Concurrent Vismodegib and Radiotherapy for Recurrent, Advanced Basal Cell Carcinoma

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Although surgical resection is curative in most patients with basal cell carcinoma (BCC), recurrent or more advanced disease may be treated with a combination of surgery and radiation. Cisplatin is sometimes used for patients with metastatic BCC, but no systemic therapy was approved for the treatment of BCC until recently with the advent of vismodegib. Response rates to systemic vismodegib were 30% and 43% for patients with metastatic and locally advanced BCC, respectively, with a median duration of response of 7.6 months.

As vismodegib becomes increasingly used, it will be important to address how to best integrate this new agent into existing therapy for advanced BCC. Improved understanding of how vismodegib interacts with other treatment modalities, including radiotherapy, would help optimize multidisciplinary therapy and clinical outcomes.

We report 2 cases of recurrent, advanced BCC treated from April 1, 2012, through October 31, 2014, with concurrent radiotherapy and vismodegib. Concurrent treatment appeared to be well tolerated and efficacious, with both patients having no evidence of progressive disease at last follow-up.

We found that the combination of vismodegib and radiotherapy is feasible for patients with recurrent or locally advanced BCC and that combined use of currently available therapies for advanced BCC warrants further prospective study.

Case 1
A man in his 60s presented with a left nasal tip BCC that was initially treated with Mohs surgery. Although this lesion had received no prior treatment and his surgery revealed no aggressive features, he developed pain and numbness 10 months later in the V2 distribution of the left cranial nerve and was initially medically managed for trigeminal neuralgia. However, his symptoms progressed during the next 3.5 years. He was ultimately evaluated and found to have left cranial nerve V1 to V3, VI, and VII palsies on examination. Concern was raised for perineural spread of the tumor that involved left cranial nerve V1 to V3, VI, and VII and the left cavernous sinus on skull base magnetic resonance imaging (MRI). Biopsy of the left V3 nerve confirmed BCC with perineural invasion. Positron emission tomography–computed tomography revealed no distant disease. He was prescribed vismodegib, 150 mg/d, with concurrent radiotherapy. The clinical area of the disease, which included the left infraorbital nerve, left cranial nerves V2, V3, and VII (including greater superficial petrosal and auriculotemporal nerve), left Meckel cave, and cavernous sinus, was treated with 66 Gy in 33 fractions. The left infratemporal fossa and parotid were treated with 50 Gy in 33 fractions. Volumetric modulated arc technique with image guidance and 6-MV

Report of Cases
With institutional review board approval of Stanford University, a search of patients who received vismodegib and concurrent radiotherapy was conducted. Two patients were identified as having been treated with vismodegib and concurrent radiotherapy from April 1, 2012, through October 31, 2014. Treatment-related toxic effects were classified according to the Common Terminology Criteria for Adverse Events.

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photonswereused.Thepatientdevelopedgrade1dermatitisandgrade1mucosistoduringradiotherapybutwastabletocompletethefullcoursetreatmentwithoutanybreaks,andhispainimprovedbymidtreatment.Hecontinuedtotakevismodegibforanadditional3monthsafterradiotherapybutstoppedtakingitbecauseoftastechanges,lossofappetite,musclecramping,andfatigue.Withafollow-upof9months,includingMRIevery3months,hehadstablediseaseapparentonimaging,hadimprovementinhisleftfacialweakness,andcontinuedtobepainfree(Figure1).

