient were discussed based on the depth and location of the tumor. These included radiation, observation, additional surgery with neurosurgical participation, or treatment with an oral Hh inhibitor, such as vismodegib.

After consultation with an oncologist and a dermatologic surgeon, it was decided to initiate treatment with vismodegib at 150 mg per day.

After using vismodegib for approximately 3 months, the patient elected to discontinue this treatment due to adverse events (AEs), primarily lethargy and dysgeusia. He was subsequently evaluated by radiation oncology and treated with radiation; the risk of radiation injury to the spinal column at this point was determined to be less than the risk of leaving the remaining

BCC untreated. At the time of publication, 6 months after this course of treatment, there is no evidence of disease. As with other high-risk patients, he will be monitored closely.

"Vismodegib represents a promising treatment option for patients with surgically non-resectable basal cell carcinomas that are not candidates for radiation therapy."

DISCUSSION

There are significant issues in the treatment of partially resected BCCs, the most salient of which has been the lack of treatment options for patients with BCCs located near vital structures. Patients with large BCCs are a second category of patient for whom treatment options have been suboptimal to date. One consideration when considering treatment options for patients with positive margins is the fact that approximately one-third of these patients are subsequently found to have no residual tumor when repeat surgery is performed.[8] Fortunately, other treatment options exist, such as topical 5-fluorouracil, topical imiquimod, photodynamic therapy, or cryotherapy.[4-7] However, these options are not sufficient for locally advanced or metastatic BCCs. In January 2012, the United States Food and Drug Administration (FDA) approved vismodegib for the treatment of metastatic BCC or locally advanced BCC that has recurred after surgery, as well as for patients who are not candidates for surgery or radiation.

Patched homologue 1 (PTCH1) normally functions to inhibit smoothened (SMO) signaling. Without this inhibition, SMO induces transcription factors in basal cells that promote cell proliferation and growth. Hedgehog is key in the development of BCC by inhibiting PTCH1, and thus eliminating the inhibition of SMO, ultimately resulting in cell proliferation.[9,10] Basal cell carcinomas most often result from loss of function mutations in PTCH1, but may also arise from activating mutations in SMO. The significance of vismodegib to BCC is in its ability to bind to and inhibit SMO, thereby bringing about crucial inhibition of basal cell proliferation regardless of whether the mutation is in PTCH1 or SMO.

In a phase 1 study to assess the safety and tolerability of vismodegib, 15 patients with locally advanced basal tumors, as with our patient, were enrolled. Two of these patients demonstrated complete clinical response, 7 showed partial response, 4 had stable disease, and 2 had progressive disease. In those who responded, median duration of response was 8.8 months.[9] A phase 2 study to further assess efficacy and safety showed complete response in 13 patients (21%) with locally advanced BCC with a median duration of response of 7.6 months and median progression-free survival of 9.5 to 1.3 months.[3]

Adverse events identified during these studies included fatigue, muscle spasms, alopecia, dysgeusia, weight loss, anorexia, dyspnea, nausea, diarrhea, arthralgias, vomiting, and constipation. Three of 10 premenopausal women developed amenorrhea. Hyponatremia, azotemia, and hypokalemia were the most serious laboratory anomalies that arose. Rare events included atrial fibrillation, dyspepsia, aspiration, back pain, corneal abrasion, dehydration, keratitis, lymphopenia, pneumonia, urinary tract infection, prolonged QT interval, cholestasis, pulmonary embolism, dehydration and/or syncope, hypocalcemia, elevated alkaline phosphatase, and hyperkalemia; most of these developed in no more than one patient.[3,9,11-13] All patients in the phase 2 trial experienced at least one AE.[3]

While the most common side effects are generally considered to be minor-to-moderate in severity, they can be unbearable for some patients. Their high frequency has resulted in many patients opting to discontinue the medication, a very unfortunate dilemma for patients in need of vismodegib as a therapeutic option. Another concern and potential limitation of vismodegib is the potential for resistance as well as a recurrence of BCC once the medication is discontinued. In one retrospective review, 21% of patients with advanced BCC experienced tumor regrowth while still on vismodegib treatment.[14]

Future options for these difficult to treat advanced BCCs are under study. Several inhibitors of GLI, a transcription factor downstream of SMO, have been identified.[10,15,16] The antifungal itraconazole is also a Hh inhibitor and is under investigation for its applicability to BCC treatment, potentially in combination with arsenic trioxide.[10] While the common AEs associated with vismodegib are thought to be a class effect of Hh inhibitors, it remains to be seen whether or not the side effects with these newer therapeutic options will be as significant or as unpleasant for patients, and how their efficacy compares to that of vismodegib.

CONCLUSION

The patient presented represents an unusual and instructive case because he presented with easily monitored disease, but no traditional treatment alternatives seemed to offer promise for disease control. The proximity of his tumor to his spinal cord mandated that some type of treatment be instituted to protect his central nervous system.

Patients with partially treated BCCs often present with similar circumstances to the patient presented in this report: they may have had Mohs surgery or other margin-controlled surgery that was not successful because of anatomic boundaries that could

not be breached. Metastatic BCC and BCCs that cannot be resected are rare. Whereas some of these non-resectable patients may be treated with radiation, many are not candidates for this modality due to proximity to vital structures. For these patients, vismodegib offers a valuable alternative for treatment.

DISCLOSURES

Kenneth Beer MD FAAD receives fees from Genentech for speaking and research. Stephanie Bayers BSBA, Daniel Kapp MD FACS, and Benjamin Slavin have no conflicts of interest to disclose.

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