Vismodegib dose reduction effective when combined with itraconazole for the treatment of advanced basal cell carcinoma

Jaeyoung Yoon, MD, PhD
Wentzville, Missouri

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INTRODUCTION

Basal cell carcinoma (BCC) is the most common cancer in the United States with an incidence of 3-4 million per year. Most cases are easily treated with high cure rates using surgical methods such as wide excision, electrodessication and curettage or Mohs micrographic surgery, and, less commonly, radiation therapy. However, advanced and metastatic BCCs are more difficult to treat. Two oral medications, vismodegib and sonidegib, have recently become an option for these patients. They work by inhibiting the intracellular hedgehog (Hh) pathway. The link between the defect of this signaling mechanism and formation of BCC was initially shown in patients with Gorlin Syndrome. Vismodegib clinical trial data have shown a response rate close to 60%. Limitations of vismodegib are the side effects experienced by most patients. Over half of the patients have mild-to-moderate adverse events, and 21.2% of the patients discontinued therapy due to this in the international, multicenter, single arm, phase II ERIVANCE BCC clinical trial by Genentech. Itraconazole is a relatively safe drug, which has long been used as an antifungal agent. Recently, it has also shown inhibitory effects on the Hh pathway. The use of oral itraconazole at doses of 200-400 mg/day showed a significant reduction of BCC size in some patients in an exploratory trial. There is some speculation that using Hh pathway inhibitors together may work better than single dosing. The binding sites on the smoothened protein of both of these Hh inhibitors appear to be at different locations. In addition, molecular simulation models show that the binding of one does not interfere with the binding of the other, suggesting that both may work together as antagonists. There are multiple examples in medicine where combining drugs regimens can improve clinical outcome, notably in HIV therapy and cancer chemotherapy. This case report describes two patients who were treated with reduced doses of both vismodegib and itraconazole for locally advanced BCCs.

CASE DESCRIPTION

Case 1

An 84-year-old man was seen in the clinic for a BCC of the left chin (Fig 1, A), which recurred 2 years after Mohs micrographic surgery. He presented with a large, fixed, ulcerated, firm tumor. Magnetic resonance imaging showed the tumor approximating the bone. He refused surgery given his age and the possibility of an extensive surgical intervention. He was administered vismodegib 150 mg once per week and itraconazole 200 mg/day.

Notable clinical improvement was observed after 4 weeks of treatment (Fig 1, B). After 12 weeks, the area was completely healed, and the tissue was more supple (Fig 1, C). He continued the medications for a total of 28 weeks. His last follow-up was 16 months.
after the initiation of treatment, and there was no clinical evidence of tumor progression (Fig 1, D).

This patient experienced body hair loss and muscle spasms of the legs, which were described as mild and tolerable. There were no laboratory abnormalities throughout the treatment.

Case 2

An 85-year-old man presented for Mohs micrographic surgery for a large BCC on his right ear (Fig 2, A). He was concerned about the risk of deformity and asked for an alternative treatment. He was placed on vismodegib 150 mg twice a week (Mondays and Fridays) and itraconazole 100 mg/day.

There was significant clinical improvement after 8 weeks of treatment (Fig 2, B). At 16 weeks, the ear was healed (Fig 2, C). The total treatment duration was 21 weeks. At his last follow-up at 16 months after the initiation of the combination therapy, no clinical evidence of tumor regrowth was observed (Fig 2, D).

DISCUSSION

The recommended dosing for vismodegib is 150 mg/day. Pharmacokinetic studies support this daily regimen for optimal blood concentration.11 In both patients presented here, a significantly lower
dose of vismodegib was used, along with a low dose of itraconazole, compared with the exploratory trial mentioned above. In case 1, one seventh of the recommended dose was given along with itraconazole 200 mg/day. And in case 2, two seventh of the recommended dose was used with itraconazole 100 mg/day. In both cases, the patients showed clearance by week 16. This suggests that combining these two agents have at least an additive effect in some patients.

Patients were monitored carefully while on combination therapy. They were seen in the clinic on a monthly basis, and bloodwork was performed at each visit. Laboratory tests included a complete metabolic panel, a complete blood count, a hepatic panel, and total creatinine kinase. There were no laboratory abnormalities throughout the duration of treatment in either patient. The patient in case 1 experienced mild muscle cramps and loss of body hair. The patient in case 2 denied any adverse effects at all. In contrast, patients who receive daily vismodegib dosed at 150 mg/day almost always experience multiple and/or moderate side effects. Using vismodegib at a reduced dose with milder side effects could make oral Hh pathway inhibition treatment more tolerable, especially for those who need long-term therapy.

It is possible that vismodegib or itraconazole alone resulted in the clinical effects observed here, although such low doses of each drug alone have not been previously reported to be as effective. It is also possible one of these drugs causes an elevated serum level of the other when used together, as they are metabolized by similar pathways through the liver. Itraconazole is an inhibitor of the cytochrome P-450 pathway\(^{12}\) and can elevate the blood concentration of vismodegib. Measuring serum levels of each drug in patients on combination therapy could help elucidate whether this is the case.

More and detailed studies are needed to confirm these observations. It would be worthwhile to further explore whether the use of lower doses of currently available oral Hh pathway inhibitors through combination therapy can help alleviate the severity of adverse events and make this treatment more tolerable for patients.

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