SKIN

IN-DEPTH REVIEW

A Review of the Risk of Cutaneous Squamous Cell Carcinoma after Vismodegib Therapy

Jenne P. Ingrassia, BA[1], Jacqueline Maher, MD[1], Abigail Cline, MD[1,2]

[1] New York Medical College, School of Medicine, Valhalla, NY
[2] New York City Health and Hospitals, Department of Dermatology, New York, NY

ABSTRACT

Introduction: Since vismodegib's approval for advanced or metastatic basal cell carcinoma, there has been concern over vismodegib's potential to induce secondary neoplasms of the skin, such as cutaneous squamous cell carcinoma (cSCC).
Objective: In this article, we provide a comprehensive review of the literature on vismodegib's relationship to cSCC.
Methods: A systematic search of PubMed and Ovid MEDLINE was performed with terms "vismodegib" AND "squamous cell carcinoma." Studies ranged from May 2013 to January 2022.
Results: 25 articles were ultimately included in the review. In total, of the 2576 patients included in the review, there were 197 cSCCs reported. The median duration of treatment with vismodegib was 3 months.
Discussion: Numerous reports have published conflicting findings. While one retrospective cohort study did find an increased risk, additional studies have found that the rates of cSCC are comparable between those exposed and those not exposed to vismodegib. Limitations of this review are only using two databases to search for articles, the limited number of published articles on the topic, and the quality of the articles included.
Conclusions: Because a causal relationship between vismodegib and cSCC has not been proven, its use should not be avoided due to concerns of causing cSCC. However, patients treated with vismodegib should be closely monitored by dermatologists to evaluate for any suspicious changes. Large-scale, prospective, multi-center studies should be performed to definitively determine the risk of cSCC and vismodegib. It has been proposed that vismodegib may select for tumor cells utilizing the Ras/MAPK pathways.

INTRODUCTION

Vismodegib is a hedgehog inhibitor (HHI) approved by the Food and Drug Administration (FDA) to treat locally advanced and metastatic basal cell carcinomas (BCCs) not treatable with surgical resection and/or radiation. While some studies found that vismodegib may increase the risk for cutaneous squamous cell carcinoma (cSCC), larger studies have reported published conflicting findings.[1,2,4] This study reviews the current literature to assess the risk of vismodegib with the development of cSCC.

METHODS

A literature search of PubMed and Ovid MEDLINE was conducted with terms "vismodegib" AND "squamous cell carcinoma." Between May 2013 and January 2022, 245 articles were identified, and 2 additional articles were found through hand-search of the literature (**Figure 1**). Removing duplicates resulted in 168 articles, of which 130 articles were excluded based on lack of relevance to the research question. 38 total articles were assessed for eligibility, and 14 were ultimately excluded based on lack of applicability. 25 articles were ultimately included in the review.

RESULTS

Of the 25 articles included in the review, 14 reported patient outcome data and statistics on cSCC development after vismodegib exposure, whereas the remaining 11 were review articles or commentaries on the topic. In this review, a total of 2576 patients were treated with vismodegib and 197 cases of cSCC were reported. The duration of vismodegib treatment until cSCC development ranged from 2 weeks to 2.7 years across all studies included. The median duration of treatment was 3 months (**Table 1**).

The initial phase II trial of vismodegib enrolled 96 patients but included safety data of patients from other trials for a total of 400 subjects receiving therapy for a median of 10 months. While the most frequently reported adverse events were muscle spasms, dysgeusia, diarrhea, and alopecia, no secondary malignancies, like cSCC, were recorded.[13] After FDA approval, an open-label study included 119 patients with BCC receiving vismodegib for a median duration of 5.5 months. Adverse events with a median safety follow-up of 6.5 months were tabulated. One patient developed recurrence of a prior cSCC, however, this adverse event was not deemed to be related to vismodegib.[3] In the years following vismodegib's approval, several studies reported[8, 9, 10, 11, 14, 15, 19, 20, 24] cSCC development after vismodegib initiation. In one patient who developed cSCC 13 months after vismodegib initiation, genetic testing from the primary BCC and the subsequent cSCC revealed shared tumor drivers, suggesting vismodegib may induce a phenotypic change from BCC to cSCC. [11] A retrospective study of 19 patients with BCC assessing vismodegib's ability to induce metatypical change of BCC demonstrated metatypical change in 5 cases and squamous change in 2 cases.[25]

A retrospective cohort study evaluated vismodegib and cSCC development in 180 patients, separated into two groups based on exposure (55 patients) or lack of exposure (125 patients) to vismodegib.[2] The overall rate of subsequent non-BCC cancers was higher in the non-exposed group than in the exposed group. However, a Cox proportional hazards regression analysis revealed an increased risk of non-BCC cancer, most frequently cSCC, in the exposed group compared to the control group (Hazard ratio: 8.12; 95% confidence interval, 3.39-11.96, $P<0.001$).[2] Invasive cSCC was more common than in-situ cSCC, suggesting vismodegib may potentiate more aggressive cSCC.[2] The median time between initial therapy and diagnosis of secondary malignancy was 0.9 years (ranging from 2 weeks to 2.7 years). However, whether cSCCs emerging just two weeks after initiation could be attributed to vismodegib remains controversial.[6] Additionally, the results of this study have not been reproducible.

