SKIN

RESEARCH LETTER

Alternative Vismodegib Dosing Regimen for Patients with Basal Cell Carcinoma

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ABSTRACT

Background: Although basal cell carcinomas (BCCs) rarely metastasize and recur, locally advanced, metastatic, and refractory disease can be devastating. Systemic treatment with vismodegib, a hedgehog pathway inhibitor, has been shown to have excellent efficacy in minimizing BCC disease burden; however, recommended dosing patterns have led to a myriad of adverse effects.
Methods: In this single institution case series, we retrospectively reviewed side effects, safety, and efficacy for an alternative vismodegib dosing pattern. Six patients unable to tolerate the traditional dosing regimen were prescribed vismodegib 150 mg daily for 7 days followed by a 21-day drug holiday and were monitored for adverse events and disease progression.
Results: All patients reported improvement or resolution of adverse events on this alternative treatment regimen and continued on this regimen for an average of 30.7 months. Four patients had no new BCC development and existing BCCs shrunk in size. One patient with basal cell nevus syndrome developed a single BCC twenty-four months into treatment and another developed a single BCC during a drug holiday for radiation therapy of squamous cell carcinoma of the lung.
Conclusion: A dosing schedule of vismodegib 150 mg daily for seven days followed by a 21-day drug holiday may provide therapeutic effects without intolerable side effects for patients who require long-term dosing.

INTRODUCTION

Basal cell carcinomas (BCCs) are the most common type of skin cancer. BCCs are unlikely to metastasize; however, locally advanced, metastatic, and refractory BCCs not amendable to surgery or radiation therapy can be destructive.[1] Systemic treatment with vismodegib, a hedgehog pathway inhibitor, has been shown to have excellent efficacy in minimizing BCC disease burden. Although efficacious, vismodigeb's side effect profile on the recommended 150 mg once daily dosing regimen can be a treatment limiting factor.[2] Adverse effects include muscle spasms, dysgeusia, alopecia, fatigue, weight loss, nausea, anorexia, and rarely amenorrhea.[1,2] For many patients, this dosing regimen is not sustainable and

various alternative long-term dosing regimens have been proposed; however, an optimal, tolerable dosing regimen to minimize both BCC burden and adverse effects is under debate. We propose an alternative dosing regimen to balance drug efficacy and tolerability.

METHODS

A single-center retrospective case series was performed at the University of Alabama at Birmingham (UAB) and reported side effects, safety, and efficacy for an alternative vismodegib dosing pattern. The alternative dosing schedule consisted of vismodegib 150 mg daily for seven days followed by a 21-day drug holiday. This dosing pattern was prescribed to six patients all followed by a single provider.

RESULTS

The average patient age was 67 years old. Three patients were female with basal cell nevus syndrome (BCNS) and three patients were men, two with extensive BCCs and one with a BCC refractory to radiation and surgery. All six patients were initially started on vismodegib 150 mg daily until experiencing intolerable side effects (mean = 2.6 months). The most common adverse effects were muscle spasms (100%), dysgeusia (100%), alopecia (67%), fatigue (50%), and nausea (50%). All patients reported improvement or resolution of most adverse effects following the initiation of the alternative dosing pattern. Individual patients reported unchanged alopecia, fatigue and muscle spasms, however, these were not treatment limiting. Patients continued this alternative treatment regimen for an average of 30.7 months. In terms of BCC disease progression and recurrence, four patients achieved reduction in BCC size and remained free of any new BCC development and two patients developed new BCCs. One patient with BCNS developed a BCC of the left nasal tip 24 months into treatment and a second patient developed a BCC during a drug-holiday for radiation of squamous cell carcinoma of the lung. After he restarted vismodegib for seven days on followed by a 21-day drug holiday, however, this new BCC decreased in size and no additional BCCs were detected. (**Table 1**)

DISCUSSION

Alternative vismodegib dosing regimens for patients with recurrent or unresectable BCCs has been reported to reduce intolerable adverse effects in patients requiring long term therapy.[3,4] Dreno et al reported an alternative vismodegib dosing regimen of 150 mg daily for 12 weeks-on/24 weeks-off/12 weeks-on was more tolerable than a dosing regimen of 150 mg oral vismodegib x 24 weeks-on/24 weeks-off/8 weeks-on. Several other studies have compared an alternative vismodegib dosing schedule of 150 mg daily with weekend-off drug holidays. Overall, both alternative regimens report a decrease in adverse effects and patients saw either remission or a significant size reduction of existing BCCs.[3,4,5,6]

An individualized vismodegib maintenance dosing regimen is ideal for patients who require long-term therapy. Our alternative long-term dosing schedule of vismodegib 150 mg daily for seven days followed by a 21-day drug holiday may provide therapeutic effects without intolerable side effects. It's not clear what maintenance schedule of vismodegib is ideal for patients requiring long-term treatment; however, future prospective studies may elucidate a regimen that

minimizes both BCC burden and adverse effects.

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Table 1. Patient demographics, indication for therapy, standard and alternative vismodegib treatment durations, adverse effects, and treatment efficacy.

Sex	Age	Indication for vismodegib therapy	Duration of vismodegib standard dosing (150 mg daily)	Basis for switching to vismodegib alternative dosing	Duration of vismodegib alternative dosing (150 mg daily x 7 days, 21-day drug holiday)	Improved symptoms after switching regimens	Unchanged symptoms after switching regimens	Worsening symptoms after switching regimens	Reported progression of disease/ recurrence of basal cell carcinomas
M	87	Extensive, unresectable BCCs (>30) of the head and neck	2.5 months	Dysgeusia Fatigue Muscle spasms	16 months	Dysgeusia Fatigue	Muscle spasms	None	No additional/recurrent BCCs
M	82	History of multiple BCCs s/p radiation & surgery	3 months	Alopecia Dysgeusia Fatigue Muscle spasms Weight loss	45 months*	Dysgeusia Fatigue Muscle spasms Weight loss	Alopecia	None	Single BCC recurrence while on drug holiday. Recurrence has decreased in size since restarting therapy
M	94	Unresectable BCC of the right ear	2 months	Anorexia Dysgeusia Muscle spasms Nausea Weight loss	34 months	Anorexia Dysgeusia Muscle spasms Nausea Weight loss	None	None	No additional BCCs. BCC of right ear remains stable and without evidence of progression
F	66	Basal cell nevus syndrome	3 months	Alopecia Dysgeusia Muscle spasms Nausea	24 months	Alopecia Dysgeusia Muscle spasms Nausea	None	None	No additional/recurrent BCCs
F	40	Basal cell nevus syndrome	3 months	Alopecia Dysgeusia Muscle spams Nausea	38 months	Alopecia Dysgeusia Muscle spams Nausea	None	None	Single BCC of left nasal tip
F	34	Basal cell nevus syndrome	2 months	Alopecia Dysgeusia Fatigue Muscle spasms	27 months	Alopecia Dysgeusia Muscle spasms	Fatigue	None	All current BCCs have decreased in size. No additional/recurrent BCCs

*Takes occasional drug holidays when receiving radiation for squamous cell carcinoma of the lung