Case 2
Amaninhis70spresentedwithaleftlowereyelidandlateralcanthalBCCthatwasinitiallytreatedwithMohssurgery.Threeyearslater,hedevelopeddiplopiaandanewmassovertheleftlateralcanthusatthesiteofhispreviousleftlowerlidreconstruction.Computedtomographyoftheorbitrevealedthickeningthatmeasured6.5 × 7.4 mm in the region of the left lower eyelid and lateral canthus, and left orbital biopsy revealedinfiltrativeBCC.Thepatientoptedfortreatmentwithvismodegib,150 mg/d, to try to shrink the lesion before resection. After 2 months of vismodegib therapy, the patient underwent an MRI of the orbit, which again revealed a left lateral orbital lesion, which measured 6.3 × 5.6 mm. He underwent a left globesparing resection with positive margins, followed by adjuvant radiotherapy, while continuing to take vismodegib. The radiotherapy target volume, which encompassed the postoperative bed at the left lateral orbit, was treated to a total dose of 51 Gy in 17 fractions using mixed 6-MeV and 9-MeV electrons. This radiotherapy schedule was chosen after discussion with the patient and consideration of his social and transportation issues. He developed grade 1 dermatitis in the radiation field during his radiotherapy. He stopped taking vismodegib 2 weeks after completion of radiotherapy because of increased fatigue, weight loss, and shortness of breath. With a follow-up of 12 months, including posttreatment MRI and regular ophthalmologic evaluations, he continues to be disease free, with dry eye managedby eye drops asthe only radiation-associated toxic effect. The left globe and lacrimal gland received mean doses of 12.5 and 22.3 Gy, respectively. Before radiation, his left eye vision with-
out correction was 20/60 (right eye vision, 20/20). At last follow-up, his vision was 20/100 in the left eye without correction (right eye vision, 20/40). Figure 2 shows pretreatment and posttreatment imaging and a radiotherapy plan.

Discussion

Vismodegib, an exciting advance in the treatment of advanced BCC, with 30% to 60% objective responses reported,3,5-7 is effective for patients with metastatic or locally advanced BCC who are not candidates for or who have had disease recurrence after surgery and/or radiation therapy. However, there are limitations to this drug because treatment duration can be limited by adverse effects, including muscle spasms, alopecia, dysgeusia, weight loss, and fatigue. Acquired resistance to Hedgehog pathway inhibition after initial response is also an increasing concern.8 In addition, cases of vismodegib-associated squamous cell carcinoma within and distant to BCC have been reported.9-11

There has been great interest in expanding the use of vismodegib and using it not just as monotherapy but as an adjuvant to existing treatments. Vismodegib therapy is being explored in the neoadjuvant setting in an attempt to reduce tumor volumes to facilitate resection12,13 or radiotherapy and even in the concurrent setting with radiotherapy.14 The interaction between radiotherapy and Hedgehog pathway inhibition has not been well studied, but available preclinical data support combining vismodegib with radiotherapy. Stimulation of Hedgehog signaling has been reported to reduce radiosensitivity in hepatocellular carcinoma,15 and inhibition of Hedgehog signaling in an esophageal cancer cell line was reported to increase radiosensitivity.16 Zeng et al17 found that although Hedgehog pathway inhibition did not alter radiosensitivity in vitro, it enhanced radiosensitivity in their in vivo non-small cell lung cancer models, suggesting that this effect may be mediated through paracrine stromal signaling. Although vismodegib’s potential for radiosensitization and synergistic efficacy with radiotherapy is promising, there is also concern for potential synergistic toxic effects.

There is scarce clinical experience to guide us on using vismodegib with concurrent radiotherapy for BCC. There has been one case report of a patient who was taking vismodegib for BCC and then developed left parietal and left zygomatic squamous cell carcinomas, which were successfully treated with radiotherapy while continuing vismodegib treatment.4 We are the first, to our knowledge, to report the treatment of BCC using concurrent radiotherapy and vismodegib. Concurrent treatment appeared to be well tolerated and efficacious, with both patients having no evidence of progressive disease at last follow-up, despite discontinuing vismodegib treatment because of adverse effects and not using any subsequent therapy. Even though proximity to normal structures can limit the use of radiotherapy in advanced BCC, both patients completed radiotherapy without significant adverse effects.

Conclusions

It can be difficult to determine optimal therapy for this heterogeneous and complex patient population with advanced BCC. Treatment should continue to be multidisciplinary, with consideration of local and systemic therapy, so that this patient population with a poor prognosis can be treated aggressively. We found that the combination of vismodegib and radiotherapy is feasible for these patients, and combined use of currently available therapies for advanced BCC warrants further prospective study.
responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of Interest Disclosures: None reported.

REFERENCES