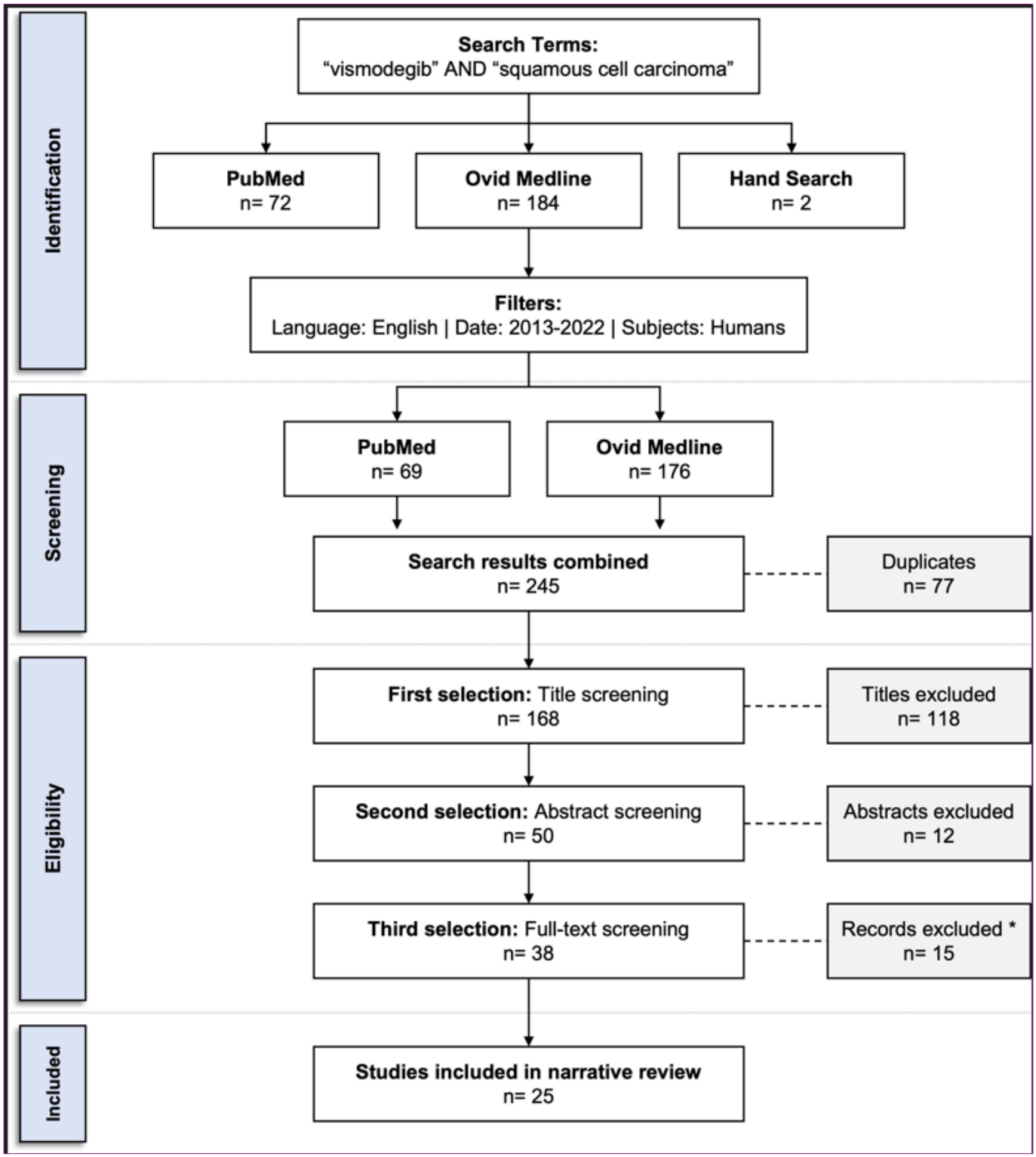

Figure 1. Study identification and selection using the preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram. *Records excluded due to topic or lack of applicability to the research question.

Table 1. Of the 25 articles included, 14 reported patient outcome data and statistics on cSCC development after vismodegib treatment. Of the 2576 patients included, there were 197 cSCCs reported. The duration of vismodegib treatment until cSCC development ranged from 2 weeks to 2.7 years. Median duration of treatment was 3 months.

