Case Report/Case Series

Vismodegib for Locally Advanced Basal Cell Carcinoma in a Heart Transplant Patient

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IMPORTANCE Immunosuppressed patients with solid organ transplants have an increased risk for nonmelanoma skin cancer. Vismodegib has been reported to be effective for select locally advanced or metastatic basal cell carcinomas. However, there is no data documenting the use and safety of vismodegib in immunosuppressed organ transplant patients.

OBSERVATIONS We describe a 78-year-old white man with a history of orthotopic heart transplant, immunosuppressed with low-dose cyclosporine, who presented to a specialty dermatology transplant clinic with multiple, recurrent, locally aggressive facial basal cell carcinomas. Through a multidisciplinary approach, the patient was started on vismodegib therapy. The pharmacokinetics of cyclosporine in the setting of vismodegib administration and weekly monitoring of cyclosporine levels ensured that therapeutic immunosuppression levels were achieved without toxic effects.

CONCLUSIONS AND RELEVANCE To our knowledge, this is the first report that details vismodegib use in an immunosuppressed heart transplant patient receiving cyclosporine therapy. With a growing immunosuppressed organ transplant population at high risk for basal cell carcinoma, therapeutic options for locally advanced or metastatic disease are limited. Vismodegib appears to be a safe option for patients receiving cyclosporine therapy with routine monitoring. Future research is needed to evaluate the safety profile of vismodegib with other immunosuppressive agents.

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Basal cell carcinoma (BCC) is the second most common type of skin cancer in solid organ transplant recipients, with a 10-fold increase in risk compared with the normal population. The majority of BCCs can be treated well with surgery and topical modalities. Only recently have nonsurgical options become available for metastatic and locally advanced BCC. Vismodegib is the first drug approved by the US Food and Drug Administration (FDA) for metastatic and locally advanced BCC; however, at this time there is limited literature on its use in transplant patients.

Report of a Case

A 78-year-old white man with a history of orthotopic heart transplant in 2001 due to valvular cardiomyopathy was referred to our dermatology specialty transplant clinic for evaluation of multiple and recurrent facial BCCs. His immunosuppression regimen consisted of monotherapy with low-dose cyclosporine (75 mg in the morning/50 mg in the evening).

Prior to his presentation in the dermatology transplant clinic, his cutaneous malignant conditions were managed with plastic surgery. In the 5 years prior to his first dermatology visit, he was given general anesthesia and taken to the operating room 7 times for a total of 27 facial excisions, including 21 for nonmelanoma skin cancers. For these he had a total of 15 flap closures, 6 of which had positive margins. On his nose alone he had 7 flap closures, 2 of which had positive margins.

During his initial evaluation in our clinic, several areas on his face were suspicious for recurrent BCC, including several nasal lesions. Five separate biopsy specimens (Figure, A) were taken from the left nasal sidewall and left nasal ala along borders of and within surgical flaps. All were found to be BCCs on histopathologic analysis.

Treatment options for the recurrent nasal BCCs were discussed with the patient including Mohs surgery, radiation therapy, and medical management with vismodegib. The patient was counseled on the likelihood of extensive defects associated with Mohs surgery, given the long-standing, recurrent, and incompletely excised tumors beneath tissue flaps in the setting of immunosuppression. The patient had become weary of additional surgery, given the number of surgical procedures he had previously and out of concern for the likely catastrophic defect further surgery would create. Therefore, the patient wanted to consider vismodegib as the sole treatment, raising a question of safety with concomitant use of vismo-
degib and cyclosporine. After discussion with the patient detailing the risks, benefits, and adverse effects of vismodegib and input from our multidisciplinary team of transplant dermatology, cardiology, pharmacology, and nephrology, the patient began vismodegib therapy, 150 mg once daily.

Because a search of the literature failed to locate any reports of vismodegib use in an immunosuppressed organ transplant patient, a protocol to determine the pharmacokinetics of cyclosporine in the setting of vismodegib administration was developed, including an area under the concentration-time curve (AUC) calculation and weekly cyclosporine level monitoring. After 1 week of concurrent administration of vismodegib, 150 mg/d, and cyclosporine, 100 mg/d, in divided doses, the patient followed normal defined procedures for attaining a cyclosporine trough level, referred to as C₀. In addition, the patient returned to the phlebotomy laboratory every 2 hours for 2 additional cyclosporine peak laboratory draws, referred to as C₂ and C₄. The resulting laboratory values were as follows: C₀ = 85 ng/mL, C₂ = 399 ng/mL, and C₄ = 202 ng/mL. Using established limited sampling strategies (LSS) equations, the calculated AUC median (range) was 1990 (1376-2480) ng × h/mL. One series in heart transplant patients correlated a measured AUC from 0 to 12 h (AUC₀-12) of 6493.1 (1993.7) ng × h/mL to a C₀ of 317.1 ng/mL.¹ This calculated AUC has allowed for interpretation of subsequent C₀ levels. Since starting vismodegib therapy, the patient’s median (range) cyclosporine C₀ levels were therapeutic at 91.5 (71-152) ng/mL. During the period of concurrent cyclosporine and vismodegib administration, monthly laboratory monitoring revealed no changes in the patient’s chronic kidney disease, with creatinine levels remaining stable at a mean (range) of 2.7 (2.2-3.0) mg/dL (to convert to micromoles per liter, multiply by 88.4). Throughout the course, the patient’s cyclosporine dosage was routinely and only minimally adjusted per standard transplant protocols with increases or decreases of no more than 25 mg per day to maintain the patient’s cyclosporine at his therapeutic target levels.