Author	Date Published	Article Type	Total Patients in Study	Number of cSCCs Reported	Duration of Vismodegib treatment until cSCC diagnosis	Key Findings
Axelson et al	2013	Phase II	138	0		No reported cases of cSCC
Chang et al	2013	Open-label, multicenter study	119	1	≤30 days	One patient died due to a recurrence of previously treated cSCC. Presumed to be unrelated to therapy with vismodegib
Aasi et al	2013	Case report	2	2	2 weeks, 7 weeks	2 patients treated with vismodegib developed new onset keratoacanthomas 2 weeks and 7 weeks after treatment
Iarrobino et al	2013	Case report	1	1	Not available	Biopsy of previous BCC treated with vismodegib after recurrence demonstrated SCC
Zhu et al	2014	Case report	2	2	4 months, 2.5years	Invasive cSCC developed near BCC after 4 months. cSCC developed at the primary site after 2.5 years of treatment.
Orouji et al	2014	Case report	1	1	4 weeks	Several distant sites of moderate to highly differentiated cSCC
Saintes et al	2014	Case report	3	3	1 to 3 months	3 patients treated with vismodegib developed cSCC. The lesions were biopsied due to poor treatment response
Ransohoff et al	2015	Case report	1	1	13 months	1 patient with metastatic BCC treated with vismodegib developed cSCC 13 months after treatment. Genetic testing revealed the SCC shared tumor drivers with the original lesion.
Poulalhon et al	2015	Case report	1	1	4 months	1 patient with BCC and adjacent SCC treated with vismodegib had progression of BCC lesion after four months. Biopsy revealed invasive SCC.
Mohan et al	2016	Case-control study	180	66	2 weeks to 2.7 years	Vismodegib was associated with an increased risk of cSCC in exposed versus those not exposed (Hazard ratio: 8.12;95% confidence interval, 3.39-11.96, P<0.001)
Bhuatani et al	2017	Retrospective cohort study	1675	73	1 year	Vismodegib was not associated with an increased risk of SCC compared to standard BCC therapy after a year (Hazard ratio: 0.57; 95% confidence interval, 0.28-1.16).
Feigenbaum et al	2017	Case report	1	1	3 months	1 patient with 4 BCCs treated with vismodegib developed infiltrative BCC with squamous differentiation.
Bancalari et al	2019	Retrospective study	19	0		Biopsy samples of BCCs before, during and after treatment with vismodegib. 5 cases had metatypical change after treatment, and 2 cases had squamous change. No cases of squamous cell carcinoma were observed.
Sekulic et al	2022	Prospective, multicenter, observational registry study	433	45	Not available, median follow up of 23.6 months	Rates of cSCCs did not significantly differ between those treated with vismodegib and not treated. The exposure-adjusted-incidence rate of cSCC after vismodegib exposure was 0.06 cases per patient- year compared to 0.07 cases per patient-year in the non-exposed group.

Two large, multicenter studies[1,4], one a retrospective cohort and the other a prospective observational registry, found that the risk of cSCC after exposure to vismodegib use was comparable to the control groups with no exposure. In 2017, a retrospective cohort study of 1675 patients compared patients treated with vismodegib from phase I and II clinical trials and patients who received standard surgical treatment for BCC. Multivariate proportional hazards analysis did not reveal an increased risk of cSCC with vismodegib use (Hazard ratio: 0.57; 95% confidence interval, 0.28-1.16).[1] In 2022, a prospective, multi-center observational registry analyzed over 500 patients with locally advanced BCC not treated with vismodegib. Overall, the study found comparable rates of cSCC between the vismodegib-treatment group (12% of patients developed cSCC, exposure-incidence rate of 0.06 cases per year) and the non-vismodegib treatment group (12% of patients developed cSCC, exposure-incidence rate of 0.07 cases per year).[4]

DISCUSSION

Since vismodegib's approval by the FDA for the treatment of invasive or metastatic BCC, there have been anecdotal concerns that vismodegib can induce cSCC. While a retrospective cohort study[2] seemed to verify that vismodegib is associated with an increased risk of cSCC, these results have not been reproduced. Based on the available findings, vismodegib does not appear to increase the risk for subsequent cSCC. It is plausible that patients who have already developed BCC are at risk of other skin cancers, like cSCC, due to shared risk factors.

As an HHI, vismodegib's role in cSCC development may be due to select tumor cells circumventing the hedgehog pathway, and instead utilizing other growth pathways, including Ras/MAPK.[2,18] Further investigation has demonstrated the importance of cilium in tumor pathway switching, with a decrease in cilium gene expression in BCCs resistant to HHIs. This results in low hedgehog pathway activation and an increase in Ras/MAPK pathway activation.[16,17]

Limitations of this review include only using two databases to search for articles and the limited number of published articles that address the research question. The quality of certain study types included in the review, such as case reports, is another limitation of this article.

CONCLUSION

The current data available on the relationship between vismodegib use and the subsequent development of cSCC is not definitive and does not demonstrate causality. With a high efficacy rate in the treatment of BCCs not amenable to surgical resection or radiation, vismodegib should not be avoided due to concerns of causing secondary cutaneous neoplasms. However, the data available does suggest that patients treated for BCC with vismodegib should be closely monitored by dermatologists to evaluate lesions for response to treatment, changes, or signs of progression. When in doubt, the lesion should always be re-biopsied. Additional large-scale, prospective, multi-center studies should be conducted to definitively evaluate the risk of vismodegib use in the development of cSCC.

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Corresponding Author:

Jenne P. Ingrassia, BA
40 Sunshine Cottage
Valhalla, NY, 10504
Phone: 914-594-4000
Fax: 914-594-3752
Email: jenneingrassia@gmail.com

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