The patient developed the relatively common and well-known adverse effects of fatigue, alopecia, and episodic leg cramps by the second month of vismodegib therapy. After 24 weeks of vismodegib therapy, the patient was hospitalized with lower gastrointestinal tract bleeding that was confirmed to be secondary to hemorrhoids, and his vismodegib therapy was withheld. This event was reported to the medical science liaison at Genentech, the manufacturer of vismodegib. No prior reporting of lower gastrointestinal tract bleeding while on vismodegib therapy was found, and the transplant team concluded that the cause for hospitalization was likely unrelated to vismodegib. After a brief period of recovery from a deconditioned state, the patient was restarted on vismodegib therapy.

After a total of 24 weeks of vismodegib therapy, the patient had subjective clinical improvement in his BCC burden. The patient underwent 2 surveillance biopsies in areas initially found to contain BCC, one on the left nasal sidewall and one on the left nasal ala, and a partial tumor response was confirmed on histopathologic analysis, with only 1 of the 2 previously involved areas still containing BCC (Figure, B). The patient is pleased with his progress and is motivated to continue with medical management despite the minor adverse events he has experienced. The patient continues to follow-up with our dermatology clinic every 2 months and will likely remain on vismodegib therapy until complete resolution of his residual BCC based on clinical and histological evaluation.

Discussion
Vismodegib is a small-molecule smoothened inhibitor indicated for the treatment of metastatic BCC and select locally ad-

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Figure. Before and 4 Months After Vismodegib Therapy

A, Five biopsy specimens along the border and within nasal flaps were consistent with basal cell carcinoma (BCC) on histopathologic analysis. B, Partial tumor response confirmed by histopathologic analysis with site A free of tumor and site B remaining positive for BCC.
Vismodegib for BCC in a Heart Transplant Patient

Advanced BCCs in adults. While initial vismodegib studies excluded organ transplant patients, to our knowledge, we have documented the first transplant patient to be started on vismodegib therapy while receiving concomitant cyclosporine, with a detailed report on safety and pharmacokinetics.

Several trials have attested to the efficacy of vismodegib owing to its inhibitory effect on the hedgehog pathway, since genetic alterations in the hedgehog pathway contribute to the progression of BCC. A phase 1 clinical trial reported that vismodegib use decreased tumor activity in metastatic and locally advanced BCC. Of 33 patients with metastatic and locally advanced BCC, 18 had an objective response to the drug on imaging, physical examination, or both. The FDA approved vismodegib in January 2012 after a multicenter study reported a response rate of 43% in 63 patients with locally advanced BCC and 30% in 33 patients with metastatic BCC.

In the phase 2 study, along with other published research on vismodegib, patients were required to have adequate organ function and transplant patients were excluded. Thus, our multidisciplinary transplant team developed a plan to evaluate for potential vismodegib-cyclosporine interactions in an immunosuppressed patient.

In vitro studies indicate that vismodegib is a substrate of the transporter P-glycoprotein (P-gp), while cyclosporine is a known P-gp inhibitor. While this pharmacokinetic dynamic has the potential to raise vismodegib levels, our patient’s course and adverse effect profile do not suggest a clinically relevant increase in vismodegib levels. However, the vismodegib-cyclosporine interaction with the greatest clinical significance is the drugs’ shared hepatic metabolism. Cyclosporine and vismodegib are both metabolized through cytochrome P450 3A4, raising concern for elevated cyclosporine levels that could be nephrotoxic and lead to worsening of hypertension and dyslipidemia.

With cyclosporine’s complex multiphasic metabolism, close monitoring was required. Assessing cyclosporine pharmacokinetics using a calculated AUC allowed for (1) an estimate of the patient’s total drug exposure over the dosing interval and (2) an understanding of the relationship of the future cyclosporine trough levels to AUC. As summarized in a review article by David et al., AUC was calculated using limited sampling strategies with 3 specifically timed sample laboratory blood sample drawings.

AUC is considered the practice standard to monitor drug levels and is more sensitive than measuring simple trough and peaks. While an AUC requires greater than 10 laboratory blood drawings, it has been shown that an AUC calculated using limited sampling strategies is an appropriate option. A new heart transplant patient requires higher levels of immunosuppression with a goal AUC of AUC0-12 of 6493 × h/mL. Our patient had his heart transplant over 10 years ago, and his goal AUC is approximately one-third the level of a de novo transplant. His calculated AUC while on vismodegib therapy was 1990 ng × h/mL, which was within his goal range of 1376 to 2480 × h/mL.

Of the 10 total medications the patient was using, omeprazole was the only other medication with potential impact on vismodegib’s efficacy. Drugs that alter gastric pH may reduce vismodegib’s bioavailability, with the potential to decrease vismodegib’s efficacy. No formal studies have demonstrated a true adverse impact on vismodegib’s efficacy with proton pump inhibitors, and our patient was continued on omeprazole therapy with a good clinical response.

Conclusions

We have documented what appears to be the first case of clinical and histopathological improvement of recurrent, locally aggressive BCCs with safe use of vismodegib in an immunosuppressed heart transplant patient while on cyclosporine therapy. The cyclosporine pharmacokinetic evaluation confirmed that while on concomitant therapies with vismodegib and cyclosporine, our patient had minimal drug-drug interactions and was appropriately immunosuppressed. Clinical monitoring with only routine and minimal cyclosporine dose adjustments further demonstrated that the 2 medications were well tolerated together. Future research is needed to evaluate the safety profile of vismodegib with other immunosuppressive agents.